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Increased sodium intake and decreased sodium excretion in ICU-acquired hypernatremia: A prospective cohort study

E.H.J. Mestrom (Eveline) [a],[*],[1], J.A. van der Stam (Jonna) [b],[c],[d],[1], M.E. te Pas (Mariska) [a],
J.G. van der Hoeven (Hans) [e], N.A.W. van Riel (Natal) [d],[f], A.J.G.H. Bindels (Alexander) [a],
A. Boer (Arjen-Kars) [b],[c], V. Scharnhorst (Volkher) [b],[c],[d]

[a] Catharina Hospital Eindhoven, Intensive Care Unit, Michelangelolaan 2, 5623 EJ Eindhoven, the Netherlands
[b] Catharina Hospital Eindhoven, Clinical Laboratory, Michelangelolaan 2, 5623 EJ Eindhoven, the Netherlands
[c] Expert Center Clinical Chemistry Eindhoven, Eindhoven, the Netherlands
[d] Eindhoven University of Technology, Department of Biomedical Engineering, De Groene Loper 3, Helix, 5612 AE Eindhoven, the Netherlands
[e] Radboud University Medical Center, Intensive Care Unit, Geert Grooteplein Zuid 10, 6525 GA Nijmegen, the Netherlands
[f] Amsterdam University Medical Centers, Department of Vascular Medicine, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands

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ABSTRACT

Purpose: To provide more in-depth insight in the development of early ICU-acquired hypernatremia in critically ill patients based on detailed, longitudinal and quantitative data.
Materials and methods: A comparative analysis was performed using prospectively collected data of ICU patients. All patients requiring ICU admission for more than 48 h between April and December 2018 were included. For this study, urine samples were collected daily and analyzed for electrolytes and osmolality. Additionally, plasma osmolality analyses were performed. Further data collection consisted of routine laboratory results, detailed fluid balances and medication use.
Results: A total of 183 patient were included for analysis, of whom 38% developed ICU-acquired hypernatremia. Whereas the hypernatremic group was similar to the non-hypernatremic group at baseline and during the first days, hypernatremic patients had a significantly higher sodium intake on day 2 to 5, a lower urine sodium concentration on day 3 and 4 and a worse kidney function (plasma creatinine 251 versus 71.9 μmol/L on day 5). Additionally, hypernatremic patients had higher APACHE IV scores (67 versus 49, $p < 0.05$) and higher ICU (23 versus 12%, $p = 0.07$) and 90-day mortality (33 versus 14%, $p < 0.01$).
Conclusions: Longitudinal analysis shows that the development of early ICU-acquired hypernatremia is preceded by increased sodium intake, decreased renal function and decreased sodium excretion.

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1. Background

Hypernatremia acquired in the intensive care unit (ICU) is a highly prevalent condition among critically ill patients. More importantly, ICU-acquired hypernatremia is associated with increased length of stay and mortality [1-7]. Considering the known impact on survival and ICU length of stay, understanding the pathophysiological drivers behind hypernatremia may be important [5]. ICU-acquired hypernatremia often takes a few days to develop, which means that

understanding hypernatremia might provide a window of opportunity for altering treatment before hypernatremia occurs [8].

Multiple causes for hypernatremia have been postulated. In general, development of hypernatremia can be explained by either a net gain in sodium or a net loss of water. A relative sodium gain can be the result of fluid resuscitation in the treatment of septic shock [9,10]. Most intravenous fluids administered in ICU care are hypertonic compared to normal intake in healthy subjects and are administered when volume therapy is required, as a dilutant for drugs and to maintain open access of catheters [7]. Another hypothesis for sodium gain is reduced sodium excretion due to impaired renal function [9]. The net loss of water could be explained by the increased excretion of electrolyte free water in urine, sweat and stool [6,7]. In addition, compensatory mechanisms such as thirst sensation might be impaired and ICU patients are dependent on the physician to manage fluid balance and hence prone to dysregulation [11-14]. Consequently, the development of hypernatremia is considered to be iatrogenic and an indicator of quality of care [6].

While the studies proposing these hypotheses reflect both the multifactorial etiology of hypernatremia and the challenge to study causes of hypernatremia, there is still a lack of quantitative data. As a possible consequence, treatment is mainly based on expert opinion. New insights and quantification are needed to better understand the development of ICU-acquired hypernatremia. Since the development of hypernatremia is a dynamic process involving water and sodium intake and excretion, collection of longitudinal data is of utmost importance.

This prospective study aimed to provide more in-depth insight in the development of hypernatremia based on detailed, longitudinal and quantitative data.

2. Methods

This prospective study was conducted at the ICU of the Catharina Hospital in Eindhoven, the Netherlands, a tertiary referral hospital with a large cardiothoracic surgery department. The ICU admits approximately 3000 patients per year. The majority of patients in ICU are admitted following cardiothoracic surgery and are discharged within 48 h. Furthermore, the ICU population is characterized by postoperative large abdominal surgery, medical and psychiatric patients but very few patients following neurotrauma or neurosurgery, nor transplant patients. Current local practice in case of hypernatremia may consist of cessation of loop diuretics, submission of water orally, prescription of thiazide diuretics and switching from saline to glucose infusion for the maintenance of intravenous lines and dilutant for drugs. The experience is that specific therapy for hypernatremia is not started until sodium levels reach 148 mmol/L or more. Clinical data, drug prescriptions and ICU and hospital outcomes are stored in the electronic medical record (EMR). All adult patients admitted to the ICU for more than 48 h between May and December 2018 were included. Exclusion criteria consisted of hypernatremia at admission, readmission to the ICU within 30 days, or transfer from another ICU. All relevant data was extracted from the EMR for analysis, except for urine samples which were collected prospectively in included patients from residual urine derived via urinary catheter. Therefore, the Dutch Law on Research Involving Human subjects Act (WMO) is not applicable. Approval for the study was obtained from the Medical Research Ethics Committees United (non-wmo W18.035) on March 12th 2018, waiving individual informed consent.

