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RESEARCH ARTICLE

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Sodium and chloride disturbances in critically ill adult patients: A protocol for a sub-study of the FLUID-ICU cohort study

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Abstract

Background: Disturbances in plasma sodium and chloride are common in adults admitted to the intensive care unit (ICU) and may affect patient outcomes. Fluid administration practices in the ICU have changed in recent years with a trend toward using more restrictive fluid strategies. These changes may have influenced the patterns and proportions of electrolyte disturbances in ICU patients. Therefore, we aim to provide contemporary data on the frequency of hypernatremia, hyponatremia, hyperchloremia, and hypochloremia in adult ICU patients, assess risk factors, and association with clinical outcomes in an international cohort.

Methods: This is the protocol for a sub-study of the FLUID-ICU study ("Fluid administration and fluid accumulation in intensive care units—an international inception cohort study"). The FLUID-ICU study is a prospective international 14-day inception cohort study with a minimum sample size of 1000 patients from more than 50 ICUs. Patients are followed daily from ICU admission to discharge or death with a maximum of 28 days. A follow-up is performed at Day 90 after ICU admission. The primary outcomes of this sub-study are the proportion of patients with hypernatremia, hyponatremia, hyperchloremia, and hypochloremia. We will assess days alive without the use of life support at Day 90, and risk factors for developing disturbances in sodium and chloride including disease severity by SMS-ICU score, type of ICU, use of diuretics, and presence of fluid accumulation. Furthermore, days alive and out of hospital and mortality at Day 90 will be reported descriptively.

Conclusion: In this study, we will provide important new epidemiological data on the burden of sodium and chloride disturbances in adult ICU patients internationally.

KEYWORDS
chloride, critical care, intensive care medicine, sodium

1 | BACKGROUND

Sodium and chloride are key electrolytes in plasma and crucial for maintaining osmolarity, fluid, and acid–base balance and cellular function.[1] Intravenous (IV) fluid administration is frequently used to secure hemodynamic stability and correct fluid and electrolyte imbalances in critically ill patients admitted to the intensive care unit (ICU). However, many IV fluids contain a supraphysiological concentration of sodium and/or chloride, causing a considerably large amount of these electrolytes to be administered daily to many ICU patients.[2,3] Sodium loading from sodium-containing fluids can lead to the expansion of extracellular fluids and may cause additional derailment in net fluid balance.[4,5] Furthermore, administration of chloride-rich solutions can lead to high plasma chloride and iatrogenic hyperchloremic acidosis.[6] ICU patients are particularly exposed to the risk of developing disturbances in plasma sodium and chloride due to substantial administration of IV fluids and the nature of critical illness.[7,8] Acute kidney injury (AKI) is common during critical illness, affecting up to half of all critically ill patients, and may cause further disruption of electrolyte balance.[9,10]

Disturbances in sodium and chloride such as hypernatremia, hyponatremia, and hyperchloremia have been associated with multiple complications in ICU patients including increased mortality, risk of AKI, longer duration of mechanical ventilation, and prolonged ICU stay.[6,11–19] Previous studies have primarily focused on patients with hypernatremia, hyponatremia, and hyperchloremia; however, recent research suggests that patients with hypochloremia may also be associated with similar complications.[18,20–22]

Over the last decades, intensive care fluid administration practices have focused on restricting fluid volumes and controlling electrolytes. These changes may have influenced the patterns, frequencies, and outcomes of ICU patients with disturbances in sodium and chloride. Therefore, new epidemiological data are needed to describe the current impact of sodium and chloride disturbances in ICU patients internationally.

1.1 | Aim

The aim of this study is to describe the occurrence of hypernatremia, hyponatremia, hyperchloremia, and hypochloremia in adult ICU patients and assess risk factors for developing these electrolyte disturbances as well as their association with clinical outcomes.

1.2 | Objectives

1. To estimate the proportion of adult ICU patients with hypernatremia, hyponatremia, hyperchloremia, and hypochloremia (on ICU admission, ICU-acquired, any).
2. To assess risk factors associated with the development of ICU-acquired hypernatremia, hyponatremia, hyperchloremia, and hypochloremia.
3. To assess the association of any hypernatremia, hyponatremia, hyperchloremia, and hypochloremia with clinical outcomes.

