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Outcomes of COVID-19 patients presenting with dysnatremia: an observational study

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Sir Aldcroft

Editor-in-Chief

BMJ Open

Cover letter for submission of an original article to BMJ Open

Almere, April 25th, 2023

Dear Sir Aldcroft,

On behalf of my co-authors, I am writing to submit our manuscript entitled ”Outcomes of COVID-19 patients presenting with dysnatremia: an observational study” to be considered for publication as original article in BMJ Open.

Together with the outbreak of COVID-19, an eruption of research arose focusing on every aspect of the disease. This also applied to the most common electrolyte disorder dysnatremia. Smaller studies performed during the first COVID-19 wave demonstrated that dysnatremia is associated with worse clinical outcomes, such as a higher need for invasive ventilation or intubation and higher mortality rates. However, research on the prognostic value of dysnatremia in later phases of the pandemic is lacking, whereas later phases of the pandemic differ significantly from the start of the pandemic due to evolution of new treatment strategies, a larger number of vaccinated patients, and newer (less pathogenic) SARS-CoV-19 variants. Besides, previous studies did not extensively study the underlying mechanism leading to dysnatremia in COVID-19 patients.

In the largest cohort to date with patients included between February 2020 and April 2022, we demonstrate that hyponatremia is associated with a higher risk of ICU admission, but not with higher need for invasive ventilation or mortality rates, which is in contrast to previous studies. Also, we show that hypernatremia is far more predictive for a worse clinical outcome than hyponatremia. Finally, we provide evidence that hyponatremia most likely results from an absolute shortage due to systemic complaints such as diarrhea rather than other disease mechanisms such as SIADH.

Dysnatremia is a frequent clinical diagnosis, as we have shown: also in COVID-19. Knowledge on the etiology and outcomes has clinical implications and may improve patient outcomes. We therefor believe that our findings will be of interest to the readers of your journal.

We declare that this manuscript describes recent work and is not under consideration for publication elsewhere, nor is it available in pre-print form. The manuscript has been read and approved for submission by all coauthors. We included patients from the ongoing CovidPredict clinical course cohort: a national database project on COVID-19. Other analyses in this project have been performed and published, see also: www.covidpredict.org and the list of publications below. A waiver for the use of hospital data was obtained from the Medical Ethical Committees of the participating centers (Amsterdam UMC; 20.131). Patients were given the opportunity to opt out.

The authors know of no conflicts of interest with this publication and any financial, research, or academic organization.

We appreciate your considerations and look forward to receiving any comments from your reviewers.

Best regards,

Lianne R. de Haan, MD

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Outcomes of COVID-19 patients presenting with dysnatremia: an observational study

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Abstract

Objectives

To evaluate the relation between dysnatremia at hospital presentation and duration of admission, risk of ICU-admission, and all-cause mortality and to assess the underlying pathophysiological mechanism of hyponatremia in COVID-19 patients. Our hypothesis is that both hypo- and hypernatremia at presentation are associated with adverse outcomes.

Design

Observational study

Setting

Secondary care; nine Dutch hospitals (2 university and 9 general hospitals)

Participants

An analysis was performed within the retrospective multicenter cohort study COVIDPredict. 7811 patients were included (60% males, 40% females) between February 24th 2020 and august 19th 2022. Patients who were ≥18 years with PCR-confirmed COVID-19, or CT with COVID-19 reporting and data system score ≥4 and alternative diagnosis were included. Patients were excluded when serum sodium levels at presentation were not registered in the database or when they had been transferred from another participating hospital.

Outcome measures

We studied demographics, medical history, symptoms, and outcomes. Patients were stratified according to serum sodium concentration and urinary sodium excretion.

Results

Hyponatremia was present in 2677 (34.2%) and hypernatremia in 126 (1.6%) patients. Patients with hyponatremia presented more frequently with diarrhea, lower blood pressure, and tachycardia. Hyponatremia was, despite a higher risk for ICU admission (OR 1.27 (1.11-1.46; p <0.001), not associated with mortality or the risk for intubation. Patients with hypernatremia had higher mortality rates

(OR 2.25 1.49 – 3.41; p <0.001) and were at risk for ICU-admission (OR 2.89 (1.83 – 4.58) and intubation (OR 2.95 (1.83 – 4.74).

Conclusions

Hypernatremia at presentation was associated with adverse outcomes in COVID-19 patients. Hypovolemic hyponatremia was found to be the most common etiology of hyponatremia.

Strengths and limitations of this study

- This study is the largest study on dysnatremia in COVID-19 so far;
- This study includes patients from different COVID-19 waves and from multiple hospitals, resulting in an heterogenous patient population;
- A relative low number of urinary samples was available for patients with hyponatremia;
- Different treatment options that became available for COVID-19 during the ongoing pandemic were not taken into account in thus study, which may have influenced the outcome of patients.

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a worldwide pandemic from February 2020 onwards. By the time of October 19th, 2022, over 621 million cases and 2.9 million deaths due to coronavirus disease 19 (COVID-19), resulting from SARS-COV-2-infection, have been reported globally[1]. The leading cause of mortality due to SARS-CoV-2 is respiratory failure due to acute respiratory distress syndrome [2-4].

Signs and symptoms as a result of COVID-19 infection vary widely, but fever, cough, and dyspnea are frequently present. Symptoms less common include anosmia, nausea, vomiting, diarrhea, and general illness[2]. Besides these clinical symptoms, several laboratory markers have been found to be indicative for COVID-19 infection. Especially elevated LDH concentration and lymphocytopenia are common[5 6]. Moreover, electrolyte disorders including hypocalcemia, hypokalemia, and dysnatremia (hypo- or hypernatremia) are seen in a substantial proportion of COVID-19 patients at the time of hospital admission[5]. Hyponatremia is also frequently present in other infectious diseases, such as pneumonia, but also in tuberculosis, meningitis, human immunodeficiency virus (HIV) infection, malaria, and leishmaniasis[7]. In COVID-19 patients, an incidence of hyponatremia between 9.9% and 38% has been reported[5 8-10], as compared to 20-30% in all hospitalized patients[11]. Hyponatremia has been inversely related to clinical outcomes in tuberculosis, pneumonia and HIV[7], and has also been related to poor outcomes in COVID-19 in retrospective studies during the first COVID-19 wave[12-14]. Hypernatremia is present only in less than 10% (general population) to 38% (intensive care unit (ICU) population) of COVID-19 patients but is associated with adverse clinical outcome[9 13 15 16].