As part of the study, urine samples were collected on a daily basis from the moment of inclusion (48 h after admission) throughout the ICU stay. These urine samples were analyzed within seven days after collection for sodium, potassium, chloride and osmolality. Additionally, corresponding blood samples were analyzed for osmolality within seven days after collection. All relevant data was extracted from the EMR, including fluid and medication intake, urine output and routine laboratory results. Both urine and plasma osmolality were measured in the clinical laboratory of the hospital using the Gonotec OSMOMAT 3000. Urine electrolytes were assessed using the Roche Cobas 8000. Direct whole blood sodium measurements obtained from the ABL835 Radiometer blood gas analyzer were used, since direct and indirect sodium measurements cannot be used interchangeably in critically ill patients [16]. Since the choice for whole blood sodium was made retrospectively, patients could be excluded after inclusion based on both plasma and whole blood sodium values.

Data was synchronized on a daily basis, to minimize differences between different data sources. This means the period from 6 am to 6 am was defined as a one-day time window. The first day of admission lasted from time of admission until 6 am which frequently leads to duration of the first day of less than 24 h. Laboratory results obtained at the beginning of the day, sampled between 3 am and 9 am, were combined with the clinical data during the day. Since urine samples reflect the previously administered fluids and medication, measurements from the urine samples collected at the end of the day were used, again sampled between 3 am and 9 am. Sodium intake within this defined period was

calculated by adding up sodium received via antibiotics, enteral feeding, saline, Ringer's Lactate, blood transfusions and sodium bicarbonate.

2.1. Definitions

Data was collected until discharge from the ICU or until the first hypernatremic state, which-ever came first. Patients without any

Table 1
General characteristics and outcomes.

	Non-hypernatremic group	Hypernatremic Group	p-value
N	113	70	
Female gender, number (%)	36 (32)	25 (36)	0.71
Age in years, median (IQR)	68 (61–74)	70 (60–76)	0.27
BMI kg/m2, median (IQR)	26 (23–29)	25 (23–30)	0.91
Specialism, number (%)			
General surgery	35 (31)	12 (17)	**0.04**
Internal medicine	11 (10)	10 (14)	0.35
Cardiothoracic surgery	49 (43)	23 (33)	0.16
Cardiology	7 (6)	11 (16)	**0.04**
Pulmonology	3 (3)	7 (10)	**0.04**
Neurology	3 (3)	4 (6)	0.29
Gastroenterology	0 (0)	1 (1.4)	0.20
Orthopedic surgery	0 (0)	1 (1.4)	0.20
Urology	4 (3.5)	1 (1.4)	0.40
Main deranged organ system on admission, number (%)			
Cardiovascular	71 (62.8)	38 (54.3)	0.25
Respiratory	13 (11.5)	18 (25.7)	**0.01**
Gastrointestinal	18 (15.9)	6 (8.6)	0.15
Metabolic	4 (3.5)	2 (2.9)	0.80
Neurologic	0 (0.0)	2 (2.9)	0.07
Miscellaneous	7 (6.2)	4 (5.7)	0.89
Postoperative patients, number (%)	78 (69)	36 (51)	**0.03**
Emergency surgery	23 (29)	16 (44)	0.18
Sepsis, number (%)	11 (9.7)	7 (10)	0.95
Cardiovascular problems after cardiothoracic surgery, number (%)	46 (40.7)	20 (28.6)	0.10
Plasma concentrations, median (IQR)			
Sodium in mmol/L	138 (135–140)	139 (137–141)	0.09
Creatinine in micromol/L	90 (68–124)	114 (78–170)	0.07
Blood urea nitrogen in mmol/L	7 (5–8)	7 (6–12)	0.09
Apache/saps scores, median (IQR)			
APACHE II	18 (14–22)	22 (16–29)	**0.01**
APACHE IV	48 (37–62)	62 (44–84)	**<0.01**
SAPS II	40 (33–48)	48 (38–60)	**<0.01**
Mortality, number (%)			
ICU	13 (12%)	16 (23%)	0.07
Hospital	15 (13%)	18 (26%)	0.05
90 day	16 (14%)	23 (33%)	**<0.01**
Length of stay, median (IQR)			
ICU in days	4 (3–5)	8 (6–13)	**<0.01**
Hospital in days	10 (7–17)	16 (10–24)	**<0.01**
Maximum sodium in mmol/L, median (IQR)	142 (140–144)	149 (147–154)	**<0.01**
Day of sodium peak, median (IQR)	NA	5 (4–7)	
Day of hypernatremia, median (IQR)	NA	4 (3–7)	
Hemodynamic support, number (%)	97 (86)	57 (81)	0.56
Respiratory support, number (%)	74 (65)	61 (87)	**<0.01**
Loop diuretics	40 (35)	25 (36)	1.00
Patients deceased during hypernatremic episodes in the ICU, %	NA	12 (17.1)	

