Critical Care Medicine

Fluctuations in Serum Sodium Level Are Associated With an Increased Risk of Death in Surgical ICU Patients*

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Objective: Dysnatremia may have an impact on outcomes in critically ill patients, but this has not been widely investigated in surgical ICU patients. We investigated the epidemiology of dysnatremia in a large cohort of surgical ICU patients and evaluated the possible influence of the time of acquisition of dysnatremia and fluctuations in serum sodium concentrations on hospital mortality in these patients.

Design: Retrospective analysis.

Setting: Fifty-bed surgical ICU.

Patients: All patients admitted to the ICU between January 2004 and January 2009.

Measurements and Main Results: Hyponatremia was defined as a serum sodium concentration <135 mmol/L and hypernatremia as a serum sodium concentration >145 mmol/L. Of the 10,923 surgical ICU patients included in the study, 1,215 (11.2%) had hyponatremia and 277 (2.5%) had hypernatremia at admission to the ICU. Among patients with normonatremia at admission to the ICU (n = 9431), the prevalence of ICU–acquired dysnatremia was 31.3%. Dysnatremia present at ICU admission (odds ratio 2.53; 95% confidence interval 2.06–3.12; p < .001) and ICU–acquired dysnatremia (odds ratio 2.06; 95% confidence interval 1.71–2.48; p < .001) were independently associated with an increased risk of in-hospital death compared to normonatremia. Dysnatremia at ICU admission (odds ratio 1.23; 95% confidence interval 1.01–1.50) was associated with a higher risk of in-hospital death, compared with ICU–acquired dysnatremia. Fluctuation in serum sodium concentration was also independently associated with an increased risk of in-hospital mortality, in patients who remained normonatremic (>6 mmol/L/ICU stay) and in those with dysnatremia (>12 mmol/L/24 hrs or >12 mmol/L/ICU stay).

Conclusions: Dysnatremia was common in surgical ICU patients and was independently associated with an increased risk of in-hospital death in these patients. Dysnatremia at ICU admission was associated with a higher risk of death compared with ICU–acquired dysnatremia. Fluctuations in serum sodium concentrations were independently associated with an increased risk of in-hospital death, even in patients who remained normonatremic during the ICU stay. (Crit Care Med 2013; 41:133–142)

Key Words: electrolyte disturbances; postoperative; prognosis; sodium

Sodium is the main extracellular cation and the most osmotically active solute in the human body (1). Under normal conditions, serum sodium is preserved within a physiologic range despite large variations in daily sodium and water intake. Sodium metabolism is tightly regulated by the kidney through the interaction of numerous neurohormonal mechanisms, including the renin–angiotensin–aldosterone system, the sympathetic nervous system, and the presence of atrial natriuretic and brain natriuretic peptides (2).

Disorders of sodium homeostasis are the most common electrolyte disturbances in clinical medicine (3). The prevalence of dysnatremia in the ICU ranges between 25% and 45% and varies according to the time of onset, the threshold for diagnosis, and the population being assessed (4–6). Dysnatremia imposes a considerable burden on healthcare resources because of its impact on morbidity and mortality (7). Even mild hyponatre-
During the study period, patients received basic infusions. Intravenous fluid administration was performed using balanced full-electrolyte infusions (E153; Serumwerk Bernburg AG, Bernburg, Germany). Colloid solutions were additionally used in some patients according to clinical indication in the form of 6% hydroxyethyl starches (130/0.4, Voluven; Fresenius-Kabi, Bad Homburg, Germany) or 4% gelatin solutions (Gelafusal; Serumwerk Bernburg AG, Bernburg, Germany). In patients with hypernatremia, half-electrolyte infusions (Jonosteril HD 5; Fresenius Kabi GmbH, Bad Homburg, Germany) were used, and intravenous medications were diluted using sodium-free solutions, e.g., Glucose 5%. During the study period, hyperoncotic intravenous solutions were not used for volume resuscitation in the ICU.

Measurement of Serum Sodium Level
Serum sodium levels were routinely checked in a venous blood sample at admission to the ICU and at least once per day at 6:00 AM during ICU stay. Samples were obtained from arterial lines at least six hourly for determination of arterial blood gases and electrolytes, including sodium, potassium, and calcium, using an automated blood gas analyzer (ABL700; Radiometer, Copenhagen, Denmark). Additional samples were obtained whenever required, according to the judgment of the attending physician (available 24 hrs/day). Repeated determination of arterial blood gases (more than four times per day), including serum electrolytes, was performed commonly in unstable cardiorespiratory patients and in those with abnormal blood sugar levels, according to our local standard operative procedures. Laboratory parameters, including results of blood gases, were transmitted automatically to the patients’ electronic charts and validated regularly for plausibility by the attending physician using an electronic signature. Only validated results were included in our analysis.