Hyponatremia in infectious diseases, including COVID-19, can have multiple etiologies but can broadly be classified in two groups based on urinary sodium excretion (USE). In general, low USE (<30 mmol/l) indicates an activation of the renin-angiotensin system (RAAS), e.g. due to hypovolemia resulting from inadequate dietary intake, vomiting or diarrhea. On the other hand, a high USE is indicative for RAAS inactivation, although diagnostics can be influenced by the use of diuretics, which could occur in patients with syndrome of inappropriate antidiuretic hormone secretion (SIADH)[17]. Antidiuretic hormone (ADH) release in infectious diseases has been linked to secretion of inflammatory marker interleukin-6[18], which is enhanced in COVID-19 patients and is nowadays also the main target

for off-label administration of interleukin-6-inhibitors, such as tocilizumab, as treatment for COVID-19[4,19]. Both etiologies (hypovolemic hyponatremia and inadequate ADH secretion) have been proposed to contribute to hyponatremia in COVID-19, although the exact mechanism is still unclear.

Hypernatremia mostly results from insufficient water intake, for example due to a defect in of the hypothalamic thirst center or lack of access to fluid intake, but can also result from diabetes insipidus, a condition characterized by ADH deficiency or resistance[20].

Previously, hypo- or hypernatremia in COVID-19 patients have been associated with worse clinical outcome from studies early in the pandemic[12-15]. However, these studies have not reported clinical parameters at presentation, making it difficult to hypothesize about the underlying etiology of the hyponatremia[14]. Also, previous studies have shown incidence rates of and outcomes associated with dysnatremia only from the early months of the pandemic and during this period, interleukin-6 inhibitors were not yet administered[13-15].

This study reports the incidence rates of hypo- and hypernatremia at the time of admission in COVID-19 patients from a large multi-center cohort study in The Netherlands including patients from multiple COVID-19 waves. Our hypothesis is that hyponatremia and hypernatremia predict adverse outcomes, including admittance to an ICU, the need for invasive ventilation, and mortality rates in patients hospitalized for COVID-19. Also, we aim to investigate possible underlying pathophysiological mechanisms based on clinical features and laboratory values at presentation.

2. Methods

2.1 Patient recruitment and public involvement

We used data from the ongoing retrospective multicenter COVIDPredict Clinical Course Cohort, containing over 6500 patients with COVID-19, recruited between February 24th, 2020, and August 9th, 2022, in nine Dutch hospitals (2 university and 9 general hospitals). Patients registered in the database when they were 18 years or older, had a positive result for SARS-CoV-2 on polymerase chain reaction (PCR) or had a COVID-19 reporting data system (CO-RADS) score of 4 (abnormalities suspicious for COVID-19) or 5 (typical COVID-19) in the absence of an alternative diagnosis[21]. A waiver for the use of hospital data was obtained from the Medical Ethical Committees of the participating centers (Amsterdam UMC; 20.131). Information on the design and the dissemination plans of our study was included in the information available to the patients on pamflet, website and orally. Patients were given the opportunity to opt out. Patients who had been transferred from another participating hospital were excluded to avoid double entries (N = 280).

2.2 Study design

Included patients were divided into three groups, based on their serum sodium concentration at admission at the participating hospital. Serum sodium concentration was corrected for serum glucose concentration, when available, as was described by Hillier, et al. [22]. Sodium concentrations were stratified in 'normonatremia' (corrected serum sodium concentration (Na) 135-145 mmol/L), hyponatremia (corrected serum sodium concentration (Na) <135 mmol/L), further subclassified as 'mild' (corrected serum sodium concentration Na 131-134 mmol/L), 'moderate' (corrected serum sodium concentration Na 126-130 mmol/L), 'severe' (corrected serum sodium concentration Na $\leq$ 125 mmol/L) (see supplemental information), and 'hypernatremia' (corrected serum sodium concentration Na $\geq$ 146 mmol/L). Serum sodium concentrations and sodium groups in the text refer to the corrected sodium concentrations unless otherwise indicated. Demographics (ethnicity, sex at birth and age), co-morbidities (according to prespecified groups, see the Supplemental Information), home medication, and presenting signs and symptoms were compared between the groups and between normonatremia and different severity categories of hyponatremia (Supplemental information). Serum concentrations of

creatinine, urea, C-reactive protein (CRP), and lactate dehydrogenasis (LDH) indicate the measured value measured at first presentation in the participating hospital. The estimated glomerular filtration rate (eGFR) was calculated form serum creatinine using the 2021 Chronic kidney disease Epidemiology Collaboration (CKD-epi) formula[23]. Modified early warning score (MEWS) and quick sequential organ failure assessment (qSOFA) were calculated based in clinical values measured at presentation. The following clinical outcome measures were compared between the groups and for the different severity categories: duration of hospitalization, admission to intensive care unit, invasive ventilation, duration of ventilation, and death. Also, the different admission-related complications were compared between the groups.

2.3 Statistical analysis

All data were analyzed using SPSS version 27. Comparisons were made between hyper-, normo-, and hyponatremia (main text) and between normonatremia, mild, moderate, and severe hyponatremia (supplemental information). Baseline numerical data were displayed as median and interquartile range and analyzed using a Kruskal Wallis test (for non-normally distributed data) or displayed as mean and standard deviation and analyzed using a one-way ANOVA (for normally distributed data). Baseline categorical data were displayed as absolute number and percentage of patients with the given condition and analyzed using a ChiSquare test. Outcome data (risk for ICU-admission, intubation, mortality rates, and complications) were assessed using a binary logistic regression model with calculation of odds ratios, adjusted for age, sex assigned at birth (either of two categorizations (male/female) based on genotype and internal and external anatomy at birth), a history of chronic kidney disease, and a history of hypertension. Duration of admission was assessed with a simple linear regression. A Cox proportional hazard regression analysis was conducted to estimate survival for patients presenting with and without hyponatremia to show the cumulative mortality over a 6-week period starting from hospital admission. For all statistical testing, a p-value of ≤ 0.05 was considered statistically significant. When the tested variable was not registered in the database, the patient was excluded from the specific analysis.

