Association between an increase in serum sodium and in-hospital mortality in critically ill patients*

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Association Between an Increase in Serum Sodium and In-Hospital Mortality in Critically Ill Patients*

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OBJECTIVES: In critically ill patients, dysnatremia is common, and in these patients, in-hospital mortality is higher. It remains unknown whether changes of serum sodium after ICU admission affect mortality, especially whether normalization of mild hyponatremia improves survival.

DESIGN: Retrospective cohort study.

SETTING: Ten Dutch ICUs between January 2011 and April 2017.

PATIENTS: Adult patients were included if at least one serum sodium measurement within 24 hours of ICU admission and at least one serum sodium measurement 24–48 hours after ICU admission were available.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: A logistic regression model adjusted for age, sex, and Acute Physiology and Chronic Health Evaluation-IV–predicted mortality was used to assess the difference between mean of sodium measurements 24–48 hours after ICU admission and first serum sodium measurement at ICU admission (Δ48 hr-[Na]) and in-hospital mortality. In total, 36,660 patients were included for analysis. An increase in serum sodium was independently associated with a higher risk of in-hospital mortality in patients admitted with normonatremia (Δ48 hr-[Na] 5–10 mmol/L odds ratio: 1.61 [1.44–1.79], Δ48 hr-[Na] > 10 mmol/L odds ratio: 4.10 [3.20–5.24]) and hypernatremia (Δ48 hr-[Na] 5–10 mmol/L odds ratio: 1.47 [1.02–2.14], Δ48 hr-[Na] > 10 mmol/L odds ratio: 8.46 [3.31–21.64]). In patients admitted with mild hyponatremia and Δ48 hr-[Na] greater than 5 mmol/L, no significant difference in hospital mortality was found (odds ratio, 1.11 [0.99–1.25]).

CONCLUSIONS: An increase in serum sodium in the first 48 hours of ICU admission was associated with higher in-hospital mortality in patients admitted with normonatremia and in patients admitted with hypernatremia.

KEY WORDS: dysnatremia; electrolyte disorders; hypernatremia; hyponatremia; intensive care unit; sodium

A considerable number of patients are admitted to the ICU with dysnatremia (1, 2), a deranged serum sodium concentration. Furthermore, a substantial number of patients develop dysnatremia during ICU admission (3–5).

Hypernatremia ([Na] > 145 mmol/L) is relatively rare at ICU admission but develops in up to 24% of patients during ICU stay (5) and is an independent risk factor for mortality in the ICU (6–9). ICU patients are predisposed to developing hypernatremia because of the administration of hypertonic solutions, renal-free water loss due to renal disease, diuretics, and gastrointestinal fluid losses.

Hyponatremia ([Na] < 135 mmol/L) is the most common electrolyte disorder in hospitalized patients (10, 11). It is a disorder of water excretion and can occur in many different conditions. Severe hyponatremia ([Na] < 125 mmol/L)

can result in neurologic symptoms, coma, and death especially if the decrease in plasma sodium develops rapidly. In ICU patients hyponatremia is often mild and is most often already present at ICU admission. Hyponatremia is independently associated with mortality (4, 5, 10, 12), which may be due to a direct causal relationship. If this association is causal, correction of hyponatremia would decrease mortality. However, we hypothesize that mild hyponatremia could also be an evolutionary adaptive mechanism in critical illness, as it is common in a wide variety of disease states. If so, the higher mortality rate in patients with mild hyponatremia would reflect the severity of the underlying illness, but increase of serum sodium, either intentional or as side effect of other treatments, would not be beneficial and could even paradoxically be harmful and decrease survival.

The objective of this study was to assess the independent association of changes in serum sodium concentration in the first 48 hours of ICU admission with mortality specifically in patients admitted with mild hyponatremia but also for severe hyponatremia, normonatremia, and hypernatremia in a large cohort of ICU patients.

METHODS

Study Design, Data Source, and Study Population

This retrospective observational study was performed on patient data from 10 ICUs in the Netherlands, including seven academic and three large teaching hospitals. Data were extracted from the Dutch National Intensive Care Evaluation (NICE) registry, a high-quality routinely collected clinical database in which 84 Dutch Intensive Cares participate, which enables to quantify and improve the quality of ICU care by offering feedback and benchmarking on patient outcomes and structure and process indicators. Per year data from 80,000 ICU admissions are collected. Details on the registry are provided elsewhere (13, 14). For this study, the NICE registry retrospectively requested all serum sodium measurements of patients admitted to the participating ICUs between January 2011 and April 2017, and these were merged with routinely collected NICE data. To avoid structural differences in serum sodium measurements from routine chemistry analyzers in central laboratories using the principle of indirect ion-selective electrode (ISE) and measurements from point-of-care blood gas analyzers applying direct ISE,

we only used serum sodium data measured with direct ISE (15). Patients were included for analysis in this study if they were present in both the NICE registry and the additional sodium database and had at least one sodium measurement within 24 hours of ICU admission and at least one sodium measurement 24–48 hours after ICU admission. The medical ethics committee of the Leiden University Medical Center was informed and had no objection to this study (G17.091). According to Dutch legislation, there was no need for informed patient consent, since this concerned a retrospective study on anonymized routinely collected data.