Definitions
Hyponatremia was defined as a serum sodium concentration <135 mmol/L and hypernatremia as a serum sodium concentration >145 mmol/L. Patients were classified according to the onset of dysnatremia into those who had abnormal sodium concentrations in the initial blood sample, analyzed within 2 hrs of admission to the ICU, and those acquiring dysnatremia thereafter. Mixed dysnatremia was defined as the occurrence of both hyponatremia and hypernatremia during ICU stay in the same patient. Daily fluctuations in serum sodium concentrations were calculated as the difference between the maximum and the minimum values obtained within 24 hrs. The maximum fluctuation in sodium concentration during ICU stay was also computed.

To assess the possible influence of blood sugar level on the epidemiology and outcome from hyponatremia, we corrected the measured serum sodium levels in hyponatremic patients using the following formula:

\[
\text{corrected sodium} = \text{measured sodium} + 0.4 \times (\text{blood sugar} - 5.5 \text{ mmol/L})
\]

Calculations were performed using the blood sugar values measured concomitantly with serum sodium from the same arterial blood sample. Patients were reclassified according to the corrected sodium, and mortality rates were compared between groups.
Statistical Analysis
Data were analyzed using SPSS 17.0 for Windows (SPSS, Chicago, IL). Discrete variables are expressed as counts (percentage) and continuous variables as means ± SD or median and interquartile range (IQR) unless stated otherwise. Categorical data were compared using the chi-square test with Yates’ correction, Fisher’s exact test, or the Cochran–Armitage trend test, as appropriate. The Kolmogorov–Smirnov test was used to verify the normality of distribution of continuous variables. Continuous variables conforming to a normal distribution were compared using analysis of variance and Student’s *t* test; otherwise the Kruskal–Wallis and Mann–Whitney *U* test were applied. A Bonferroni correction was done for multiple comparisons.

We performed a logistic regression multivariate analysis with hospital outcome as the dependent factor to investigate the possible influence of dysnatremia on hospital outcome. Variables considered for the multivariate modeling included demographic data, comorbidities, Simplified Acute Physiology Score II and Sequential Organ Failure Assessment scores on admission, the site of surgery, and whether surgery was emergency or electively performed. All variables included in the model were tested for colinearity. A Hosmer and Lemeshow goodness-of-fit test was performed, and odds ratios (ORs) (95% confidence interval [CI]) were computed. In the whole cohort, two models were constructed: model #1 including dysnatremia at admission to the ICU and model #2 classifying dysnatremia according to the time of acquisition in the ICU and including ICU length of stay (LOS) as a covariate. Another multivariate model was performed in patients with normonatremia at admission to the ICU to assess the impact of ICU-acquired dysnatremia on hospital outcome, using the same covariates mentioned above. To further assess the impact of fluctuations in serum sodium levels on outcome, we performed logistic regression analyses as detailed above with hospital outcome as the dependent variable in patients with normonatremia throughout ICU stay and in those who had dysnatremia at any time during ICU stay. Fluctuations in serum sodium levels were introduced as categorical variables in the multivariate models. A *p* value < 0.05 was considered significant.

RESULTS
A total of 10,923 consecutively admitted surgical ICU patients were included in the cohort. The baseline characteristics of the study population are summarized in Table 1. Cardiothoracic, digestive, and neurosurgery were the most common types of surgical intervention (47.2%, 24.3%, and 16.0%, respectively). Overall ICU mortality was 4.8%, and hospital mortality was 8.7%. The median ICU LOS was 1 (IQR 1–3) day.

Dysnatremia at ICU Admission
The prevalences of hyponatremia and hypernatremia at ICU admission were 11.1% (*n* = 1,215) and 2.5% (*n* = 277), respectively (Fig. 1). Patients with hypernatremia were younger, had fewer comorbid conditions, and were more likely to be admitted to the ICU after emergency, trauma, and neurosurgery than patients with normonatremia. Patients with hyponatremia were older, and had a higher prevalence of comorbidities than patients with normonatremia (Table 2). Patients with hypo- or hypernatremia at admission to the ICU had higher severity scores at ICU admission and a higher prevalence of chronic renal failure than those with normonatremia. Patients with hypernatremia had higher Sequential Organ Failure Assessment scores and were more commonly referred to the ICU after emergency, trauma, and neurosurgery compared to patients with hyponatremia.