Data of hypernatremia patients was analyzed until first sodium concentration > 145 mmol/L. Data of patients without hypernatremia was analyzed until discharge from ICU. P-values in bold are <0.05.

whole blood sodium concentration above the upper laboratory reference limit (145 mmol/L) were assigned as the "non-hypernatremic group". Patients who ultimately developed hypernatremia were assigned to the "hypernatremic group". These patients' first hypernatremic blood sampling was not part of the dataset. As mentioned before, treatment for hypernatremia in this ICU is usually not started below 148 mmol/L. Therefore, no treatment effect is expected in the collected data until first hypernatremic state. The 90-day mortality was defined as the number of days between date of admission in ICU and date of decease.

2.2. Statistical analyses

The longitudinal behavior of the data derived from the two patient groups was compared at baseline and on daily basis using the Chi-squared and Mann-Whitney U tests. A p-value $p < 0.05$ was considered statistically significant. Analyses were performed using R-studio (version 1.2.1335 and R version 3.6.0). Visual representations were made using ggplot2 (version 3.2.1). In the boxplots, the lower and upper hinges indicate the 25th and 75th percentile. The lower and upper extremes extend from the hinge to the smallest or largest value no further than 1.5 times the inter-quartile range, the distance between the 25th and 75th percentile. Results outside this range are shown as outliers. Missing data were not replaced or imputed.

3. Results

During the study period, 1888 patients were admitted to the ICU. A total of 200 patients met inclusion criteria. Of these patients, 17 were excluded from further analysis for the following reasons: whole blood sodium >145 mmol/L in the first 24 h of admission ($N = 13$), no whole blood sodium measurements available during ICU stay ($N = 3$) and readmission within 30 days ($N = 1$).

Hypernatremia developed in 70 patients of the remaining 183 patients (38%). The number of patients in both groups declined over time, since only data was analyzed from the period before hypernatremia developed or from the period in ICU before normonatremic patients were discharged. This decrease in patients over time resulted in a study population that was too small for analysis after day 5. There were no patients receiving renal replacement therapy before the development of hypernatremia.

Baseline characteristics of the two groups are shown in Table 1. Age, gender and BMI were not significantly different in both groups. No statistically significant differences were found between sodium, creatinine and blood urea nitrogen (BUN) concentrations at admission. Both ICU and hospital mortality were higher in hypernatremic patients, but the difference was not statistically significant ($p \geq 0.05$). However, 90-day mortality was significantly higher in the hypernatremic group. Patients developing hypernatremia had received more corticosteroids and less angiotensin converting enzyme inhibitors (see Supplemental file 1 for
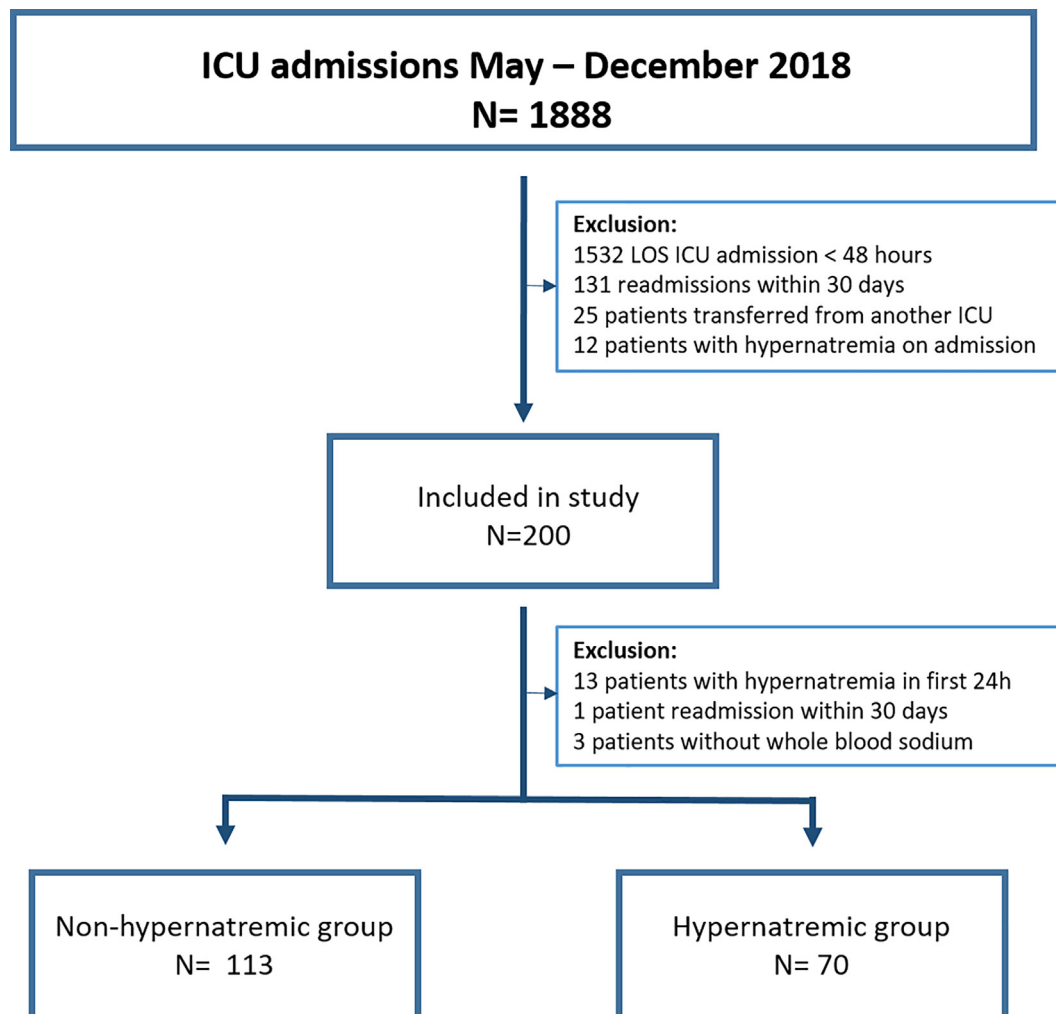