Definitions

To assess the change of serum sodium during the first 48 hours of ICU admission, we calculated $\Delta48$ hr-[Na], that is, the difference between the mean of serum sodium measurements 24–48 hours after ICU admission (mean-$[Na]_{24-48\,hr}$) and the first serum sodium measurement at ICU admission ($[Na]_{first}$) ($\Delta48$ hr-[Na] = mean-$[Na]_{24-48\,hr}$–$[Na]_{first}$). $\Delta48$ hr-[Na] was categorized as follows: $\Delta48$ hr-[Na] < –10 mmol/L, $\Delta48$ hr-[Na] $\geq$ –10 and < –5 mmol/L, $\Delta48$ hr-[Na] $\geq$ –5 and < 5 mmol/L, $\Delta48$ hr-[Na] $\geq$ 5 and < 10 mmol/L, and $\Delta48$ hr-[Na] $\geq$ 10 mmol/L. All sodium definitions are provided in **Table 1**. If $\Delta48$ hr-[Na] was a positive number, serum sodium had increased during the first 48 hours of ICU admission, and if the $\Delta48$ hr-[Na] was negative, serum sodium had decreased during the first 48 hours of ICU admission. Furthermore, patients were categorized according to their serum sodium at admission $[Na]_{first}$ as severe hyponatremia ($[Na]_{first}$ < 125 mmol/L), mild hyponatremia ($[Na]_{first}$ $\geq$ 125 and < 135 mmol/L), normonatremia ($[Na]_{first}$ $\geq$ 135 and < 145 mmol/L), and hypernatremia ($[Na]_{first}$ $\geq$ 145 mmol/L). To explore the possibility that the association of $\Delta48$ hr-[Na] with in-hospital mortality could be influenced by too rapid change in serum sodium, we assessed velocity of change in serum sodium in the first 48 hours of ICU admission (V_{max}-$\Delta[Na]$). V_{max}-$\Delta[Na]$ was defined as the highest velocity of change in serum sodium between $[Na]_{first}$ and any sodium measurement obtained within 48 hours of admission and at least 2 hours after the first serum sodium. V_{max}-$\Delta[Na]$ was categorized as follows: < –5.0 mmol/L/24 hr, $\geq$ –5.0 and < –2.5 mmol/L/24 hr, $\geq$ –2.5 and < 2.5 mmol/L/24 hr, $\geq$ 2.5 and < 5.0

TABLE 1.
Sodium Definitions

Sodium-Related Parameter	Definition
$[Na]_{first}$	The first serum sodium measurement within 24 hr of ICU admission.
$\Delta48$ hr-$[Na]$	The difference between the mean of serum sodium measurements 24–48 hr after ICU admission and the first serum sodium measurement within 24 hr of ICU admission ($\Delta48$ hr-$[Na] = $ mean $[Na]_{24-48\,hr}$-$[Na]_1$).
$[Na]_{max}$	The highest serum sodium measurement during ICU admission.
V-$[Na]_{max}$	Velocity of reaching the highest serum sodium measurement during ICU admission.
V_{max}-$\Delta[Na]$	Maximum velocity of change in serum sodium in the first 48 hr of ICU admission. Calculated as the difference in serum sodium at admission and a sodium measurement within 48 hr after admission, divided by the time between these two measurements. As patients can have several serum sodium measurements within 48 hr, V_{max}-$\Delta[Na]$ is the highest velocity of all pairs of measurements in a patient. Only if sodium measurements were taken more than 2 hr apart, velocity was calculated.

mmol/L/24 hr, ≥ 5.0 and < 7.5 mmol/L/24 hr, ≥ 7.5 and < 10.0 mmol/L/24 hr, and ≥ 10.0 mmol/L/24 hr.

Outcomes and Statistical Analysis

We analyzed the association between $\Delta48$ hr-$[Na]$ and in-hospital mortality by logistic regression (primary analysis). A second model described the association between V_{max}-$\Delta[Na]$ and in-hospital mortality (secondary analysis). Also, a subgroup analysis of the association between $\Delta48$ hr-$[Na]$ and in-hospital mortality was performed in two subgroups of patients with and without intracerebral pathology as reason for ICU admission. Intracerebral pathology was defined as patients with one or more of the following reasons for admission: neurologic abscess, coma/change in level of consciousness, cerebrovascular accident/stroke, encephalitis, epidural/subdural/intracranial hematoma, (obstructive) hydrocephalus, meningitis, neurologic neoplasm, nontraumatic coma due to anoxia/ischemia, subarachnoid hemorrhage/arteriovenous malformation, subarachnoid hemorrhage/intracranial aneurysm, surgery for abscess/infection cranial, burr hole placement, surgery for epidural/subdural/intracranial hematoma, surgery for (excluding transsphenoidal) neoplasm cranial, surgery for seizures intractable, surgery for subarachnoid hemorrhage/intracranial aneurysm, and ventriculostomy. The multivariate models were adjusted for age, sex, and Acute Physiology and Chronic Health Evaluation (APACHE)–IV–predicted mortality. To further examine the association between $\Delta48$ hr-$[Na]$ and in-hospital mortality, we also described sodium variables over the entire ICU admission period for all patients and separately for patients whose serum sodium increased during the first 48 hours ($\Delta48$ hr-$[Na] > 5.0$ mmol/L).