2 | METHODS

2.1 | Study design and setting

This is a protocol for a sub-study of the FLUID-ICU study ("Fluid administration and fluid accumulation in intensive care units").[23] The FLUID-ICU study is an international inception cohort study with routinely available data collected prospectively in multiple ICUs during 14-day inception periods at each site. The included patients are followed daily until discharge or death with a maximum of 28 days from ICU admission. A follow-up is performed on Day 90 after ICU admission. Additional details on the study design have been published in the FLUID-ICU protocol.[23]

2.2 | Population

The FLUID-ICU study includes adult (≥18 years) patients acutely admitted to the participating ICUs. Patients with major burns (more than 10% of the body surface area leading to the present ICU admission) or previously enrolled patients are excluded. For this sub-study, all patients included in the FLUID-ICU cohort with one or more registered sodium or chloride values in any blood sample (arterial, venous) will be eligible for inclusion.

2.3 | Approvals

The FLUID-ICU study is registered at ClinicalTrials.gov (NCT06258616) and approved by the Centre of Health in the Capital Region of Denmark (R-23078246). The Danish Committee on Health Research Ethics in the Capital Region of Denmark waived the need for ethical approval (F-23073392). National or local investigators obtain all relevant approvals required by national and regional authorities in the participating countries.

3 | OUTCOMES AND VARIABLES

3.1 | Data variables

Data collected upon ICU admission and daily during ICU stay include patient characteristics (age, sex, height, body weight, reason for ICU admission, comorbidities, sepsis, or septic shock), ICU-specific data (type and size of ICU, country), lowest blood pressure within the 24 h of ICU admission, use of respiratory support, vasopressors or inotropes, renal replacement therapy, extracorporeal membrane oxygenation (ECMO), fluid input, fluid output, administration of diuretics, and blood samples (sodium, chloride, potassium, glucose, creatinine). The presence of fluid accumulation is assessed daily and upon ICU admission for all

TABLE 1 Primary outcomes.

Primary outcomes	Definition	Subgroups (timing)	Subgroups (severity)[11,24]
Number of patients with hypernatremia	Patients with one or more plasma sodium (P-Na) >145 mmol/L[11,25–28,a]	• On ICU admission[b] • ICU-acquired[c] • Any[d]	• Mild (145 < P-Na ≥150 mmol/L) • Moderate (150 < P-Na ≥155 mmol/L) • Severe (P-Na>155 mmol/L)
Number of patients with hyponatremia	Patients with one or more P-Na < 135 mmol/L[11,24,29,a]	• On ICU admission[b] • ICU-acquired[c] • Any[d]	• Mild (135 mmol/L > P-Na ≤130 mmol/L) • Moderate (130 mmol/L > P-Na ≤125 mmol/L) • Severe (P-Na < 125 mmol/L)
Number of patients with hyperchloremia	Patients with one or more values chloride >106 mmol/L in any blood sample[6,22,30,31]	• On ICU admission[b] • ICU-acquired[c] • Any[d]	• Chloride >106 mmol/L
Number of patients with hypochloremia	Patients with one or more values of chloride <98 mmol/L in any blood sample[6,22,30,31]	• On ICU admission[b] • ICU-acquired[c] • Any[d]	• Chloride <98 mmol/L

[a]For patients with blood glucose >12 mmol/L, the sodium level will be adjusted according to the following formula: $P\text{-}Na_{measured} + 0.4x$ (blood glucose $-$ 5 mmol/L) $=$ $P\text{-}Na_{adjusted}$.[32]
[b]On ICU admission: at the time of ICU admission.
[c]ICU-acquired: only during ICU stay.
[d]Any: composite of on ICU admission and any time during ICU stay.

included patients by local study investigators using a predefined definition based on daily fluid balance, cumulative fluid balance, development in body weight, and clinical signs such as peripheral edemas, pulmonary edema, or congestion.[17] Length of ICU stay, hospital stay, and mortality are recorded during a 90-day follow-up.

3.2 | Primary outcomes

The primary outcomes are presented in Table 1.

3.3 | Secondary outcomes

1. Days alive without the use of life support at Day 28.

Definition: Days alive without the use of life support is defined as the total number of days alive without the use of renal replacement therapy, invasive mechanical ventilation, continuous use of vasopressors or inotropes, or ECMO within 28 days after ICU admission.

2. Days alive and out of hospital at Day 90.

Definition: The total number of days alive and out of hospital will be assessed from the index hospital admission (where the patient was included in the FLUID-ICU study), and calculated based on the date of hospital discharge, readmission days (if any) and date of death (if any) within 90 days. Patients who die during ICU admission will be assigned zero days alive and out of hospital.