Fig. 1. Flowchart of study procedure.

all relevant administered medication in the study population). Diarrhea developed in 14 patients with hypernatremia and 2 patients without hypernatremia. In 5 out of 14 cases (7%), diarrhea occurred before hypernatremia.

As shown in Table 1, the median highest sodium concentration in hypernatremic patients was 149 mmol/L and this concentration was reached on ICU day 5. The median time until they reached sodium concentration > 145 mmol/L, was 4 days after ICU admission.

The right graph in Fig. 2 shows similar sodium intake at admission (7.6 g, $p = 0.71$), whereas from day 2 onwards, sodium intake was significantly higher in hypernatremic patients (day 2, 8.4 versus 5.3 g $p < 0.01$; day 3, 6.0 versus 3.9 g $p < 0.01$; day 4, 6.6 versus 3.9 g $p < 0.01$; day 5, 6.0 versus 3.9 g $p = 0.03$). A decrease in sodium intake was visible over time in both groups, with the largest decrease in the non-hypernatremic group. As shown in the middle graph in Fig. 2, the volume of fluids administered was similar except on day 2, when the hypernatremic group received more fluids that the non-hypernatremic group (median 2.86 versus 2.11 L/day; p 0.01). An additional table contains more detailed numbers regarding sodium and fluid intake (see Supplemental file 2).

Fig. 3 shows the median contribution of different sodium sources to the patients' total sodium intake. Ringer's lactate was the largest contributor of total sodium intake in the beginning of ICU admission in both patient groups, decreasing from 76% on day 1 to 20.4–25.0% on day 5. Meanwhile, an increase was found over the consecutive admission days in patient who later developed hypernatremia in the relative contribution of sodium from enteral feeding (1.0% to 14.6%), saline (5.5% to 28%) and antibiotics (10.9% to 27.4%). Supplemental file 3 shows more detailed percentages regarding different sodium sources.

Fig. 4 shows that sodium concentrations measured in the urine of hypernatremic patients were significantly lower than those measured in non-hypernatremic patients (31.1 versus 51.8 mmol/L on day 3, $p = 0.02$; 39.2 versus 113.1 mmol/L on day 4, $p < 0.01$). As the urine

volume in both groups did not differ, similar urine volume with a lower sodium concentration indicates a lower sodium excretion in patients who developed hypernatremia. Additionally, a lower osmolality was found in these patients' urine from day 4 onwards (486 versus 618 mOsmol/kg on day 4, $p < 0.01$; 434 versus 590 mOsmol/kg on day 5, p < 0.01). See Supplemental file 4 for more detailed numbers regarding urinary sodium excretion and osmolality.

Fig. 5 shows that significantly higher plasma creatinine concentrations were found in patients who developed hypernatremia from day 2 onwards with the largest mean difference of 251 versus 71.9 μmol/L in non-hypernatremic patients on day 5 ($p < 0.01$). Plasma BUN concentrations were significantly higher on days 2, 4 and 5 in patients who developed hypernatremia (largest difference on day 5: 16.2 versus 6.9 mmol/L, p < 0.01). Supplemental file 5 contains more detailed numbers regarding creatinine and BUN measurements.

Fluid balances were not significantly different between groups. Supplemental file 6 shows positive fluid balances in the first two days were followed by gradually more negative fluid balances in the consecutive admission days.

4. Discussion

This prospective study aimed to collect detailed, longitudinal, and quantitative data on the development of early ICU-acquired hypernatremia within the first five days in critically ill patients. The main findings are that on the days before the first hypernatremic state, patients who develop hypernatremia show significantly increased sodium intake, decreased urinary sodium excretion and reduced kidney function compared to non-hypernatremic patients.