Patients with hypernatremia or hyponatremia at ICU admission had higher ICU (13.7% and 8.9% vs. 4.0%) and hospital (18.8% and 16.5% vs. 7.4%) mortality rates (both *p* < 0.001

### Table 1. Characteristics of the Study Group at Admission to the ICU

| Characteristic                               | n = 10,923 |
|----------------------------------------------|------------|
| Age, yrs, mean ± SD                          | 63±14      |
| Male, n (%)                                  | 6905 (63.2)|
| Severity scores, mean ± SD                  |            |
| Simplified Acute Physiology Score II         | 38.9±18.3  |
| Sequential Organ Failure Assessment Score    | 6.3±3.7    |
| Comorbidities, n (%)                         |            |
| Diabetes mellitus                            | 5899 (54.0)|
| Arterial hypertension                        | 2582 (23.6)|
| Cancer                                       | 2247 (20.6)|
| Heart failure                                | 1543 (14.1)|
| Renal failure                                | 859 (7.9)  |
| Cirrhosis                                    | 352 (3.2)  |
| Hematologic cancer                           | 128 (1.2)  |
| Type of surgery at admission day, n (%)      |            |
| Cardiothoracic                               | 5153 (47.2)|
| Gastrointestinal                             | 2650 (24.3)|
| Neurosurgery                                 | 1751 (16.0)|
| Trauma                                       | 456 (4.2)  |
| Other*                                       | 913 (8.4)  |
| Type of intervention, n (%)                  |            |
| Elective surgery                             | 8113 (74.3)|
| Emergency surgery                            | 2810 (25.7)|
| Mortality rates, n (%)                       |            |
| ICU mortality                                | 525 (4.8)  |
| Hospital mortality                           | 954 (8.7)  |
| ICU length of stay, days, median (interquartile range) | 1 (1–3)  |

*Otorhinolaryngologic, obstetric/gynecologic, oral, and maxillofacial surgery.*
Dysnatremia did not occur during ICU stay in 59.4% (n = 6,483) of the whole cohort. The prevalence of ICU-acquired hyponatremia was 13.6% (n = 1,483) and of hypernatremia, 9.1% (n = 995). Four hundred seventy patients (4.3%) experienced at least one episode of hyponatremia and of hypernatremia (mixed dysnatremia) during their ICU stay. The prevalence of ICU-acquired dysnatremia increased in patients with longer ICU LOS. Only 2.6% of patients who stayed in the ICU for >14 days remained normonatremic during ICU stay.

Patients with ICU-acquired hyponatremia, hypernatremia, and mixed dysnatremia had higher severity scores at admission to the ICU, a higher prevalence of cirrhosis and chronic renal failure at admission, and were more commonly admitted to the ICU after emergency surgical procedures compared to patients with normonatremia (Table 3). Patients who acquired hypernatremia in the ICU were older, had higher severity scores, more frequently had chronic renal failure and diabetes mellitus, and were more likely to be admitted after emergency interventions compared to those with ICU-acquired hyponatremia. Patients who experienced mixed dysnatremia during ICU stay, had the highest severity scores and prevalence of chronic renal failure, and were more commonly admitted to the ICU after emergency surgery than the other groups (Table 3).

Patients with all forms of ICU-acquired dysnatremia had higher ICU and hospital mortality rates and longer ICU LOS compared to those who were normonatremic throughout their ICU stay (Table 4). Patients who developed hypernatremia alone or in combination with hyponatremia had higher ICU and hospital mortality rates than those with ICU-acquired hyponatremia (Table 3). In a multivariable logistic regression analysis, ICU-acquired hyponatremia (OR 1.32; 95% CI 1.02–1.72; p = 0.036), hypernatremia (OR 2.98; 95% CI 2.36–3.76; p < 0.001), and mixed dysnatremia (OR 2.42; 95% CI 1.70–3.46; p < 0.001) were independently associated with in-hospital mortality (Table S2, Supplemental Digital Content 1, http://links.lww.com/CCM/A594). However, after multivariable adjustment in the whole cohort, dysnatremia at ICU admission was associated with an increased risk of in-hospital death, compared with ICU-acquired dysnatremia (OR 1.23; 95% CI 1.01–1.50; p = 0.038).