Data for continuous variables are presented as medians with interquartile ranges or means with SDs. Categorical data are presented as percentages. The nonparametric Wilcoxon signed-rank test was used for continuous data, and a chi-square test was used for categorical data. All statistical analyses were performed using R-studio 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). A p value of less than 0.05 was considered statistically significant.

RESULTS

Between January 2011 and April 2017, 125,876 patients were admitted to the participating ICUs, and of these, a total of 36,660 patients (29%) were included for analysis (**Supplementary Fig. 1**, http://links.lww.com/CCM/G540; **legend**, http://links.lww.com/CCM/G545). Exclusion from analysis was often when no serum sodium data were available at 24–48 hours after admission ($n = 32,976$) or because sodium was measured by indirect ISE ($n = 50,603$). Baseline characteristics of excluded patients are provided in **Supplemental Table 1** (http://links.lww.com/CCM/G541).

Patient demographics are shown in **Table 2**. At ICU admission, 497 patients (1.4%) had severe hyponatremia, 8,068 (22.0%) had mild hyponatremia, 25,965 (70.8%) had normonatremia, and 2,130 (5.8%) had hypernatremia. Overall, compared with nonsurvivors, survivors were younger, had less comorbidities, had lower APACHE-IV score, and had a shorter length of ICU stay.

$[Na]_{first}$, $\Delta48$ hr-$[Na]$, maximum serum sodium measurement during entire ICU admission ($[Na]_{max}$),

TABLE 2.
Baseline Characteristics Categorized by First Serum Sodium Measurement at ICU Admission

	Severe Hyponatremia [Na]$_{first}$ < 125 mmol/L, N = 497 (1.4%)		Mild Hyponatremia [Na]$_{first}$ 125–135 mmol/L, N = 8,068 (22.0%)		Normonatremia [Na]$_{first}$ 135–145 mmol/L, N = 25,965 (70.8%)		Hypernatremia [Na]$_{first}$ > 145 mmol/L, N = 2,130 (5.8%)	
	Survivors	Non-survivors	Survivors	Non-survivors	Survivors	Non-survivors	Survivors	Non-survivors
Number of patients	348	149	6,190	1,878	20,926	5,039	1,411	719
Age, mean (SD), yr	58.9 (15.6)	60.6 (14.9)	61.5 (15.2)	64.6 (13.8)	60.0 (15.8)	64.3 (14.5)	55.5 (17.2)	60.5 (15.9)
Sex, n (%) (female)	159 (45.7)	69 (46.3)	2,372 (38.3)	695 (37)	7,577 (36.2)	1,944 (38.6)	541 (38.4)	264 (36.8)
Admission type, n (%)								
Pneumonia	51 (14.7)	10 (6.7)	623 (10.1)	223 (11.9)	1,456 (7.0)	485 (9.6)	186 (13.2)	95 (13.2)
Trauma	10 (2.9)	3 (2.0)	198 (3.2)	37 (2.0)	1,635 (7.8)	240 (4.8)	201 (14.3)	77 (10.7)
Cardiac arrest	10 (2.9)	17 (11.4)	282 (4.6)	259 (13.8)	1,543 (7.4)	974 (19.3)	41 (2.9)	62 (8.6)
Sepsis	35 (10.1)	18 (12.1)	560 (9.1)	257 (13.7)	884 (4.2)	387 (7.7)	129 (9.1)	85 (11.8)
Intracerebral pathology	24 (6.9)	11 (7.4)	379 (24.6)	179 (9.5)	2,024 (9.7)	810 (16.1)	190 (13.5)	116 (16.1)
Other urgent surgery	31 (8.9)	9 (6.0)	942 (15.2)	167 (8.9)	2,557 (12.2)	512 (10.2)	131 (9.3)	53 (7.4)
Other elective surgery	12 (3.4)	2 (1.3)	1,622 (26.2)	164 (8.7)	6,614 (31.6)	471 (9.4)	106 (7.5)	25 (3.5)
Other medical	174 (50.0)	78 (52.3)	1,557 (25.2)	584 (31.1)	4,117 (19.7)	1,140 (22.6)	420 (29.8)	198 (27.5)
Other	1 (0.3)	1 (0.7)	27 (0.4)	8 (0.4)	96 (0.5)	20 (0.4)	7 (0.5)	8 (1.1)
Severity of illness								
Acute Physiology and Chronic Health Evaluation-III score, median (IQR)	74 (58–91.3)	99 (82–126)	69 (53–86)	96 (76–120)	60 (46–79)	93 (73–116)	71 (54–90)	99 (81–124)
Mechanical ventilation at ICU admission, n (%)	194 (55.7)	102 (68.5)	4,599 (74.3)	1,484 (79.0)	17,346 (82.9)	4,399 (87.3)	1,155 (81.9)	614 (85.4)
Confirmed infection, n (%)	98 (28.2)	44 (29.5)	1,521 (24.6)	621 (33.1)	3,030 (14.5)	1,198 (23.8)	380 (26.9)	237 (33.0)
Vasoactive drugs at ICU admission, n (%)	174 (50.0)	108 (72.5)	4,071 (65.8)	1,386 (73.8)	13,800 (65.9)	3,768 (74.8)	810 (57.4)	517 (71.9)
Plasma chloride concentration at ICU admission, mean (SD), mmol/L	90.5 (8.0)	94.1 (7.7)	103.5 (5.7)	102.4 (5.8)	107.6 (4.8)	107.2 (5.5)	112.6 (7.0)	113.5 (7.4)
Arterial pH at admission, mean (SD)	7.4 (0.1)	7.3 (0.1)	7.4 (0.1)	7.3 (0.1)	7.4 (0.1)	7.3 (0.1)	7.4 (0.1)	7.3 (0.1)
Comorbidities, n (%)								
Renal insufficiency or dialysis	30 (8.6)	22 (14.8)	613 (9.9)	244 (13)	1,161 (5.5)	476 (9.4)	77 (5.5)	43 (6.0)
Cirrhosis	21 (6.0)	27 (18.1)	184 (3.0)	130 (6.9)	440 (2.1)	149 (3.0)	41 (2.9)	40 (5.6)
Cardiovascular disease	21 (6.0)	15 (10.1)	488 (7.9)	197 (10.5)	1,459 (7.0)	427 (8.5)	55 (3.9)	39 (5.4)
Malignancy (metastasized)	24 (6.9)	22 (14.8)	458 (7.4)	312 (16.6)	1,064 (5.1)	504 (10.0)	85 (6.0)	120 (16.7)
Length of stay ICU, median (IQR), hr	78.9 (49.7–168.5)	97.9 (60.4–217.8)	88.7 (49.2–167.4)	123.3 (61.1–253.2)	86.5 (47.8–170.8)	126.2 (66.1–264.3)	148.4 (70.3–336.8)	129.3 (64.6–285.7)