Before the onset of hypernatremia, the median daily sodium intake was at least 50% higher in hypernatremic patients than in patients who did not develop hypernatremia. The largest difference in sodium intake was on day 4, when a 70% higher sodium intake was found in
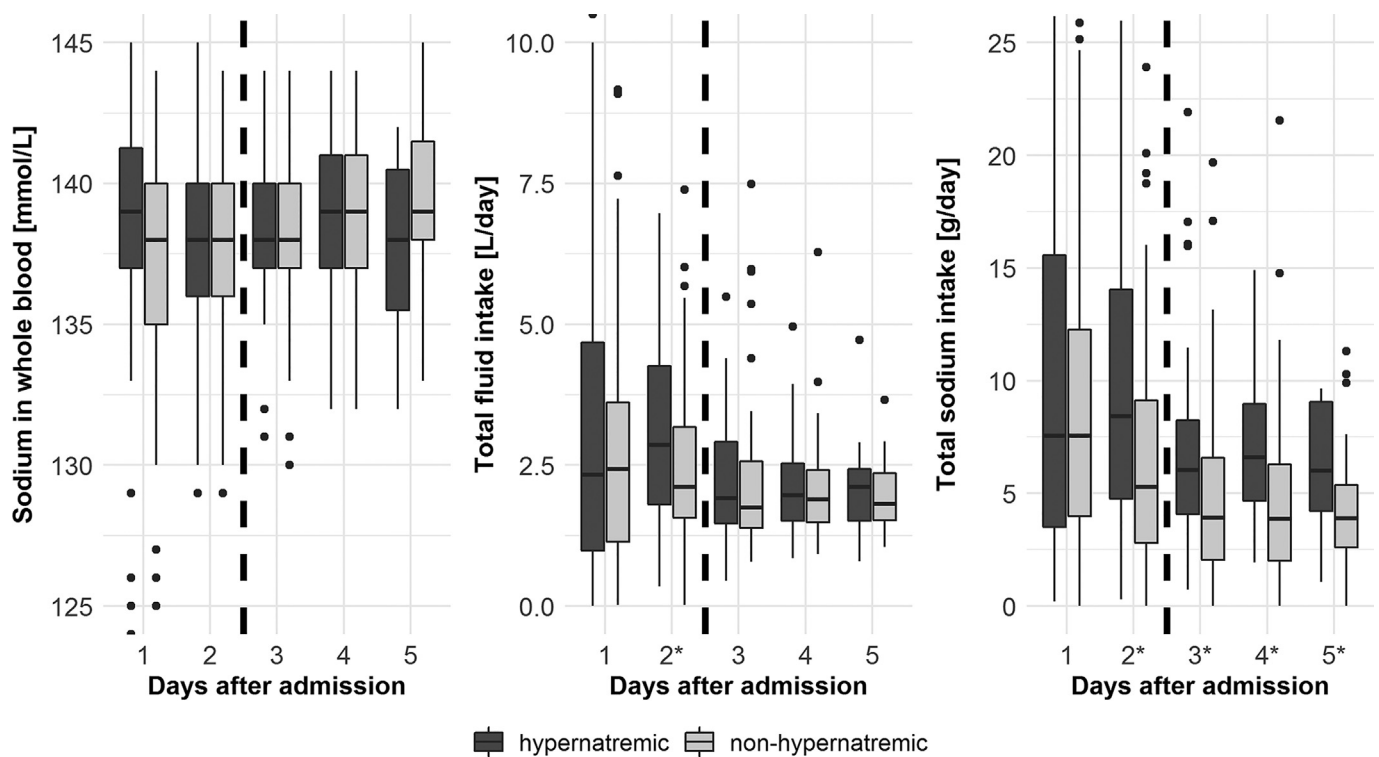

Fig. 2. Median sodium in whole blood (left), total fluid intake (middle) and total sodium intake (right) during the first 5 days of ICU admission.* p-value < 0.05 on that specific day. The dashed lines indicate the moment of inclusion.

patients who developed hypernatremia. Our findings confirm the work from several other studies that identified [7,8,15,17] or addressed [13,18,19] sodium load as a contributing factor in the development of hypernatremia. Since previous studies often did not report the exact sodium load, comparison of our day-to-day results to their findings was not possible. Bihari et al. found comparable sodium and fluid imbalances, but their study focused on other outcomes than hypernatremia [18]. In contrast to our findings, the study of IJzendoorn et al. found that sodium load was not different between hypernatremic patients and patients without hypernatremia [19]. This contrast can be explained by the fact that IJzendoorn et al. calculated cumulative sodium balances at 48 h after ICU admission, while the main difference in sodium load between the two groups in our study was found more than 48 h after admission.

The present study did not only measure increased sodium intake but also a 50% lower sodium excretion and reduced urine osmolality in patients who developed hypernatremia. These findings indicate that the hypernatremic group loses capacity to concentrate urine. This

concentration defect could be explained by recovery of acute kidney injury which seems to be characterized by restoration of water diuresis in the first phase and natriuresis in a later phase. As a consequence, the increased electrolyte free water diuresis causes an imbalance in plasma sodium balance resulting in hypernatremia. However, this explanation is not entirely supported by this study which shows increased plasma creatinine concentrations on the day of the last normal sodium but no clear recovery pattern yet. Similar to our study, Lindner et al. also observed increased electrolyte free water clearance in 45 hypernatremic patients but they could not compare this outcome with a control group [8]. Despite a different definition of hypernatremia, decreased sodium output was found in both the present and Lindner's studies.