Fluctuations in Serum Sodium Concentrations
The median fluctuations in serum sodium concentrations within 24 hrs and during ICU stay were 4 (IQR 2–7; range: 0–41) mmol/L/day and 5 (IQR 3–8; range: 0–53) mmol/L/ICU stay, respectively. In 10,396 patients (95.2%), the maximum daily fluctuation was reached within 4 days of admission to the ICU (89.5% on the second day following admission to the ICU). The maximum fluctuation in serum sodium levels during ICU stay was reached within the first week following admission to the ICU in 10,075 patients (92.3%); on the second day of ICU admission in 8,049 patients (73.7%). Maximum fluctuations in serum sodium were positively correlated to ICU and hospital mortality (Figs. 3 and 4). Reaching the maximum fluctuation in serum sodium levels within 24 hrs was associated with a higher mortality rate than reaching a maximum fluctuation during ICU stay (Figs. 3 and 4). In patients who remained normonatremic during ICU stay, fluctuation in serum sodium concentrations >6 mmol/L during ICU stay was independently associated with an increased risk of in-hospital death (OR 1.55; 95% CI 1.04–2.31; p = 0.033; Table S3, Supplemental Digital Content 1, http://links.lww.com/CCM/A594). Likewise, in patients with dysnatremia present at admission to the ICU or acquired during ICU stay, fluctuations in serum sodium concentrations >12 mmol/L per day or during the ICU stay were independently associated with an increased risk of in-hospital death (Table S4, Supplemental Digital Content 1, http://links.lww.com/CCM/A594).

The Impact of Blood Sugar Level on the Epidemiology of and Outcome From Hyponatremia
Among the 1,215 patients with hyponatremia at admission to the ICU, 102 (8.4%) had blood sugar–corrected sodium levels within the normal range, i.e., translational hyponatremia. The measured sodium levels in patients with translational hyponatremia at admission to the ICU ranged from 130 to 134

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**Figure 1.** Schematic representation of the study population according to the presence of dysnatremia at admission to the ICU and the development of dysnatremia during ICU stay.
mmol/L. ICU (5.9% vs. 8.5%, p = 0.369) and hospital mortality rates (13.7% vs. 14.7%, p = 0.795) were similar in patients with translational hyponatremia at admission to the ICU and hypo-natremic patients within the same category of measured sodium levels. Of 1,483 patients with secondary hyponatremia, only 44 (3%) had blood sugar–corrected sodium levels within the normal range throughout ICU stay. The ICU (6.8% vs. 3.1%, p = 0.168) and hospital mortality rates (6.8% vs. 6.7%, p = 0.984) were similar in patients with translational hyponatremia during ICU stay and in other patients with ICU-acquired hyponatremia.

**DISCUSSION**
In this large cohort of surgical ICU patients, dysnatremia occurred in >40% of patients at some point during ICU stay; almost 97.5% of patients requiring >14 days of treatment in the