3. Results

3.1 Incidence of dysnatremia at presentation

At the time of August 9th, 2022, the database contained 11.382 records. Serum sodium concentrations at admission were available for 8278 (73 %) admissions of 7811 patients (170 double entries due to readmittance: 297 patients had been transferred from or previously admitted to another participating hospital and transfer records were therefore excluded). 6673 patients were included based on a positive result for SARS-CoV-2 PCR and 1138 were included based on a CO-RADS score 4 or 5 in the absence of an alternative diagnosis. When patients were readmitted, the admission with the abnormal sodium level at presentation (in case of hyponatremia or hypernatremia) or the first admission (in case sodium concentrations were normal for both presentations) was included.

Of the included 7811 patients with COVID-19, 2677 (34.3%) presented with hyponatremia (corrected blood serum Na <135 mmol/L), and 126 (1.6%) presented with hypernatremia (corrected blood serum Na $\geq$ 146 mmol/L). Of the patients presenting with hyponatremia, 1957 (25.1%) presented with blood serum Na ranging 131-134 mmol/L ('mild'), 582 (7.5%) presented with blood serum Na ranging 126-130 mmol/L ('moderate'), and 138 (1.8%) with blood serum Na $\leq$ 125 mmol/L ('severe'), Supplemental Figure 1. 1888 patients were included after the start of the SARS-CoV-19 vaccination campaign in the Netherlands (6th of January 2021) of whom 445 were vaccinated (N = 319 for two doses or more).

3.2 Patient characteristics of patients presenting with dysnatremia

Table 1 shows the characteristics of patients with hyponatremia and hypernatremia compared to patients presenting with normal sodium concentrations at presentation. Both hypo- and hypernatremia occurred more often in males than in females (Table 1), except for 'severe' hyponatremia (Supplemental Table 2). Mean age in patients with and without hyponatremia differed slightly, where patients presenting with 'moderate' or 'severe' hyponatremia were significantly older (median age 68.1 and 70.6 years). Patients with hypernatremia were also older, with a mean age of 72.5 years. Body mass index (BMI) in

patients presenting with hyponatremia was slightly lower than in patients with normonatremia and also lower in patients presenting with hypernatremia. Abnormal sodium concentration at presentation was associated with chronic kidney disease. Patients with hyponatremia, especially those with severe hyponatremia, more often had a history of hypertension, but this difference was not significant for the subgroup of patients that did not use diuretics (36.4% (normonatremia) vs. 39.1% (hyponatremia); p = 0.003; Chi-square test). Hypo- and hypernatremia were not associated with a history of chronic heart, pulmonary or liver disease, (see Supplemental Table 1 for definitions). As for the use of medication, the use of thiazide diuretics (Table 1) was higher in patients with hyponatremia, but the use of diuretics in general or loop diuretics did not differ between the groups, nor did the use of selective serotonin (and noradrenalin) reuptake inhibitors (SSRIs/SNRIs). The use of immunosuppressives was also higher in patients presenting with hyponatremia as compared to people with normal sodium concentration at presentation.

3.3 Signs and symptoms of patients presenting with dysnatremia

Patients with hyponatremia more often presented with diarrhea and anosmia compared to patients without hyponatremia (Table 2) but vomiting or nausea as presenting symptoms were not associated with hyponatremia. In the hypernatremia group, confusion was more often present compared to normonatremia. A prolonged capillary refill, which could indicate dehydration, was more often present in the hypernatremia group and patients with hypernatremia also had a slightly higher heart rate. Hyponatremia was also associated with a slightly higher heart rate and, additionally, a slightly lower systolic blood pressure, although not clinically relevant. Both patients with hypernatremia as well as patients with hyponatremia had a lower eGFR, which was more pronounced in the former. Enhanced blood urea concentration was only associated with hypernatremia.

Blood CRP and LDH concentrations were higher in patients with hyponatremia as compared to normonatremia (Table 2). In contrast, FiO2 and CT-severity scores did not significantly differ between the groups. Clinical score systems MEWS and qSOFA[24] (Table 2) differed significantly between the groups, but these differences were not clinically relevant.

A duration of COVID-19 related-complaints for 14 days or less was associated with a slightly lower serum sodium concentration (136.2 mmol/L (≤ 14 days) vs. 136.6 (>14 days); $p = 0.019$; one-way ANOVA) compared to patients that had complaints for 15 days or more.

3.4 Clinical outcomes in patients presenting with hyponatremia and hypernatremia

Hypernatremia was associated with higher mortality or palliative discharge rates as compared to normo- and hyponatremia groups (Table 3 and Figure 1). Moreover, patients with hypernatremia had a higher risk for ICU-admission and invasive ventilation. Hyponatremia was not associated with increased mortality / palliative discharge rates (Table 3). Although there was a trend towards increased mortality in patients with severe hyponatremia, these results were not statistically significant due to the low number of patients that presented with sodium levels below 125 mmol/L. After excluding patients with a 'do not intubate' order, hyponatremia was associated with a higher need for ICU-admission, but not with invasive ventilation (Table 3). Hyponatremia corrected for glucose was used for all statistical testing, but as some other studies used uncorrected hyponatremia[13 14], we also tested if uncorrected hyponatremia was associated with different outcomes. Without correction for serum glucose concentration, hyponatremia was still associated with a slightly higher rate of ICU admission (OR 1.43 (1.25 – 1.62); p < 0.001) and with the need for intubation (OR 1.26 (1.10 – 1.46); p = 0.001), but not with death or palliative discharge rates (OR 1.11 (0.97 – 1.28); p = 0.13). Despite the correlation with ICU admission in patients with hyponatremia, duration of admission when adjusted for age, sex assigned at birth, and a history of chronic kidney disease and hypertension was not significantly longer in this group. Similar outcomes were obtained for patients with conformed COVID-19 (SARS-CoV-2 PCR positive; 6673 patients) only, although in this subgroup ICU admission was no longer significantly higher for patients with hyponatremia.

As the COVID-19 pandemic progressed, the incidence of adverse outcomes was significantly lower in patients with normo-, and hyponatremia at presentation that were admitted after 20-09-2020 (2nd to 4th quartile) as compared to those admitted before 20-09-2020 (1st quartile; Figure 2), whereas hypernatremia was associated with a higher risk for ICU admission and invasive ventilation for patients that were admitted after 26-01-2022 (4th quartile; compared to patients admitted in the 1st quartile).

Administration of tocilizumab and COVID-19 vaccination were too infrequently reported to make a statement about the possible effects of these interventions on outcome measures.