IQR = interquartile range, [Na]$_{first}$ = first serum sodium measurement at ICU admission.

time to $[Na]_{max}$, and velocity of reaching $[Na]_{max}$ during entire ICU stay are shown in **Table 3** and **Supplementary Table 2** (http://links.lww.com/CCM/G542). In patients admitted with mild hyponatremia, normonatremia, or hypernatremia, mean $\Delta 48$ hr-$[Na]$ and $[Na]_{max}$ were higher in nonsurvivors.

The association between in-hospital mortality and $\Delta 48$ hr-$[Na]$ (primary analysis) is shown in **Figure 1**. In patients with severe hyponatremia at ICU admission (< 125 mmol/L), an increase of serum sodium was associated with lower mortality ($\Delta 48$ hr-$[Na]$ 5–10 mmol/L odds ratio [OR], 0.49 [95% CI, 0.29–0.83]; $\Delta 48$ hr-$[Na]$ > 10 mmol/L OR, 0.43 [95% CI, 0.25–0.74]). In all other patients, an increase of serum sodium was associated with higher mortality. In patients with mild hyponatremia at ICU admission (125–135 mmol/L), the OR for in-hospital mortality was 1.10 (95% CI, 0.97–1.25) for $\Delta 48$ hr-$[Na]$ 5–10 mmol/L, and the OR was 1.17

TABLE 3.

Description of Serum Sodium Over Entire ICU Stay for All Patients With Mild Hyponatremia or Normonatremia at ICU Admission and a Subgroup of Patients With an Increase of Serum Sodium During the First 48 Hours of ICU Admission (Difference Between Mean of Sodium Measurements 24–48 hr After ICU Admission and First Serum Sodium at Admission) > 5 mmol/L

Descriptives	Mild hyponatremia $[Na]_{first}$ 125–135 mmol/L, N = 8,068			Normonatremia $[Na]_{first}$ 135–145 mmol/L N = 25,965		
	Survivors	Nonsurvivors	p	Survivors	Nonsurvivors	p
All patients						
Number of patients	6,190	1,878		20,926	5,039	
$[Na]_{first}$, mean (SD), mmol/L	131.9 (2.3)	131.4 (2.5)	< 0.01	138.4 (2.4)	138.7 (2.5)	< 0.01
$\Delta 48$ hr-$[Na]$, mean (SD), mmol/L	2.9 (3.6)	3.8 (4.0)	< 0.01	0.0 (3.4)	1.3 (4.3)	< 0.01
$[Na]_{max}$, mean (SD), mmol/L	138.5 (5.5)	140.5 (6.8)	< 0.01	141.9 (4.6)	144.7 (6)	< 0.01
Time to $[Na]_{max}$, median (IQR), hr	31.9 (14.6–62.9)	40.3 (20.8–109.0)	< 0.01	20.3 (6.5–48.0)	31.4 (11.2–78.2)	< 0.01
V-$[Na]_{max}$, median (IQR), mmol/L/24 hr	3.6 (1.9–6.6)	3.5 (1.9–6.6)	0.37	2.1 (0.4–5.1)	2.8 (1.1–6.2)	< 0.01
Subgroup $\Delta 48$ hr-$[Na]$ > 5 mmol/L						
Number of patients	1,685	650		1,606	817	
$[Na]_{first}$, mean (SD), mmol/L	130.9 (2.6)	130.6 (2.7)	0.02	137.8 (2.4)	138.4 (2.1)	< 0.01
$\Delta 48$ hr-$[Na]$, mean (SD), mmol/L	7.5 (2.4)	8.0 (3.4)	0.01	6.8 (2.2)	8.1 (3.8)	< 0.01
$[Na]_{max}$, mean (SD), mmol/L	141.9 (5.4)	143.4 (6.3)	< 0.01	147.4 (4.9)	150.1 (5.8)	< 0.01
Time to $[Na]_{max}$, median (IQR), hr	39.5 (27.6–65.5)	41.2 (26.5–82.5)	0.22	36.7 (25.6–53.9)	37.7 (25.1–55.2)	0.67
V-$[Na]_{max}$, median (IQR), mmol/L/24 hr	5.2 (3.7–7.8)	5.5 (3.6-9.0)	0.09	5.2 (3.8–7.7)	6.0 (4.2–10.3)	< 0.01