| TABLE 2. Characteristics and Outcome of the Study Cohort According to the Serum Sodium Level at Admission to the ICU |
|-------------------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------|
| Normonatremia n = 9431                                      | Hyponatremia n = 1215                                       | Hypernatremia n = 277                                       |
| Age, yrs, mean ± SD                                         | 63±14                                                      | 65±13<sup>a</sup>                                           | 56±19<sup>gi</sup>                                           |
| Male, n (%)                                                 | 5966 (63.3)                                                | 776 (63.9)                                                  | 163 (58.8)                                                   |
| Severity scores, mean ± SD                                 |                                                            |                                                            |
| Simplified Acute Physiology Score II                       | 37.9±18                                                    | 45.3±18.2<sup>a</sup>                                      | 46.1±20.0<sup>a</sup>                                       |
| Sequential Organ Failure Assessment score                  | 6.1±3.7                                                    | 7.3±3.7<sup>d</sup>                                         | 8.1±4.3<sup>f</sup>                                         |
| Comorbidities, n (%)                                        |                                                            |                                                            |
| Diabetes mellitus                                          | 5083 (53.9)                                                | 712 (58.6)<sup>c</sup>                                      | 104 (37.5)<sup>id</sup>                                      |
| Arterial hypertension                                      | 2287 (24.2)                                                | 265 (21.8)                                                  | 30 (10.8)<sup>ig</sup>                                      |
| Cirrhosis                                                  | 259 (2.7)                                                  | 79 (6.5)<sup>d</sup>                                         | 14 (5.1)                                                     |
| Cancer                                                     | 2020 (21.4)                                                | 194 (16.0)<sup>d</sup>                                      | 33 (11.9)<sup>d</sup>                                        |
| Renal failure                                              | 667 (7.1)                                                  | 157 (12.9)<sup>d</sup>                                      | 35 (12.6)<sup>d</sup>                                        |
| Heart failure                                              | 1342 (14.2)                                                | 177 (14.6)                                                  | 24 (8.7)<sup>ia</sup>                                        |
| Hematologic cancer                                         | 99 (1.0)                                                   | 27 (2.2)<sup>d</sup>                                         | 2 (0.7)                                                      |
| Type of surgery at admission day, n (%)                    |                                                            |                                                            |
| Gastrointestinal                                           | 2307 (24.5)                                                | 283 (23.3)                                                  | 60 (21.7)<sup>ig</sup>                                      |
| Cardiothoracic                                             | 4432 (47.0)                                                | 658 (54.2)                                                  | 63 (22.7)<sup>ig</sup>                                      |
| Neurosurgery                                               | 1549 (16.4)                                                | 122 (10.0)                                                  | 80 (28.9)<sup>ig</sup>                                      |
| Trauma                                                     | 360 (3.8)                                                  | 44 (3.6)                                                    | 52 (18.8)<sup>ig</sup>                                      |
| Other<sup>a</sup>                                           | 783 (8.3)                                                  | 108 (8.9)                                                   | 22 (7.9)<sup>ig</sup>                                        |
| Type of intervention, n (%)                                |                                                            |                                                            |
| Emergency surgery                                          | 2232 (23.7)                                                | 433 (35.6)<sup>d</sup>                                      | 145 (52.3)<sup>ig</sup>                                      |
| Elective surgery                                           | 7199 (76.3)                                                | 782 (64.4)<sup>d</sup>                                      | 132 (47.7)<sup>ig</sup>                                      |
| Mortality rates, n (%)                                     |                                                            |                                                            |
| ICU mortality                                              | 379 (4.0)                                                  | 108 (8.9)<sup>d</sup>                                       | 38 (13.7)<sup>ia</sup>                                      |
| Hospital mortality                                         | 701 (7.4)                                                  | 201 (16.5)<sup>d</sup>                                      | 52 (18.8)<sup>a</sup>                                        |
| ICU length of stay, days, median                           | 1 (1–3)                                                    | 1 (1–4)<sup>d</sup>                                         | 3 (1–14)<sup>ag</sup>                                       |

<sup>a</sup>Otorhinolaryngologic, obstetric/gynecologic, oral, and maxillofacial surgery.  
<sup>b</sup>p = 0.05–0.01 compared to normonatremia.  
<sup>c</sup>p < 0.001 compared to normonatremia.  
<sup>d</sup>p = 0.05–0.01 compared to hyponatremia.  
<sup>g</sup>p = 0.01–0.001 compared to hyponatremia.  
<sup>f</sup>p = 0.01–0.001 compared to normonatremia.
In our cohort, mild deviations from normal sodium levels were associated with higher mortality rates. The nature of our study does not enable us to determine the reasons underlying this effect. Hyponatremia can lead to cerebral edema, a potentially life-threatening complication (24), and hypernatremia has been associated with aggravated peripheral insulin resistance and hyperglycemia, impaired hepatic gluconeogenesis and lactate clearance (25, 26), neurological impairment (seizures, intracerebral hemorrhage, coma, death), ICU-acquired delirium, myelinolysis, and rhabdomyolysis) (27, 28), and impaired cardiac function (29, 30). Disturbances in serum sodium levels may also be a marker of underlying disease severity. Nevertheless, after adjustment for possible confounders, including severity of illness, we found that dysnatremia was independently associated with a higher risk of in-hospital death, regardless of the time of onset. Several studies have reported similar results in mixed (6, 11, 12) and medical ICU patients (9, 10, 14). This observation could be useful in risk stratification of ICU patients. We also found that dysnatremia at admission to the ICU was independently associated with a higher risk of in-hospital death compared with ICU-acquired dysnatremia. Disturbances in serum sodium level at admission to the ICU may reflect chronic derangements or may be related to the severity of the initial insult prior to ICU admission with, subsequently, an additional impact on outcome.

The possible influence of fluctuation in serum sodium concentrations on outcome has been poorly investigated. In a matched case-control study, Hoorn et al (11) reported a more acute rise in serum sodium concentrations in patients who died with hypernatremia. A rate of change in serum concentration of ≥12 mmol/L/day during the ICU stay was also related with higher mortality in patients following cardiac surgery (22). In our study, we demonstrated that greater fluctuations in serum sodium levels were independently associated with an increased risk of in-hospital death, not only in patients with dysnatremia but also in those with normal serum sodium levels throughout ICU stay. In dysnatremic patients, this could be explained either by the well-known deleterious effects of dysnatremia or the adverse effects of rapid correction of serum sodium levels as previously reported (11, 22). ICU and hospital mortality rates associated with reaching the maximum fluctuation in serum sodium level within 24 hrs were higher than those associated with reaching the maximum fluctuation later during ICU stay, supporting the hypothesis that time may be a crucial factor in dysnatremia-related adverse outcomes.