3. All-cause mortality at Day 90.

3.4 | Data collection and management

Data will be collected from routinely available data in medical records, laboratory reports, and fluid charts from ICU admission and daily during ICU stay until discharge or death, with a maximum of 28 days. A follow-up is performed on Day 90 after ICU admission by assessing medical records, national registers, or as appropriate according to local and national regulations.

4 | STATISTICAL CONSIDERATIONS

Continuous variables will be presented as medians with interquartile ranges (IQRs) and categorical variables as numbers with corresponding percentages (%). A significance level of 0.01 will be applied to account for the anticipated large number of analyzed outcomes.

4.1 | Sample size

In this sub-study, the sample size is fixed and determined by the FLUID-ICU cohort, with at least 1000 patients included.

4.2 | Descriptive analysis

We will descriptively present the primary outcomes as numbers with the corresponding %. Sodium and chloride levels will be categorized based on the predefined clinical thresholds of hypernatremia, hyponatremia, hyperchloremia, and hypochloremia based on previous literature[11,22,24–31] (Table 1).

Additionally, the following secondary outcomes will be presented descriptively for all patients and patients with hypernatremia, hyponatremia, hyperchloremia, and hypochloremia:

1. Number of days alive and out of hospital at Day 90 (medians, [IQR]).
2. All-cause mortality at Day 90 (number, %).

4.3 | Risk factor analysis

Cox competing risk analysis will be used to assess risk factors for developing hypernatremia, hyponatremia, hyperchloremia, and hypochloremia during ICU admission (ICU-acquired) with death and discharge as competing events. We will assess disease severity by the Simplified Mortality Score for Intensive Care Unit (SMS-ICU score, a continuous score from 0 to 42 points)[33,34] and type of ICU (medical, surgical, mixed, neuro, cardio-thoracic) as baseline risk factors, and dynamically assess the use of diuretics (y/n) and presence of fluid accumulation estimated by local FLUID-ICU investigators (y/n) as risk factors that present during ICU stay. A univariable plus a multivariable model with all risk factors included and additionally adjusted for sex will be performed. Patients with disturbances in sodium or chloride on ICU admission will not be included in the analysis. The results will be presented as cause-specific hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) for each risk factor.

4.4 | Days alive without the use of life support

We will assess the crude and adjusted association between the number of days alive without the use of life support Day 28 for all patients, and by the presence of hypernatremia, hyponatremia, hyperchloremia, or hypochloremia using linear regression with bootstrapping. The model will be adjusted for disease severity by SMS-ICU score,[33,34] sex, and type of ICU (medical, surgical, mixed, neuro, cardio-thoracic).

4.5 | Missing data

Missingness will be reported as numbers with percentages. Complete case analysis will be performed if missing data is less than 5% for an outcome. If more than 5% of the patients have missing data for any variable, we will use multiple imputations.[35] If multiple imputation is used, we will report analyses on the imputed data as primary analyses and perform corresponding complete case analyses as supplementary material. Local investigators were contacted throughout the study to reduce missingness.

5 | DISCUSSION

Sodium and chloride disturbances appear to be common in ICU patients and may be associated with an increased risk of adverse outcomes. Intensive care fluid administration practices may have changed over the last decades, and contemporary data on fluid-induced harm caused by derailment in the sodium and chloride balance is warranted.

The strengths of the study include a preplanned study protocol, adherence to STROBES guidelines[36] and a comprehensive data set with a large sample collected prospectively from more than 1000 patients from multiple sites and countries. However, there are also some limitations to the study. This proposed study is a sub-study, and the data collection has been done in alignment with the aims of the FLUID-ICU study. The primary objectives are descriptive and explorative, and due to the nature of the study, there is a risk of confounding in the analysis. Despite these limitations, the study is valuable as it addresses a critical gap in understanding the impact of disturbances in sodium and chloride in ICU patients and provides important data on the proportion of patients with sodium and chloride disturbances from a large international perspective.

6 | CONCLUSION

This outlined sub-study will provide important, new epidemiological data on hypernatremia, hyponatremia, hyperchloremia, and hypochloremia in adult ICU patients. The results will guide future clinical trials on ICU management of disturbances in sodium and chloride.

AUTHOR CONTRIBUTIONS

CM, SW, MSL, MHB and MHM designed the study. CM drafted the manuscript with input and contributions from all authors.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data sharing does not apply to this article as no datasets were generated or analysed during this current study protocol.

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