3.5 Complications associated with hyponatremia at presentation

After correction for sex assigned at birth, age, and a history of chronic kidney disease and hypertension, the course of disease of patients with hyponatremia was more often complicated by an aspergillosis pneumonia and physical decline. Patients with hypernatremia more often suffered from acute respiratory distress syndrome, more frequently received treatment for septic shock (defined as the need for vasopressors in order to maintain mean arterial blood pressure >65 mmHg and blood lactate level >2 mmol/L, in the absence of other causes including hypovolemia), more frequently suffered from delirium. Excessive fluid resuscitation for the treatment of hypo- or hypernatremia could lead to congestive heart failure, however, the incidence of this complication was low and did not occur more often in patients with abnormal sodium values at presentation.

3.6 Urinary sodium excretion related to patients' characteristics and outcomes

USE was measured in 185 (6.9%) patients with hyponatremia of whom 145 (78%) patients did not use diuretics (48 with mild, 67 with moderate, and 30 with severe hyponatremia, respectively). USE ranged from 5.0 to 239 mmol/L (median 30.0 mmol/L). Urinary osmolarity (UOL) was measured in 81 (3.0%) patients who did not use diuretics; in 26 with 'mild', 37 with 'moderate', and 18 with 'severe' hyponatremia, with a range of 8 - 1007 mOsmol/kg (median 496 mOsmol/kg). Urinary investigation of 23 patients (21% of patients in whom both USE and UOL were measured) complied to the definition of SIADH (USE ≥ 30 mmol/L and UOL $\geq$ 100 mOsmol/kg in the absence of diuretics and in the absence of signs of hypovolemia (systolic blood pressure < 90 mmHg or heart rate $\geq$ 100 BPM)).

Patients were divided in two groups based on USE. Seventy-two (49.7% of urinary sodium measurements) patients had low USE (< 30 mmol/L) which indicates RAAS activation. Seventy-three (50.3%) patients had high USE (≥ 30 mmol/L) which indicates RAAS inactivation (Supplemental Table 5). A low USE was associated with a higher CRP (111 (52.5 – 163) mmol/L vs. 70 (35.0 – 154) mmol/L;

p = 0.028) and LDH (351 (270 – 491) U/L vs. 273 (227- 434) U/L; p = 0.021) at presentation (Supplemental Table 5), but not associated with symptoms such as nausea / vomiting or clinical signs of hypovolemia, such as tachycardia or hypotension. Outcome measures, such as duration of admission, ICU admission, or death/palliative discharge, did not differ between patients with a low and high USE.

4. Discussion

In this large multicenter observational cohort study, including 7811 patients with COVID-19 included over a long period of time and multiple phases of the COVID-pandemic, we found that hyponatremia was highly prevalent but not associated with higher mortality rates. Although less prevalent, hypernatremia was associated with a three-to-four-fold increased risk of worse outcome in terms of higher risk for ICU-admission, intubation, and mortality. Hyponatremia was also associated with a higher risk for ICU-admission, but not for intubation. Admission of patients with hyponatremia was more frequently complicated by aspergillosis pneumonia and physical decline and patients with hypernatremia more often suffered from sepsis and delirium. Hypo- and hypernatremia were more prevalent in elderly patients, those with chronic kidney disease, and lower body weight. Hyponatremia in COVID-19 patients appeared to have multiple etiologies, but hypovolemic hyponatremia was found to be predominant.

Hyponatremia is a common finding among COVID-19 patients, with an incidence of 34.3% in our study. This incidence is higher than previously reported rates between 9.9% and 30%[5 13 14 25-29], but is in line with Voets, et al. [9] Tezcan, et al. [30] and Sarvazad, et al. [10], who reported rates of 34%, 35.8% and 38%, respectively (the latter study included only patients without underlying disease). The incidence of hyponatremia among patients with COVID-19 is found to be higher compared to hyponatremia in other pneumonias: 5.4%- 28%[7 31]. Hyponatremia is most common in pneumonias caused by viral pathogens (e.g. rhinovirus, respiratory syncytial virus, (para)influenza virus, and adenovirus) with a incidence reported of 17.6%, as compared to 13.8% in patients with bacterial pneumonias[31]. Patients presenting with hyponatremia in our study were significantly older compared to patients with normonatremia. Possibly this could be due to age-related tubular atrophy and subsequent decreased urine concentrating capacity and sodium reabsorption[32]. Although previous studies reported various underlying conditions as risk factor for hyponatremia, including diabetes[13], we only found that patients with chronic kidney disease and those with a slightly lower BMI were at risk for presenting with dysnatremia.

Hypernatremia is less common among COVID-19 patients compared to other pneumonias, with an incidence of 1.6% in our study. This number is lower than the incidences reported previously (2.9 %-38%) [9 13 27 28] and also lower than 5.3% reported in patients with a community acquired pneumonia[33]. Patients with hypernatremia were older than patients with normo- or hyponatremia. These age

differences were in line with our expectations, since age-related impairment of the thirst mechanism and barriers to accessible fluids (e.g. due to immobilization or dementia) could lead to inadequate fluid intake with consequent hypernatremia[20].

Hyponatremia in infectious diseases can have multiple etiologies, of which SIADH and hypovolemia are the most common[7]. In this study we showed that both etiologies seem to play a role in COVID-19 patients. Among patients with hyponatremia a higher incidence of diarrhea and anosmia (which could lead to decreased appetite) was found. Clinical investigations showed an increased heart rate and slightly decreased systolic blood pressure, suggesting hypovolemic state as a possible underlying cause for hyponatremia. This hypovolemic state could result from a reduced dietary intake as well as from dehydration due to diarrhea. The low median USE (30 mmol/L) in a proportion of patients also points to extrarenal sodium loss and a hypovolemic status[34]. However, USE was only reported for a small number of patients and thus should be interpreted as supportive measurement rather than hard indicator.

Moreover, patients presenting with hyponatremia had higher LDH and CRP serum concentrations and lower eGFR. A relationship between serum CRP and sodium concentration was found in other infectious diseases. Previous reports ascribed this phenomenon to release of cytokines such as interleukin-6 and interleukin-1β[35], which proposedly cause hyponatremia by affecting ADH-secretion, thus causing SIADH[18]. Since interleukin-6 and interleukin-1β are also enhanced in COVID-19-infected patients[36 37], a similar mechanism could be of action in COVID-19-infected patients with hyponatremia.