To the best of our knowledge, ours is the first study to explore the possible influence of fluctuations in serum sodium levels in normonatremic patients. Acute changes in serum levels in normonatremic patients. Acute changes in serum
sodium level, even though within the normal range, may be expected to trigger rapid changes in serum osmolarity with subsequent neurohormonal and metabolic consequences similar to acute dysnatremia. Especially in the postoperative setting, the neurological manifestations of these acute fluctuations in sodium level may be masked due to sedation.

| TABLE 3. Characteristics and Outcome of Patients With ICU–Acquired Dysnatremia and Those Who Remained Normonatremic During the ICU |
|---------------------------------------------------------------|
| **Normonatremia** | **Hyponatremia** | **Hypernatremia** | **Mixed Dysnatremia** |
| **n = 6483** | **n = 1483** | **n = 995** | **n = 470** |
| **Age, yrs, mean ± SD** | 63 ± 14 | 62 ± 14 | 66 ± 14 | 61 ± 16 |
| **Male, n (%)** | 4067 (62.7) | 1042 (70.3) | 558 (56.1) | 299 (63.6) |
| **Severity scores, mean ± SD** | | | | |
| Simplified Acute Physiology Score II | 34.4 ± 16.9 | 39.9 ± 17.5 | 50.1 ± 16.9 | 53.7 ± 15.6 |
| Sequential Organ Failure Assessment score | 5.3 ± 3.4 | 6.7 ± 3.5 | 8.8 ± 3.4 | 9.8 ± 3.1 |
| **Comorbidities, n (%)** | | | | |
| Diabetes mellitus | 3493 (53.9) | 755 (50.9) | 594 (59.7) | 241 (51.3) |
| Arterial hypertension | 1511 (23.3) | 407 (27.4) | 266 (26.7) | 103 (21.9) |
| Cirrhosis | 128 (2.0) | 73 (4.9) | 38 (3.8) | 20 (4.3) |
| Cancer | 1605 (24.8) | 239 (16.1) | 141 (14.2) | 35 (7.4) |
| Renal failure | 302 (4.7) | 112 (7.6) | 146 (14.7) | 107 (22.8) |
| Heart failure | 870 (13.4) | 224 (15.1) | 178 (17.9) | 70 (14.9) |
| Hematologic cancer | 73 (1.1) | 13 (0.9) | 10 (1.0) | 3 (0.6) |
| **Type of surgery at admission day, n (%)** | | | | |
| Gastrointestinal | 1813 (28.0) | 247 (16.7) | 179 (18.0) | 68 (14.5) |
| Cardiothoracic | 2882 (44.5) | 840 (56.6) | 503 (50.6) | 207 (44.0) |
| Neurosurgery | 971 (15.0) | 265 (17.9) | 170 (17.1) | 143 (30.4) |
| Trauma | 236 (3.6) | 51 (3.4) | 45 (4.5) | 28 (6.0) |
| Other* | 581 (9.0) | 80 (5.4) | 98 (9.8) | 24 (5.1) |
| **Type of intervention, n (%)** | | | | |
| Emergency surgery | 1151 (17.8) | 435 (29.3) | 398 (40.0) | 248 (52.8) |
| Elective surgery | 5332 (82.2) | 1048 (70.7) | 597 (60.0) | 222 (47.2) |
| **Outcome, n (%)** | | | | |
| ICU mortality | 91 (1.4) | 48 (3.2) | 161 (16.2) | 79 (16.8) |
| Hospital mortality | 299 (4.6) | 100 (6.7) | 209 (21.0) | 93 (19.8) |
| **ICU length of stay, days, median (interquartile range)** | 1 (1–1) | 1 (1–4) | 4 (2–10) | 17 (8–27) |

*Otorhinolaryngologic, obstetric/gynecologic, oral, and maxillofacial surgery.

p = 0.05–0.01.

p < 0.01–0.001.

p < 0.001 compared to normonatremia.

p < 0.05–0.01.

p < 0.01–0.001.

p < 0.001 compared to hyponatremia.

p < 0.05–0.01.

p < 0.01–0.001.

p < 0.001 compared to hypernatremia.