IQR = interquartile range, $[Na]_{first}$ = first serum sodium measurement at ICU admission, $[Na]_{max}$ = maximum serum sodium measurement during entire ICU admission, V-$[Na]_{max}$ = velocity of reaching $[Na]_{max}$ during entire ICU stay, $\Delta 48$ hr-$[Na]$ = difference between mean of sodium measurements 24–48 hr after ICU admission and $[Na]_{first}$.

Data are presented separately for survivors and nonsurvivors. Data are shown for all patients and separately for a subgroup of patients with a $\Delta 48$ hr-$[Na]$ > 5 mmol/L. Continuous data are presented as mean with SD and median with interquartile range (IQR). The p values represent the difference between survivors and nonsurvivors, $p < 0.05$ was considered statistically significant. For patients with severe hyponatremia or hypernatremia at ICU admission, see Supplementary Table 2 (http://links.lww.com/CCM/G542).
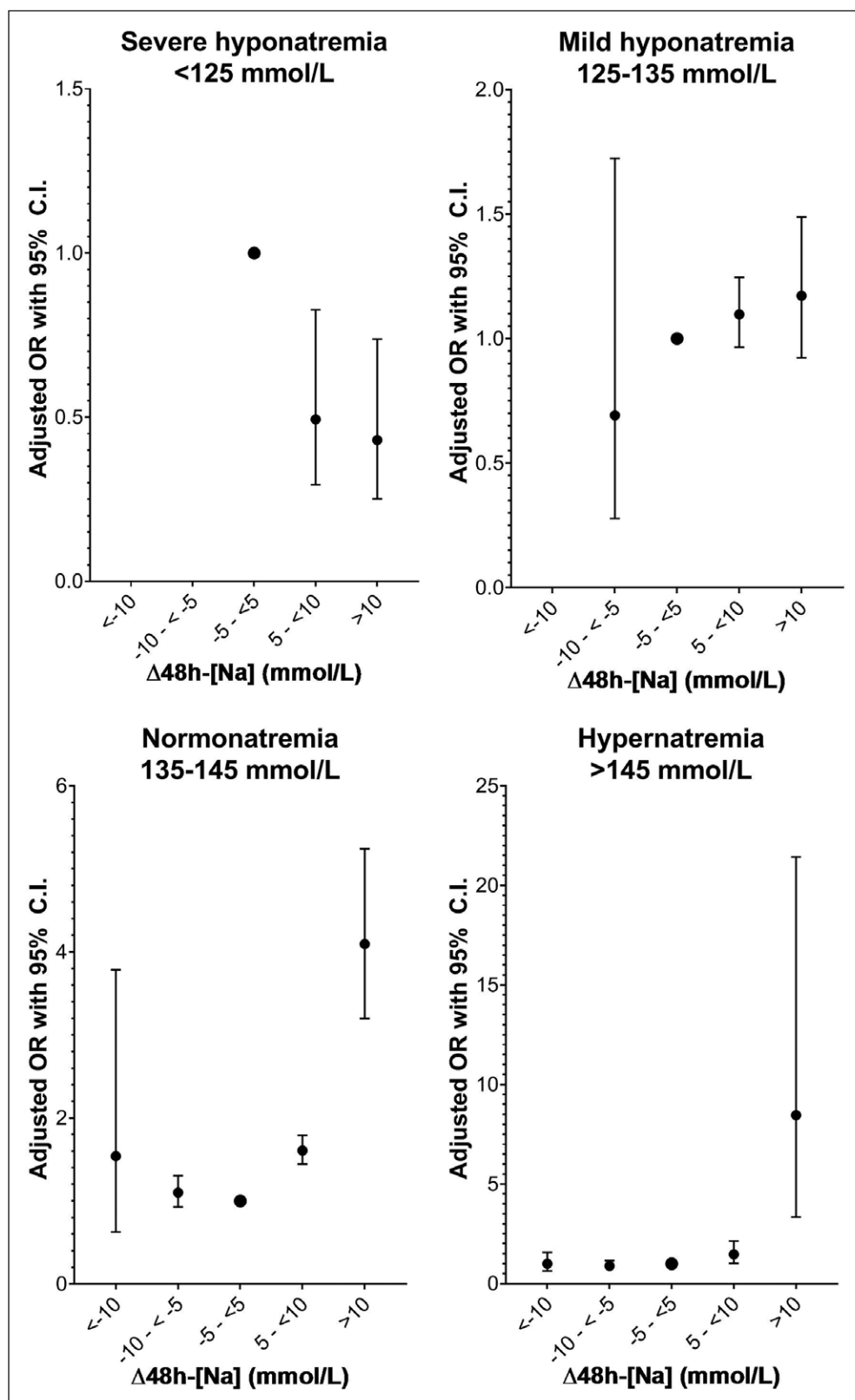
Figure 1. Association between in-hospital mortality and Δ48 hr-[Na] for ICU patients categorized by first serum sodium measurement at ICU admission. The adjusted odds ratios (ORs) for risk of in-hospital mortality using logistic regression. Adjusted for age, sex, and Acute Physiology and Chronic Health Evaluation-IV predicted mortality. Δ48 hr-[Na] of −5 to 5 mmol/L was used as reference category. Δ48 hr-[Na] = difference between mean of sodium measurements 24–48 hr after ICU admission and first serum sodium at admission in mmol/L.