In fact, Frontera, et al. [14] found that interleukin-6 levels in COVID-19 patients were progressively higher as the degree of hyponatremia worsened. In our study, however, only 21% of USE + UOL samples complied to the definition of SIADH and in contrast to this theory, a correlation between low urinary sodium excretion and serum CRP concentration was found (Supplemental Table 5). Cuesta, et al. [38] found an incidence of SIADH of 46% in all patients with hyponatremia and community acquired pneumonia. The overall incidence of SIADH in our study seems to suggest that SIADH is a less frequent cause of hyponatremia among COVID-19 patients, compared to hyponatremia in patients with other pneumonias. This is possibly because COVID-19 more often causes diarrhea thereby also leading to other causes of hyponatremia. Although previous SIADH was most reported as the underlying mechanism in previous studies[29], the underlying mechanism in our population could be different due to

the fact that patients from later COVID-19 waves were included. Later COVID-19 variants and group immunity have led to less critically ill patients during later COVID-19 waves, which could reduce the number of patients suffering from SIADH. The fact that in our study urinary investigation was not performed in all patients with hyponatremia may suggest that hyponatremia was not persistent or was otherwise not found to be severe enough to do so.

As expected, patients with hyponatremia more frequently used thiazide diuretics, as thiazide diuretics are associated with a higher risk for developing hyponatremia[39]. The use of immunosuppressives was also related to hyponatremia, which could be related to a possible (relative) glucocorticoid deficiency resulting from iatrogenic adrenal insufficiency due to the (prior) prescription of steroids[40 41].

We did not find a significant association between hyponatremia and the risk of mortality or intubation, although ICU admission rates were higher in the hyponatremia group. These results are in line with Martino, et al. [27], who reported that patients with hyponatremia compared to those with normonatremia, and those stratified in different hyponatremia severity groups had similar risks for ICU admission, mechanical ventilation in ICU, length of hospital stay, and death. This is in contrast with previous studies, in which the presence of hyponatremia at presentation was independently associated with disease severity and prolonged hospital stay [31] and was thought to be an independent predictor of hospital mortality[13 14 29], especially when not corrected for serum glucose concentration[15]. These results are also not in line with higher serum CRP and LDH concentrations in hyponatremic patients, indicating that these patients might be more ill compared to normonatremic patients[42 43]. We hypothesize that dehydration with hyponatremia combined with a high LDH and CRP serum concentration were reasons for hospital admittance. Other pathophysiologic mechanisms leading to worse outcome were absent in these patients, favoring a relatively good outcome. The observed trend towards increased mortality in patients with severe hyponatremia was also demonstrated by [13] and Frontera, et al. [14]. However, the latter study obtained statistically significant results with a lower number of patients (36 / 4645 (1%) stratified as severe hyponatremia based on sodium levels $\leq$ 120 mmol/L versus 1.8% in our study), which could not be confirmed by our study.

There are two possible explanations for the difference in outcomes compared with previous studies. First, our study population differed to that of previous studies[13 14 29]. Both Frontera, et al. [14], Ruiz-Sánchez, et al. [13], and Hirsch, et al. [15] included only patients that were admitted during the spring

of 2020; the beginning of the COVID-19 pandemic, whereas our study included patients from the start of the COVID-19 pandemic until October 2021. We showed that mortality, ICU-admission, and intubation rates in the normo- and hyponatremia groups differed significantly between patients that were included during the spring of 2020 versus patients that were included in later COVID-19 waves. These differences in mortality most likely relate to increased knowledge of the disease, new treatments such as dexamethasone and tocilizumab, and the fact that the vaccination campaign against COVID-19 started in January 2021. These differences in patient cohorts and treatment strategies could affect outcomes and thus could lead to different results as compared to other studies. We hypothesize that the fact we did not found a higher risk of adverse outcome in patients with hyponatremia in contrast to previous studies was partly because the overall mortality decreased as the pandemic continued.

Second, Frontera, et al. [14] and Ruiz-Sánchez, et al. [13] studied uncorrected sodium concentration at presentation as prognostic factor and found increased mortality rates in these patients, while others, who corrected for serum glucose concentration when these exceeded 10 mmol/L, found no association between hyponatremia and mortality[44]. Hirsch, et al. [15] demonstrated that hyponatremia was only associated with an increased mortality risk prior to correction for serum glucose concentration, but the association vanished after correction for glucose. These results were similar to other, non-COVID-19 studies[45]. In our study, uncorrected hyponatremia was, besides an increased risk for ICU admission, also associated with an increased risk for intubation, which was not the case for corrected hyponatremia. This indicates that a similar effect could be explanatory for the different results between our study and others[13 14].

In contrast to the results found in patients with hyponatremia, hypernatremia was significantly associated with ICU-admission, intubation, and death. Although serum CRP and LDH concentration in these patients did not differ significantly compared to normonatremic patients, CT-severity scores at admission in combination with higher MEWS and qSOFA scores indicate that a higher percentage of lung tissue was affected in these patients. Moreover, elevated serum urea concentration, lower eGFR, and a prolonged capillary refill indicate dehydration also in this patient group. Together, these findings indicate a more critically ill patient group which could explain worse clinical outcomes. Hypernatremia as predictor of worse clinical outcomes has been previously reported in COVID-19[13] and other pneumonias[33].

Our study is the largest study on hyponatremia in COVID-19 so far and includes over 7000 patients from different hospitals in the Netherlands. More importantly, our study included patients from different COVID-19 waves and from multiple hospitals, both university and general, resulting in an heterogenous patient population and leading to results that are applicable to the current situation. We believe this is a major strength of our study. Moreover, a large amount of clinical data was available for each patient, allowing us to interpret the associations we found with the help of patient background information. For example, vital signs at admission were reported, giving us a better view on the patients' condition at admission than in previous studies[13 14] and allowing us to make more substantiated statements about the presumed underlying etiology.

This study also has several limitations. Firstly, although urinary samples were available for 185 patients with hyponatremia, this number was low relative to the total number of patients with hyponatremia included in our study. Also, the duration of hyponatremia and the expected etiology of the hyponatremia in participating patients was not provided. Second, treatment protocols between participating hospitals differed, and the study did not take into account the different treatment options that became available for COVID-19 during the ongoing pandemic. This may have influenced outcome of patients. Lastly, we were unable to study specific treatment options for hyponatremia in patients.