Normonatremia: serum sodium levels ≥135 mmol/L and ≤145 mmol/L; Hyponatremia: serum sodium levels <135 mmol/L; Hypernatremia: serum sodium levels >145 mmol/L; Mixed dysnatremia: patients who experienced at least one episode of hyponatremia and one of hypernatremia during ICU stay.
and may be aggravated by preexisting conditions, such as hypoxia and low cardiac output (31). Although correction rates of hyponatremia up to 12 mmol/L per day have been recommended (32), this observation was based on retrospective data and has not been confirmed in prospective randomized trials. Central pontine myelinolysis, a serious complication of rapid correction of hyponatremia, has been reported at correction rates >12 mmol/L per day, depending on the time of onset of hyponatremia (13). Furthermore, in patients with prolonged hypernatremia, treatment with hypotonic fluids may cause cerebral edema, which can lead to coma and death (33). It may not be surprising, therefore, that acute severe fluctuations in serum sodium levels within the normal range may adversely influence outcome. Our data suggest that rapid changes in

### TABLE 4. Characteristics and Outcome According to Time of Onset of Dysnatremia

|                                      | Normonatremia n = 6483 | Dysnatremia at ICU Admission n = 1492 | ICU-Acquired Dysnatremia n = 2948 |
|--------------------------------------|-------------------------|--------------------------------------|----------------------------------|
| **Age, yrs, mean ± SD**              | 63 ± 14                 | 63 ± 15                              | 63 ± 14                          |
| **Male, n (%)**                      | 4067 (62.7)             | 939 (62.9)                           | 1899 (6.4)                       |
| **Severity scores, mean ± SD**       |                         |                                      |                                  |
| Simplified Acute Physiology Score II | 34.4 ± 16.9             | 45.4 ± 18.6<sup>d</sup>              | 45.5 ± 18.0<sup>d</sup>          |
| Sequential Organ Failure Assessment score | 5.3 ± 3.4              | 7.5 ± 3.8<sup>c</sup>               | 7.9 ± 3.6<sup>c,g</sup>          |
| **Comorbidities, n (%)**             |                         |                                      |                                  |
| Diabetes mellitus                    | 3493 (53.9)             | 816 (54.7)                           | 1590 (53.9)                      |
| Arterial hypertension                | 1511 (23.3)             | 295 (19.8)<sup>c</sup>              | 776 (26.3)<sup>c</sup>           |
| Cirrhosis                            | 128 (2.0)               | 93 (6.2)<sup>h</sup>                | 131 (4.4)<sup>h</sup>            |
| Cancer                               | 1.605 (24.8)            | 227 (15.2)<sup>d</sup>              | 415 (14.1)<sup>d</sup>           |
| Renal failure                        | 302 (4.7)               | 192 (12.9)<sup>d</sup>              | 365 (12.4)<sup>d</sup>           |
| Heart failure                        | 870 (13.4)              | 201 (13.5)                           | 472 (16.0)<sup>c</sup>           |
| Hematologic cancer                   | 73 (1.1)                | 29 (1.9)<sup>h</sup>                | 26 (0.9)<sup>i</sup>             |
| **Type of surgery on admission day, n (%)** |                     |                                      |                                  |
| Gastrointestinal                     | 1813 (28.0)             | 343 (23.0)<sup>b</sup>              | 494 (16.8)<sup>d</sup>           |
| Cardiothoracic                      | 2882 (44.5)             | 721 (48.3)<sup>b</sup>              | 1550 (52.6)<sup>d</sup>          |
| Neurosurgery                         | 971 (15.0)              | 202 (13.5)<sup>b</sup>              | 578 (19.6)<sup>d</sup>           |
| Trauma                               | 236 (3.6)               | 96 (6.4)<sup>b</sup>                | 124 (4.2)<sup>d</sup>            |
| Other<sup>a</sup>                    | 581 (9.0)               | 130 (8.7)<sup>b</sup>               | 202 (6.9)<sup>d</sup>            |
| **Type of intervention, n (%)**      |                         |                                      |                                  |
| Emergency surgery                    | 1151 (17.8)             | 578 (38.7)<sup>d</sup>              | 1081 (36.7)<sup>d</sup>          |
| Elective surgery                     | 5332 (82.2)             | 914 (61.3)<sup>d</sup>              | 1867 (63.3)<sup>d</sup>          |
| **Outcome, n (%)**                   |                         |                                      |                                  |
| ICU mortality                        | 91 (1.4)                | 146 (9.8)<sup>b</sup>               | 288 (9.8)<sup>d</sup>            |
| Hospital mortality                   | 299 (4.6)               | 253 (17.0)<sup>d</sup>              | 402 (13.6)<sup>d</sup>           |
| ICU length of stay, days, median     | 1 (1–1)                 | 1 (1–5)                              | 3 (1–11)                         |

<sup>a</sup>Otorhinolaryngologic, Obstetrical/gynecologic, Oral, and maxillofacial surgery.
<sup>b</sup>p = 0.05–0.01.
<sup>c</sup>p < 0.01–0.001.
<sup>d</sup>p < 0.001 compared to normonatremia.
<sup>e</sup>p = 0.05–0.01.
<sup>f</sup>p < 0.01–0.001.
<sup>g</sup>p < 0.001 compared to dysnatremia at ICU admission.