The development of increased creatinine and BUN concentrations preceding the development of hypernatremia suggest impaired renal function in the hypernatremic group as a contributor in the development of hypernatremia. Our findings are in line with the findings of Hoorn et al., who investigated increased renal water loss in a population comparable to our study population [11]. Similar to our study, they
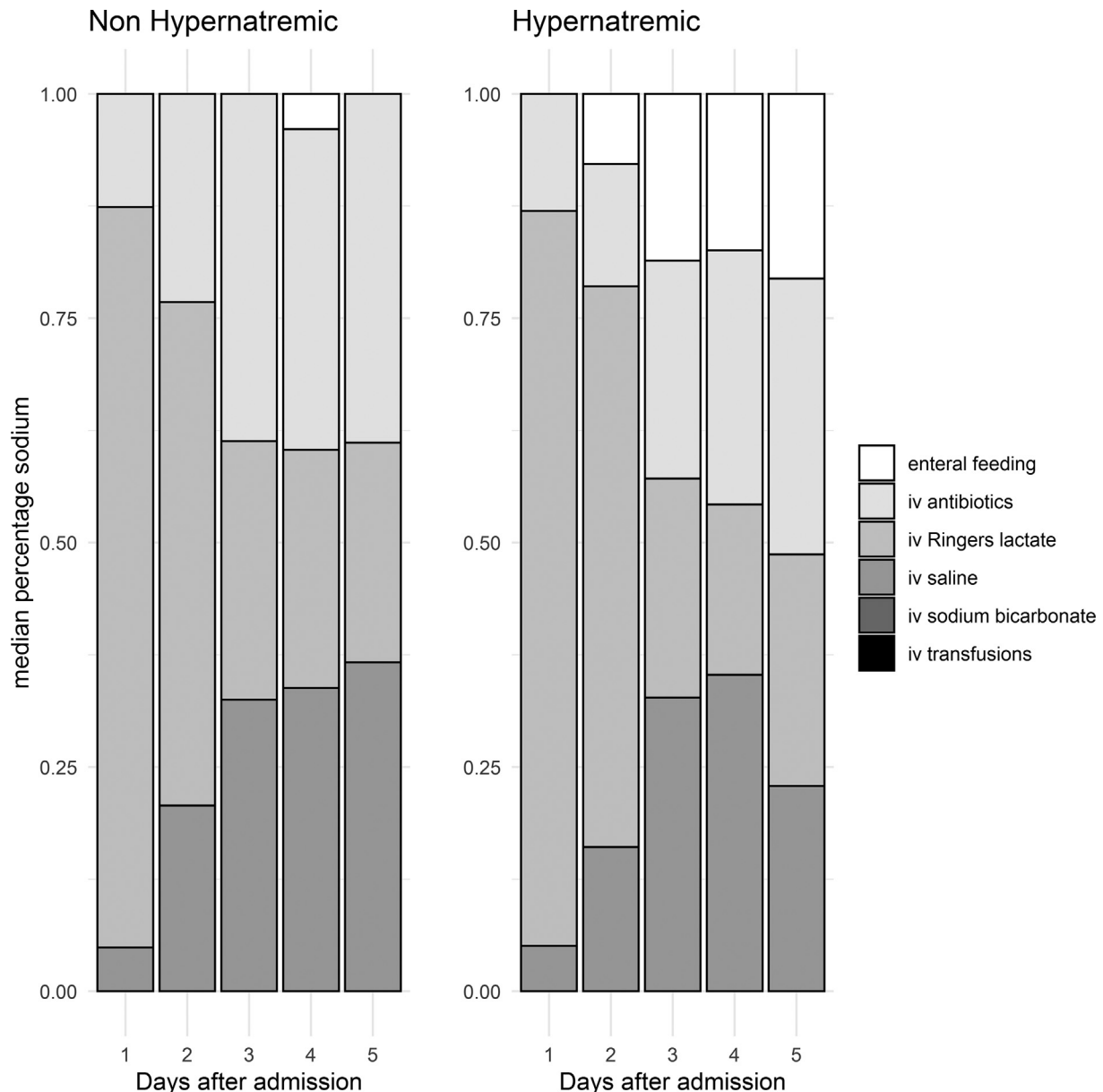

Fig. 3. Distribution of the sources of sodium intake during the first 5 days of ICU admission; the represented distribution is based on the median sodium intake from the different sources.

found that renal dysfunction and renal concentrating defects were significantly more frequent in hypernatremic patients than in controls. Comparison on day to day level was not possible since no longitudinal analysis was presented. Supporting our findings, Lindner et al. described acute renal failure in 35% of hypernatremic patients [8].

The significantly higher administration of corticosteroids in the hypernatremic group could have contributed to development of hypernatremia through sodium retention due to aldosterone effect in the kidneys. Another explanation could be that corticosteroids reflect the observation of more severely ill patients in the hypernatremia group who are more likely to have corticosteroid prescriptions. The significantly higher number of ACE inhibitors in the non-hypernatremic group can be explained by the fact that this type of medication is more commonly prescribed in patients who are recovering well and face discharge soon, which is usually not the phase in which hypernatremia develops.

Despite many differences between the present study and other studies, our findings regarding increased mortality and length of stay of hypernatremic patients were comparable to previous publications. Although differences in ICU and hospital mortality rates between the groups in our study were not statistically significant, we suspect that this can be explained by the sample size. Besides, APACHE II and IV scores and SAPS scores, all reflecting the patient's condition during the first 24 h of ICU admission, were significantly higher in patients who later developed hypernatremia. This can be explained by a larger percentage of elective postoperative patients in the control group who generally were in a relatively good condition in the first 24 h after surgery without signs of organ failure and were fit enough to even undergo surgery in the first place. The hypernatremic group consists of significantly more cardiology and pulmonology patients and emergency surgery, more likely to have (multi)organ failure in the first 24 h of admission.