(95% CI, 0.92–1.49) for Δ48 hr-[Na] greater than 10 mmol/L. Combining the last two categories, the OR for mortality was 1.11 (95% CI, 0.99–1.25) for patients with mild hyponatremia at admission and Δ48 hr-[Na] greater than 5 mmol/L.

To explore if the association between an increase in serum sodium and in-hospital mortality could be unique for patients with too rapid increase of serum sodium, we also analyzed the association between mortality and V_{max}-Δ[Na], that is, the highest velocity of increase between the first measured serum sodium at ICU admission and any of the serum sodium measurements taken between 24 hours and 48 hours after admission (**Fig. 2**). In patients with mild hyponatremia, the ORs for mortality were similar for subgroups with 2.5–5 mmol/L/24 hr (OR, 1.07 [95% CI, 0.88–1.30]), 5–7.5 mmol/L/24 hr (OR, 1.14 [95% CI, 0.93–1.40]), 7.5–10 mmol/L/24 hr (OR, 1.02 [95% CI, 0.83–1.27]), and greater than 10 mmol/L/24 hr (OR, 1.17 [95% CI, 0.99–1.38]). In patients with normonatremia at admission, there was an association between an increase of serum sodium and mortality for all V_{max}-Δ[Na] groups with higher ORs for higher V_{max}-Δ[Na]. In patients
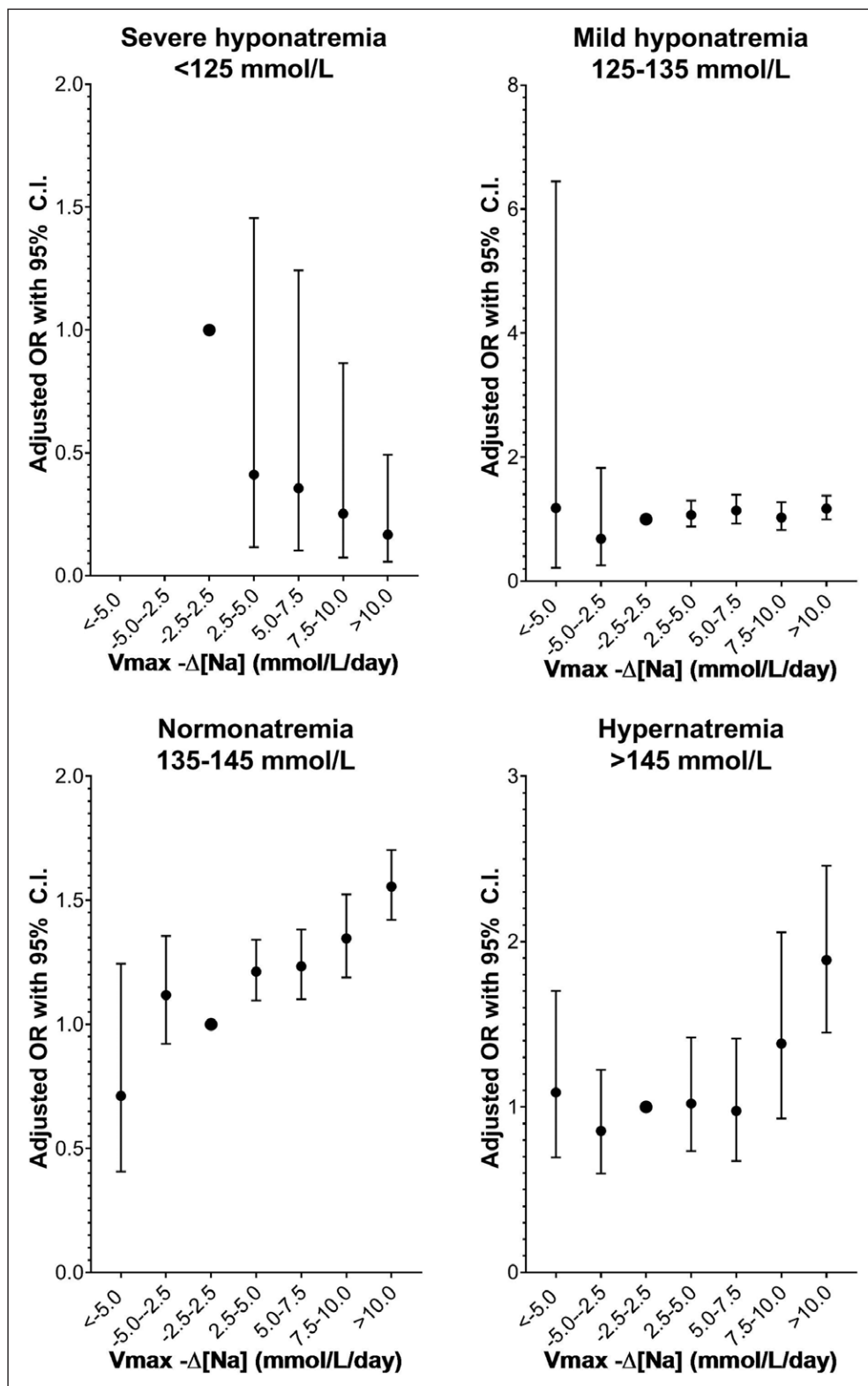
Figure 2. Association between in-hospital mortality and V_{max}-Δ[Na] for ICU patients categorized by first serum sodium measurement at ICU admission. The adjusted odds ratios (ORs) for risk of in-hospital mortality using logistic regression. Adjusted for age, sex, and Acute Physiology and Chronic Health Evaluation-IV predicted mortality. V_{max}-Δ[Na] of −2.5 to 2.5 mmol/L/d was used as reference category. V_{max}-Δ[Na] = the difference in serum sodium at admission and a sodium measurement within 48 hr after admission, divided by the time between these two measurements, maximum velocity is the highest velocity of all pairs of measurements in a patient in mmol/L/24 hr.