Our results indicate that although hyponatremia is highly prevalent among COVID-19 patients, hyponatremia is not associated with adverse clinical outcome. The presence of hypernatremia, however, is more worrisome and clinicians should be aware of the poorer prognosis in these patients. To better understand the etiology of hyponatremia in COVID-19, future studies should focus on the clinical course of hyponatremia during admission and record the duration of hyponatremia and treatment given. Preferably, urinary samples will be obtained in all patients presenting with COVID-19 and hyponatremia to further determine etiology. Moreover, further research is needed to elucidate the incidence and possible mechanism of SIADH in relation to disease severity and inflammation. More specifically, studies on the relationship with interleukin-6 would be of interest, because of the interleukin-6 antagonist tocilizumab is used in the treatment of patients with moderate to severe COVID-19.

5. Conclusion

Hyponatremia is a common electrolyte disorder found in one third of patients hospitalized with COVID-19. Risk factors for hyponatremia include male sex assigned at birth, a slightly lower BMI, chronic kidney disease, hypertension, the use of thiazide diuretics, and the use of immunosuppressives. We found that hyponatremia was not associated with a higher need for invasive ventilation nor with mortality. In contrast, hypernatremia was associated with worse outcomes as compared to normonatremia. As for the underlying pathophysiological mechanism, hypovolemic hyponatremia was thought to be the predominant underlying pathophysiological mechanism in COVID-19 patients. Other causes of hyponatremia, such as SIADH, were found to be less prevalent.

Competing of interest

The authors declare that there is no conflict of interest.

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Authors contributions

- L.R. de Haan contributed to data entry in the COVIDPredict database, data analysis and interpretation, and drafted the article.
- M. ten Wolde contributed to data entry in the COVIDPredict database, data analysis and interpretation, and critically revised the article.
- M. Beudel contributed to data entry in the COVIDPredict database, and critically revised the article.
- R.H. Olde Engberink contributed to data entry in the COVIDPredict database, and critically revised the article.
- B. Appelman contributed to data entry in the COVIDPredict database, and critically revised the article.

- E.K. Haspels-Hogervorst contributed to data entry in the COVIDPredict database, and critically revised the article.
- D. Rusch contributed to data entry in the COVIDPredict database, and critically revised the article.
- N.C. Gritters-van den Oever contributed to data entry in the COVIDPredict database, and critically revised the article.
- S. Simsek contributed to data entry in the COVIDPredict database, and critically revised the article.
- N. Paternotte contributed to data entry in the COVIDPredict database, and critically revised the article.
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- H. Moeniralam contributed to data entry in the COVIDPredict database, and critically revised the article.
- N. Bokhizzou contributed to data entry in the COVIDPredict database, and critically revised the article.
- K. Brinkman contributed to data entry in the COVIDPredict database, and critically revised the article.
- R.A. Douma contributed to data entry in the COVIDPredict database, data analysis and interpretation, and critically revised the article.

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Figure legends

Figure 1. Hazard ratios of cox proportional survival curves for survival probability for each sodium value adjusted for age, sex assigned at birth, a history of chronic kidney disease, and a history of hypertension. The grey area indicates the normonatremia. Table shows hazard ratios for covariates and sodium as a continuous variable (**A**). Cox proportional survival curves at the mean of covariates for (**B**) unadjusted 6-week mortality stratified by normo-, hypo-, and hypernatremia, (**C**) 6-week mortality adjusted for age, sex assigned at birth, a history of chronic kidney disease, and a history of hypertension stratified in normo-, hypo-, and hypernatremia. *** indicates a p-value <0.001

Figure 2. Odds ratio for adverse outcomes (death / palliative discharge (**A**), intensive care unit admission (**B**) invasive ventilation (**C**)) in each quartile compared to patients in the first quartile (admitted before 27-03-2020; N = 2002) for patients with hypo-, hyper-, or normonatremia at admission. * Indicates a p-value <0.05, ** indicates a p-value < 0.01, *** indicates a p-value <0.001 for the odds ratio as calculated by binary logistic regression. **(D)** incidence of hypo-, normo-, and hypernatremia in each quartile, *** indicates a p-value <0.001 as compared to the first quartile for the chi-square statistic with Bonferroni post-hoc correction.

Table 1 – Comparison of patient characteristics between COVID-19 patients with hypo-, normo-, and hypernatremia

	Hyponatremia Na 134 mmol/L N = 2677	**Normonatremia** Na 136 – 145 mmo/L N = 5008	**Hypernatremia** Na 146 mmol/L N = 126
Sex assigned at birth (N (%))	♂ 1673 (62.5%) ♀ 1003 (37.5%) p = 0.002	♂ 2946 (58.8 %) ♀ 2060 (41.2 %)	♂ 84 (66.7%) ♀ 42 (33.3%)
Age (median age in years (IQR))	N = 2675 67.0 (58.0-77.0) p < 0.001	N = 5008 66.1 (55.0-76.0)	N = 126 72.5 (62.8 – 80.3) p < 0.001
BMI (median BMI in kg/m^2 (IQR))	N = 1740 27.2 (24.2 – 31.1) p = 0.009	N = 3374 27.7 (24.6 – 31.6)	N = 91 25.0 (22.2 – 29.1) p < 0.001
Order 'Do not intubate' (N (%))	440 / 1442 (30.5 %)	796 / 2469 (32.2 %)	39 / 77 (50.6 %) p = 0.004
Chronic cardiac disease (N (%))	760 / 2666 (28.5%) p = 0.07	1334 / 4982 (26.8 %)	42 / 123 (34.1 %) p = 0.07
Hypertension (N (%))	1055 / 2374 (44.4 %) p = 0.002	1889 / 4586 (41.2 %)	64 / 120 (53.3 %)
Chronic pulmonary disease (N (%))	466 / 2662 (17.5 %) p = 0.75	844 / 4979 (17.0 %)	19 / 122 (15.6 %) p = 0.75
Chronic kidney disease (N (%))	329 / 2379 (13.8 %) p < 0.001	491 / 4587 (10.7 %)	26 / 121 (21.5 %) p < 0.001
Moderate to severe liver disease (N (%))	30 / 2662 (1.1 %) p = 0.46	50 / 4972 (1.0 %)	0 / 123 (0.0 %) p = 0.46
Diabetes (N (%))	664 / 2662 (24.9 %) p = 0.39	1261 / 4972 (25.4 %)	38 / 125 (30.4 %) p = 0.39
Immunosuppressives (N (%))	192 / 2283 (8.4 %) p = 0.002	295 / 4445 (6.6 %)	2 / 118 (1.7 %)
Thiazide diuretics (N (%))	258 / 2671 (9.7 %) p = 0.015	394 / 4994 (7.9 %)	7 / 125 (5.6 %)
Loop diuretics (N (%))	187 / 2671 (7.0 %) p = 0.22	389 / 4994 (7.8 %)	13 / 125 (10.4 %) p = 0.22
SSRIs / SNRIs (N (%))	78 / 2671 (2.9 %) p = 0.69	164 / 4994 (3.3 %)	4 / 125 (3.2 %) p = 0.69