This finding of higher APACHE scores in the hypernatremic group is in line with previous studies that also found correlations to severity of illness, as reflected by APACHE scores [5,6]. However, research has shown that hypernatremia is an independent risk factor for ICU mortality, irrespective of differences in APACHE scores [5,6]. The discussion remains if hypernatremia is a sign of critical illness or an independent contributor to mortality [17].

Further comparison of our results to other studies is challenging due to the heterogenic study designs and varying definitions of ICU- acquired hypernatremia. In the present study, the upper laboratory reference limit of 145 mmol/L was chosen as the cut-off value, to analyze available data up to the point where the physician should start to intervene. Using a higher cut-off value would allow these interventions to disturb study results, stressing the importance of choosing the right cut-off value for censoring the data.

A strength of this study is that we analyzed longitudinal data, which was aligned at ICU admission. This approach is in contrast with the study of Choo et al., who first described course over time in a larger ICU population and synchronized their data on the day of reaching sodium concentrations of 150 mmol/L, for hypernatremic patients, or the highest sodium concentration for non-hypernatremic patients [7]. A limitation of the approach of Choo et al. is that it does not account for factors such as the sodium intake or the source of sodium which change over time, as shown in Figs. 1 and 2. In contrast, our approach allows for incorporating patient-specific differences in factors such as sodium intake during subsequent admission days. Additionally, our data alignment strategy allows comparison between data of new patients, for whom future sodium concentrations are unknown. This makes our synchronization technique more suitable for achieving study results that can be used in clinical practice.
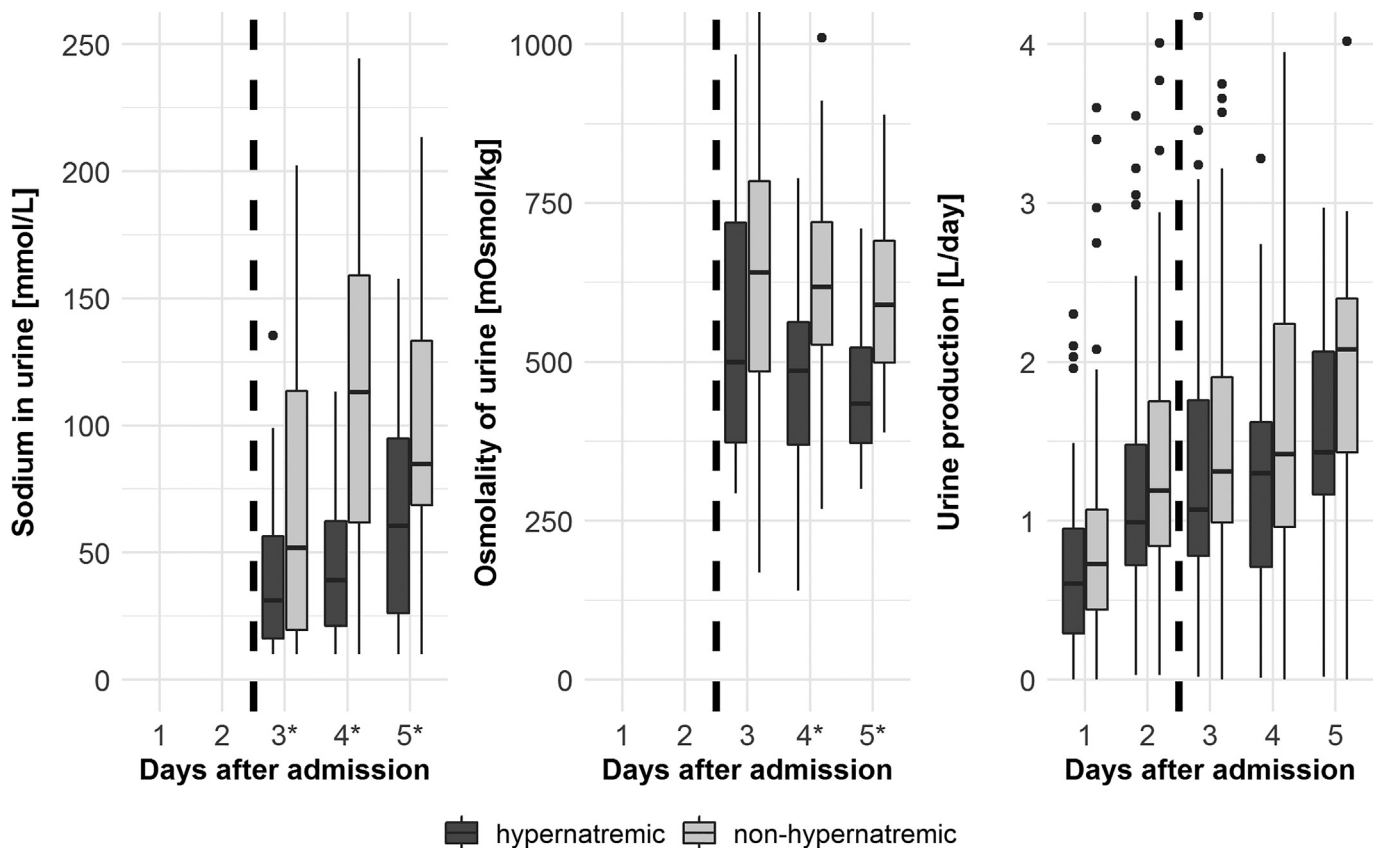