with hypernatremia at admission, mortality was highest in patients with a V_{max}-Δ[Na] greater than 7.5 mmol/L/24 hr. In patients with severe hyponatremia at ICU admission (< 125 mmol/L), the ORs for mortality were lowest for patients with the most rapid increase of serum sodium.

A description of serum sodium levels during the entire ICU admission period is given in Table 3 (for patients admitted with mild hyponatremia and normonatremia) and Supplemental Table 2 (http://links.lww.com/CCM/G542) (all patients including severe hyponatremia or hypernatremia at admission). The 75th percentiles for [Na]$_{max}$ in patients admitted with mild hyponatremia were 144 mmol/L and 147 mmol/L for survivors and nonsurvivors, respectively. No difference between survivors and nonsurvivors was found in the rate at which the maximum serum sodium concentrations were reached during ICU admission. In 2,335 patients with mild hyponatremia at ICU admission and a Δ48 hr-[Na] greater than 5 mmol/L, 86 (3.6%) (**Supplemental Fig. 2**, http://links.lww.com/CCM/G543) developed severe hypernatremia (> 155 mmol/l) during ICU admission, and 40

of them died (46%). In total 2,423 had normonatremia at ICU admission and a Δ48 hr-[Na] greater than 5 mmol/L. Of these patients, 313 (12.9%) developed severe hypernatremia (> 155 mmol/L) during ICU admission, of whom 177 (56.0%) died. For patients admitted with normonatremia, the 75th percentiles for [Na]$_{max}$ were 150 mmol/L and 154 mmol/L for survivors and nonsurvivors, respectively. The rate at which [Na]$_{max}$ was reached was higher in nonsurvivors with a 75th percentile of 10.3 mmol/L/24 hr compared with 7.7 mmol/L/24 hr in survivors.

The association between Δ48 hr-[Na] and in-hospital mortality was similar for patients with and without an intracerebral condition as reason for admission is shown in (Supplemental Fig. 2, http://links.lww.com/CCM/G543; and **Supplemental Fig. 3**, http://links.lww.com/CCM/G544 [legend, http://links.lww.com/CCM/G545]).

DISCUSSION

In this large multicenter observational cohort study of ICU patients, we aimed to assess the independent association of changes in serum sodium in the first 48 hours of ICU admission with in-hospital mortality for patients admitted with severe and mild hyponatremia, normonatremia, and hypernatremia. An increase of serum sodium (Δ48 hr-[Na] > 5 mmol/L) in the first 48 hours of ICU admission was independently associated with a higher risk for mortality for patients admitted with normonatremia and hypernatremia. Although not significant, a similar trend was found for patients admitted with mild hyponatremia. For patients with severe hyponatremia, an increase in serum sodium in the first 48 hours of ICU admission was independently associated with a lower risk for mortality.

It is well known that both hyponatremia and hypernatremia at ICU admission are associated with higher mortality (5). Our study is the first to find an association between an increase in serum sodium in the first 48 hours of ICU admission and mortality. It is known that hyponatremia at ICU admission is associated with a higher mortality, and so it has been assumed that correction of hyponatremia would lead to lower mortality (1, 3, 6, 11, 12, 16). However, this is not supported by our findings in patients admitted with mild hyponatremia, where no difference in mortality was seen and where a nearly significant higher mortality was observed. This questions the common practice of correcting serum sodium when it is too low. This would merit further clinical randomized studies to investigate the causality of our findings.

Given the observational nature of our investigation, the association between a positive Δ48 hr-[Na] and mortality cannot be assumed to be causal, as a variety confounding factors we did not investigate may exist. We adjusted for confounding by age, sex, and the APACHE-IV–predicted mortality which includes the severity of illness, reason for ICU admission, and comorbidities. However, it remains possible that a positive Δ48 hr-[Na] acted as a proxy for severity of illness. For example, we cannot exclude that patients with severe illness and high risk of death were treated more aggressively with isotonic and hypertonic fluids leading to an increase in serum sodium concentrations. Unfortunately, in our database, there are no data on administration of fluids or treatment for dysnatremias. In the Netherlands, hypertonic saline may be administered for patients with cerebral edema, a groups of patients with a high risk of mortality. Therefore, we performed a subgroup analysis in patients with and without intracerebral pathology. We found that the association between a positive Δ48 hr-[Na] and in-hospital mortality was similar in patients with or without intracerebral pathology.