BMI = body mass index; IQR = interquartile range; % = percentage of patients in this group with indicated characteristic; SSRI = Selective Serotonin Reuptake inhibitor; SNRI = Selective Serotonin and Noradrenalin Reuptake inhibitor. Significance was assessed using a Kruskal Wallis test with post-hoc correction (for numerical data; non-normally distributed) or Chi-square test (for categorical data). p – values for all groups indicate the adjusted significance after post-hoc correction when compared to the normonatremia group. When no p – value was provided there was no significant difference compared to the normonatremia group. Subgroup analyses for hyponatremia is provided in the supplemental information.

Table 2 – Comparison of signs and symptoms at presentation between COVID-19 patients with hypo-, normo-, and hypernatremia

Signs and symptoms	**Hyponatremia** Na 134 mmol/L N = 2677	**Normonatremia** Na 136 – 145 mmo/L N = 5008	**Hypernatremia** Na 146 mmol/L N = 126
Nausea / vomiting (N (%))	679 / 2273 (29.9 %) p = 0.04	1150 / 4129 (27.9 %)	16 / 83 (19.3 %) p = 0.04
Diarrhea (N (%))	804 / 2298 (35.0%) p < 0.001	1146 / 4157 (27.6 %)	15 / 82 (18.3 %)
Anosmia (N (%))	244 / 1904 (12.8 %) p = 0.002	352 / 3330 (10.6 %)	1 / 66 (1.5 %)
Confusion (N (%))	311 / 2319 (13.4%)	651 / 4381 (14.9 %)	45 / 105 (42.9 %) p < 0.001
Seizures (N (%))	10 / 1977 (0.5%) p = 0.20	31 / 3452 (0.9 %)	0 / 80 (0.0 %) p = 0.20
FiO2 (median fraction (IQR))	N = 1159 0.36 (0.28-0.50) p = 0.05	N = 2084 0.36 (0.28 – 0.50)	N = 67 0.44 (0.30 – 0.80) p = 0.05
SBP (mean SBP in mmHg (SD))	N = 2648 132 (± 22) p < 0.001	N = 4971 135 (±23)	N = 120 135 (± 25) p = 1.00
HR (mean HR in BPM (SD))	N = 2661 92 (±18) p = 0.003	N = 4965 91 (±20)	N = 123 95 (±25) p = 0.034
Disturbed capillary refill (N (%))	81 / 863 (9.4 %)	93 / 1369 (6.8 %)	6 / 33 (18.2 %) p = 0.008
Blood urea level (median level n mmol/L (IQR))	N = 2549 6.3 (4.5 – 9.3) p = 0.87	N = 4776 6.2 (4.5 – 9.2)	N = 115 12.6 (7.9 – 25.3) p < 0.000
eGFR rate using 2021 CKD-epi creatinine equation in (median clearance in ml/min/1.73 m^3 (IQR))	N = 2656 64 (45 – 90) p < 0.001	N = 4983 68 (46 – 94)	N = 125 41 (24 – 71) p < 0.001
CT-severity score (mean score (SD))	N = 909 12.4 (±5.5) p = 0.58	N = 1401 12.1 (±5.6)	N = 30 14.5 (±7.2) p = 0.06
Blood CRP level (median level in mg/L (IQR))	N = 2646 93.1 (49.0 – 154) p < 0.001	N = 4939 70.8 (28.0 – 131)	N = 123 75.0 (29.0 – 148) P = 1.00
Blood LDH level (median level in U/L (IQR))	N = 2238 349 (268 – 471) p < 0.001	N = 4226 323 (247 – 426)	N = 89 363 (255 – 447) p = 0.52

MEWS (median score (IQR))	N = 2337 3.0 (2.0 – 4.0) p < 0.001	N = 4055 3.0 (2.0 – 4.0)	N = 103 4.0 (2.0 – 5.0) p < 0.001
qSOFA (median score (IQR))	N = 2373 1.0 (0.0 – 1.0) p = 1.00	N = 4131 1.0 (0.0 – 1.0)	N = 104 1.0 (1.0 – 1.0) p < 0.001

SBP = systolic blood pressure; HR = heart rate; eGFR = estimated glomerular filtration rate; CKD-epi = chronic kidney disease Epidemiology Collaboration; CT = computed tomography; BPM = beats per minute; IQR = interquartile range; SD = standard deviation; CRP = c-reactive protein; LDH = lactate dehydrogenase; MEWS = modified early warning score; sSOFA = quick sequential organ failure assessment. % = percentage of patients in this group with indicated characteristic. Significance was assessed using a Kruskal Wallis test with post-hoc correction (for numerical data) or Chi-square test (for categorical data). p – values for all groups indicate significance when compared to the normonatremia group. When no p – value was provided there was no significant difference to the normonatremia group. Subgroup analyses for hyponatremia is provided in the supplemental information.