Fig. 4. Sodium concentration (left) and osmolality (middle) measured in the collected urine portions, daily urine production (right). * p-value < 0.05 on that specific day. The dashed lines indicate the moment of inclusion.
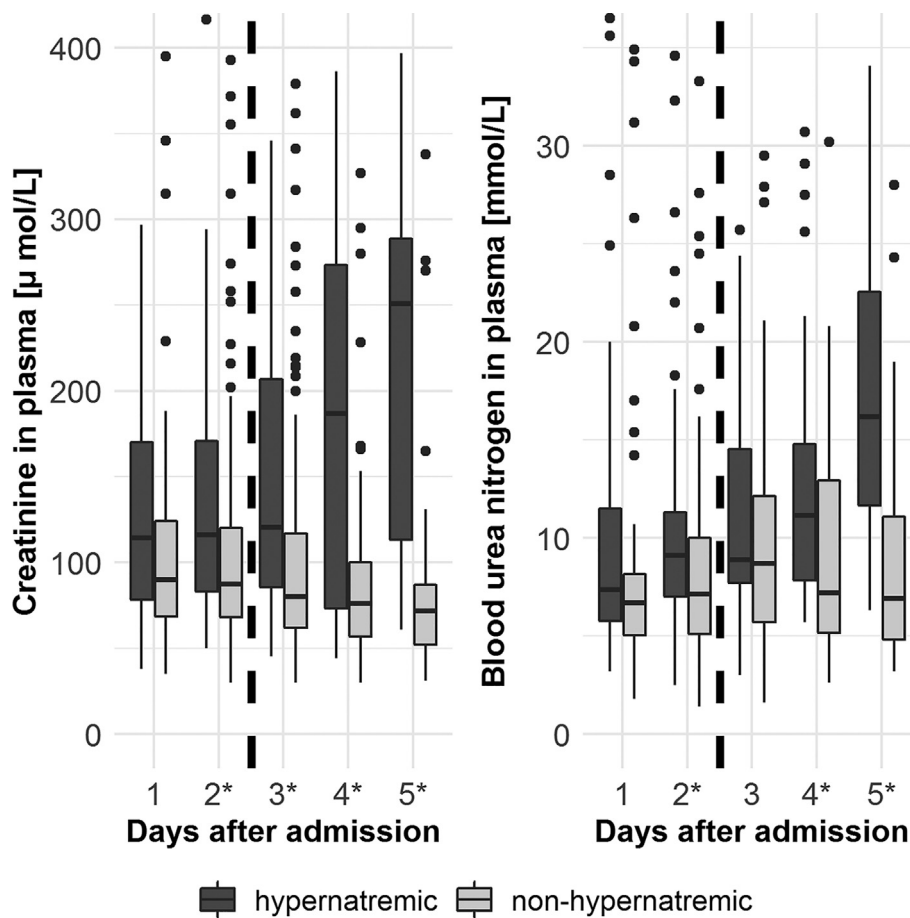
Fig. 5. Concentrations of creatinine (left) and blood urea nitrogen (right) in plasma.* p-value < 0.05 on that specific day. The dashed lines indicate the moment of inclusion.

Although this study was performed in a large population and includes both longitudinal data and urine analyses, there are several limitations. First, urine portions were used instead of 24-h urine collection which would have resulted in a more accurate approximation of total sodium output. Nevertheless, the present study found the same conclusions in terms of decreased sodium excretion as the study by Lindner et al. who investigated 24-hour urine samples [8]. Second, no urine samples were collected during the first two days since patients were included into the trial after being admitted in the ICU for 48 h. However, since our other results showed most differences after 48 h, we are confident that our study captured the most important differences. Missing data occurred mostly in urine analyses and in laboratory tests which are not routinely measured in a daily pattern. Missing urine samples (approximately 25% of the expected urine samples) can be explained by the study procedure where nursing staff was requested to collect the urine samples around 6 am. Regular checks took place if urine samples were taken so they could be corrected in case of missed sample within a 3 h time window. If a missing sample was discovered during the twice weekly analysis of the urine samples, it was too late collect it again. Third, no statements about trend over consequent days in ICU can be made because our statistical analysis focused on within day comparison between the two subpopulations. Fourth, our study was performed in a single center which means the results could be influenced by local practice and local patient population. However, since this holds true for most, if not all, ICU populations we assume that our population-based analyses revealed insights that hold true for other ICU populations as well. Fifth, after five days the number of patients was too small to draw any statistical conclusions which might result in bias towards causes of

hypernatremia which typically occur later in the course of ICU admission. Sixth, it is unknown if hypernatremia developed after ICU discharge although it is known that the incidence of hypernatremia in the general ward is low.

The contribution of this study is the establishment of a quantitative framework for the understanding of development of early ICU-acquired hypernatremia. Future research should aim to investigate prediction models in order to enable ICU staff to detect early signs of progression to hypernatremia and to prevent hypernatremia by altering treatment accordingly.

5. Conclusions

Longitudinal data analysis of prospectively collected data in critically ill ICU patients showed increased sodium intake, decreased sodium excretion and decreased kidney function in the days before the first hypernatremic state in patients with early ICU acquired hypernatremia compared to non-hypernatremic patients. These findings improve our understanding and raise the possibility to develop prediction models in order to enable physicians to alter treatment.

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Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2021.02.002.

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