Normonatremia: serum sodium levels ≥135 mmol/L and ≤145 mmol/L; dysnatremia at ICU admission: serum sodium levels <135 mmol/L or >145 mmol/L in the first data set after admission; ICU-acquired dysnatremia: initially normal serum sodium levels and abnormal levels at some point during ICU stay.
Laboratory Investigation

Critical Care Medicine

www.ccmjournal.org

141

Figure 3. Bar chart representing ICU and hospital mortality rates according to the maximum fluctuation in serum sodium concentrations during ICU stay. \( p < 0.001 \) for ICU and hospital mortality among groups (Cochran–Armitage trend test).

Figure 4. Bar chart representing ICU and hospital mortality rates according to the maximum daily fluctuation in serum sodium concentration. \( p < 0.001 \) for ICU and hospital mortality among groups (Cochran–Armitage trend test).

serum sodium levels within the normal range should be recognized early and therapeutic approaches, especially volume replacement, should be adapted to avoid such fluctuations. Whether active correction of these fluctuations could improve outcome or not should be investigated in properly designed prospective studies. Again, although a cause–effect relationship cannot be determined from these data, this information may, nevertheless, be useful in risk stratification of ICU patients.

Hyperglycemia results in the movement of free water from the intracellular to the extracellular space resulting in a decrease in the serum sodium without any alteration in the total body water, a phenomenon called translational hyponatremia. Data on the epidemiology and prognostic value of translational hyponatremia, especially in the postoperative settings, are scanty. In 331 patients with acute heart failure, Milo-Cotter et al (34) reported that translational hyponatremia occurred in 47% of hyponatremic patients. The authors (34) found that the hyponatremia was not associated with poor outcome when associated with hyperglycemia. The study was limited, however, by the small number of patients. In our study, translational hyponatremia was observed in 8.4% of patients with hyponatremia at admission to the ICU and in 3% of patients with secondary hyponatremia. Nevertheless, patients with translational hyponatremia had similar outcomes to other hyponatremic patients. Therefore, although correction of measured sodium levels may have a therapeutic implication in hyponatremic patients with hyperglycemia, this correction is not necessary in terms of prognostication in these patients.

Our study has some limitations. First, the multivariable approach is limited by the variables included in the analysis and a possible influence of unmeasured variables on the results cannot be excluded. Second, marked elevation of lipids and proteins in plasma leads to an artifactual decrease in serum sodium concentration because a larger relative proportion of plasma is occupied by excess lipid or proteins (35). These possible confounding factors were not measured routinely in our patients and may have influenced our results. Third, we did not elaborate on the causes of dysnatremia or on relevant therapeutics, such as fluid regimen, because of the retrospective nature of the study. This is, however, a common limitation of the previous studies on the subject (6, 8, 10, 12, 14). However, we adjusted for several factors in the multivariate analysis that may reflect the underlying pathophysiology of dysnatremia, such as comorbidities, surgical interventions, the severity of illness, and the degree of organ dysfunction/failure as assessed by the Sequential Organ Failure Assessment scores. Fourth, abnormalities in serum sodium levels may have been more commonly detected in more severely ill patients, in whom repeated measures were performed during the ICU stay. Nevertheless, the severity of illness was considered in the multivariate analysis, which should therefore have corrected for this factor. Fifth, repeated measures of serum sodium levels may have increased the probability of erroneous results because of technical issues related to handling of samples and measurement errors. However, laboratory values in our ICU are routinely checked for plausibility by the attending physician, and only validated values were considered in our analysis. Finally, the results of our study cannot be extrapolated to other nonsurgical ICU patients.
CONCLUSIONS
In surgical ICU patients, dysnatremia is common and is independently associated with an increased risk of in-hospital death, regardless of the time of onset, although dysnatremia at ICU admission is associated with a higher risk of death compared with ICU-acquired dysnatremia. Fluctuation in serum sodium concentrations was independently associated with an increased risk of in-hospital death, even in patients who remained normonatremic during their ICU stay. These data may be important in the risk stratification of surgical ICU patients.

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