The association between mortality and Δ48 hr-[Na] is not necessarily caused by the change in serum sodium during those first 48 hours. Another confounder may be that patients with a high Δ48 hr-[Na] more often develop hypernatremia at a later stage, which is a well-known risk factor for mortality (7, 9, 17). Indeed, in our cohort, nonsurvivors had higher mean values for maximum serum sodium during their entire ICU admission compared with survivors, although still within normal values. Focusing on patients who had mild hyponatremia at ICU admission and who had a Δ48 hr-[Na] greater than 5 mmol/L, severe hypernatremia developed in only 3.6%, and almost half of these patients died. Another possible confounder could be the velocity of increase in sodium. It is well known that in patients with hyponatremia, too rapid increase in serum sodium may lead to osmotic demyelination (10, 18–21). Dutch national guidelines allow a maximum correction speed for hyponatremia of less than 10 mmol/L in the first 24 hours and less than 18 mmol/L in the first 48 hours (22). For acute hyponatremia, initially, a correction speed of 1–2 mmol/L/hr is

accepted. In chronic hyponatremia or if risk factors for osmotic demyelination are present, a maximum correction speed of less than 8 mmol/L/24 hr is advised. In our study, we therefore assessed the maximum velocity of increase of serum sodium (V_{max}-Δ[Na]). Indeed, a high maximum velocity of increase of serum sodium greater than 10 mmol/L/24 hr was associated with the highest risk of mortality, except in patients admitted with severe hyponatremia. Importantly, this high velocity does not imply that serum sodium increased more than 10 mmol/L over the first 24 hours, as the highest velocity was assessed between two measurements often few hours apart. Unfortunately, we do not have data on the occurrence of osmotic demyelination, for example, on MRI. In the patients with severe hyponatremia at ICU admission, maximum velocity of increase of serum sodium greater than 10 mmol/L/24 hr was associated with the lowest risk of mortality compared with the slower velocities. Most likely, severe hyponatremia at ICU admission is more often acute, with lower risk of osmotic demyelination after correction of serum sodium. Interestingly, in patients with normonatremia, risk for mortality was also higher if serum sodium increased slowly with maximum velocity of increase of serum sodium 2.5–5.0 mmol/L/24 hr, or 5.0–7.5 mmol/L/24 hr, well within the limits considered safe in guidelines.

Our findings differ from previous observational studies that found that correction of dysnatremia was independently associated with lower mortality. Darmon et al (23) found that a higher serum sodium correction rate between day 1 and day 3 of admission was associated with a lower day 28 mortality in ICU patients. Furthermore, in an observational study of ICU patients with hyponatremia (< 135 mmol/L), a lower mortality was found in patients with corrected hyponatremia compared with patients without correction (2). Unfortunately, mild hyponatremia (125–135 mmol/L) was not assessed separately, and no information was given at what time after admission correction of hyponatremia had occurred. Our findings also differ from findings in hospitalized non-ICU patients, where mortality was higher for patients with persistent hyponatremia in their final sodium value (11).

The large cohort size from different types of ICU covering a long period of time is a strength of our study. Further strengths were that severe and mild hyponatremia were assessed separately and that Δ48

hr-[Na] was also studied in patients with normal or high serum sodium concentrations. Also, in our study, we uniformly studied serum sodium assessed by the direct ion-selective method. This is important because serum sodium may differ substantially if direct and indirect ion-selective methods are applied, especially in ICU patients (15). Direct ion-selective methods are mostly preferred over the indirect method (24).

Several limitations merit discussion. Because of the observational nature of this study, causality cannot be inferred. Although we have attempted to control for APACHE-IV–predicted mortality, sex, and age, it remains possible that unmeasured confounders remain. Furthermore, a limitation of our dataset was that information about the nature of dysnatremia at admission (acute or chronic, symptomatic or asymptomatic), treatments, IV fluids, fluid balance, and cause of death was not available in our database. It is likely that in most patients in our cohort, except for patients with severe hyponatremia, hyponatremia was asymptomatic. Similarly, we think that except in patients with severe hyponatremia, the increase in sodium was mostly an unintentional treatment effect, a side effect of other treatments or fluid management. However, we could not verify this. Specific consideration should be given to serum chloride concentrations. As chloride and sodium concentrations show considerable collinearity, it is not possible to distinguish effects of increasing serum sodium concentrations from increasing serum chloride levels. Last, we performed our study in a population admitted from 2011 to 2017. Treatment may now be different with a trend toward more conservative fluid management and increasing use of relatively balanced electrolyte fluids that have a lower sodium concentration than normal saline. However, although this may influence the occurrence rate of increasing sodium, it is unlikely that this would alter the association between increasing sodium and outcome.

We show that an increase in serum sodium during the first 48 hours of ICU admission is associated with increased mortality in ICU patients with normonatremia or hypernatremia at admission. Only in patients admitted with severe hyponatremia (< 125 mmol/L), an increase in serum sodium was associated with lower mortality. Our findings should be confirmed in other settings, and future interventional trials are necessary to determine optimal policy, especially in patients with mild hyponatremia. Our findings suggest substantive

increases in serum sodium should be avoided in patients with normonatremia and hypernatremia.

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