Table 3 – Comparison of clinical outcomes between COVID-19 patients with hypo-, normo-, and hypernatremia

Outcome	**Hyponatremia** Na 134 mmol/L N = 2677	**Normonatremia** Na 136 – 145 mmo/L N = 5008	**Hypernatremia** Na 146 mmol/L N = 126
Death or palliative discharge (N (%))	405 / 2360 (17.2 %) [A]OR 1.04 (0.91 – 1.20) p = 0.56	729 / 4568 (16.0 %)	42 / 119 (35.3 %) [A]OR 2.25 (1.49 – 3.41) p < 0.001
ICU-admission (N (%)), 'do not intubate' excluded	439 / 1923 (22.8 %) [A]OR 1.27 (1.11 – 1.46) p < 0.001	710 / 3778 (18.8 %)	32 / 80 (40.0%) [A]OR 2.89 (1.83 – 4.58) p < 0.001
Invasive ventilation (N (%)), 'do not intubate' excluded	352 / 1889 (18.6 %) [A]OR 1.12 (0.97 – 1.30) p = 0.121	623 / 3706 (16.8 %)	29 / 77 (37.7 %) [A]OR 2.95 (1.834 – 4.74) p < 0.001
Discharge alive within 42 days; N indicating the number of non-censored cases	N = 1527 [A]HR 0.96 (0.90 – 1.02) p = 0.15	N = 2747	N = 52 [A]HR 0.78 (0.59 – 1.03) p = 0.08
Complications	Na 134 mmol/L N = 1821	Na 136 – 145 mmo/L N = 3206	Na 146 mmol/L N = 82
Bacterial pneumonia (N (%))	289 / 2212 (13.1 %) [A]OR 1.12 (0.96 – 1.31) p = 0.14	501 / 4307 (11.6 %)	18 / 109 (16.5 %) [A]OR 1.44 (0.85 – 2.40) p = 0.17
Aspergillosis pneumonia (N (%))	67 / 1915 (3.5 %) [A]OR 1.44 (1.03 – 1.99) p = 0.031	83 / 3442 (2.4 %)	5 / 90 (5.6 %) [A]OR 2.26 (0.89 – 5.74) p = 0.084
ARDS (N (%))	224 / 2223 (10.1 %) [A]OR 1.08 (0.91 – 1.29) p = 0.377	404 / 4323 (9.3 %)	17 / 110 (15.5 %) [A]OR 1.78 (1.05– 3.04) p = 0.033
Treatment for septic shock (N (%)) *	94 / 2153 (4.4 %) [A]OR 1.33 (1.01 – 1.74) p = 0.04	135 / 4175 (3.2 %)	12 / 109 (11.0 %) [A]OR 3.37 (1.80 – 6.33) p < 0.001

Congestive heart failure (N (%))	64 / 2235 (2.9 %) [A]OR 0.95 (0.70 – 1.29) p = 0.73	125 / 4352 (2.9 %)	2 / 111 (1.8 %) [A]OR 0.48 (0.12 – 1.96) p = 0.31
Physical decline (N (%))	576 / 2116 (27.2 %) [A]OR 1.22 (1.08 – 1.38) p < 0.001	950 / 4126 (23.0 %)	30 / 106 (28.3 %) [A]OR 1.18 (0.77 – 1.82) p = 0.44
Delirium (N (%))	237 / 2136 (11.1 %) [A]OR 0.99 (0.83 - 1.17) p = 0.88	451 / 4146 (10.5 %)	27 / 107 (25.7 %) [A]OR 2.25 (1.42 – 3.56) p < 0.001

*ICU = Intensive care unit; ARDS = acute respiratory distress syndrome. [A]OR = adjusted odds ratio; odds ratio adjusted for sex assigned at birth, age, a history of chronic kidney disease, and a history of hypertension. [A]HR = adjusted hazard ratio; hazard ratio adjusted for sex assigned at birth, age, a history of chronic kidney disease, and a history of hypertension * Treatment for septic shock was defined as the need for vasopressors in order to maintain mean arterial blood pressure >65 mmHg and blood lactate level >2 mmol/L, in the absence of other causes including hypovolemia. Significance was assessed using a cox proportional-hazard model at the mean of the covariates (discharge alive) or logistic regression (all other values). p – values for all groups indicate significance when compared to the normonatremia group.*

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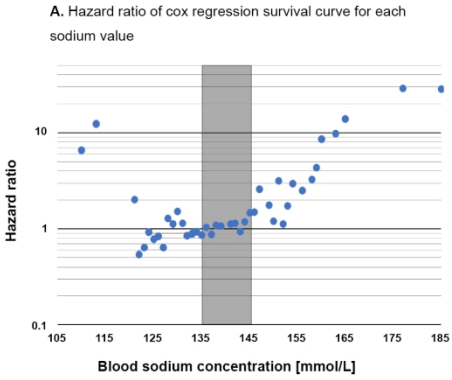
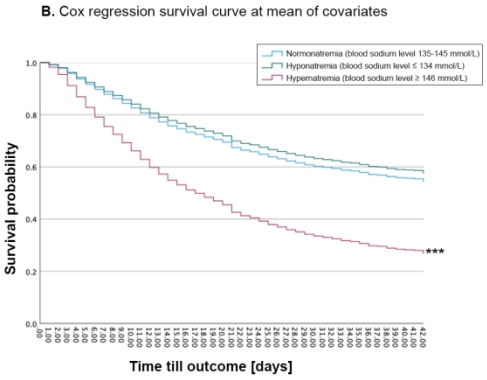


Covariate	Hazard ratio (95% CI)	*p* - value
Male sex assigned at birth	1.241 (1.094 - 1.407)	< 0.001
Age (years)	1.062 (1.056 - 1.068)	< 0.001
History of hypertension	1.116 (0.988 - 1.260)	0.077
History of chronic kidney disease	1.372 (1.182 - 1.592)	< 0.001
Sodium (mmol/L)	1.020 (1.008 - 1.032)	0.001



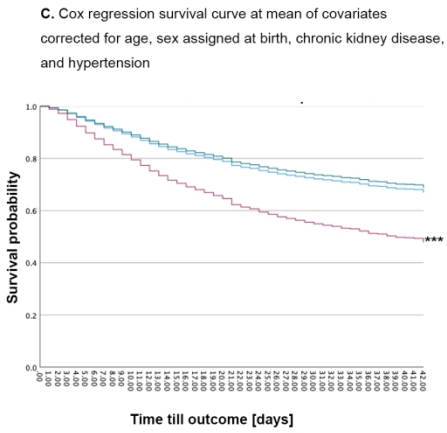


Figure 1. Hazard ratios of cox proportional survival curves for survival probability for each sodium value adjusted for age, sex assigned at birth, a history of chronic kidney disease, and a history of hypertension. The grey area indicates the normonatremia. Table shows hazard ratios for covariates and sodium as a continuous variable (A). Cox proportional survival curves at the mean of covariates for (B) unadjusted 6-week mortality stratified by normo-, hypo-, and hypernatremia, (C) 6-week mortality adjusted for age, sex assigned at birth, a history of chronic kidney disease, and a history of hypertension stratified in normo-, hypo-, and hypernatremia. *** indicates a p-value <0.001

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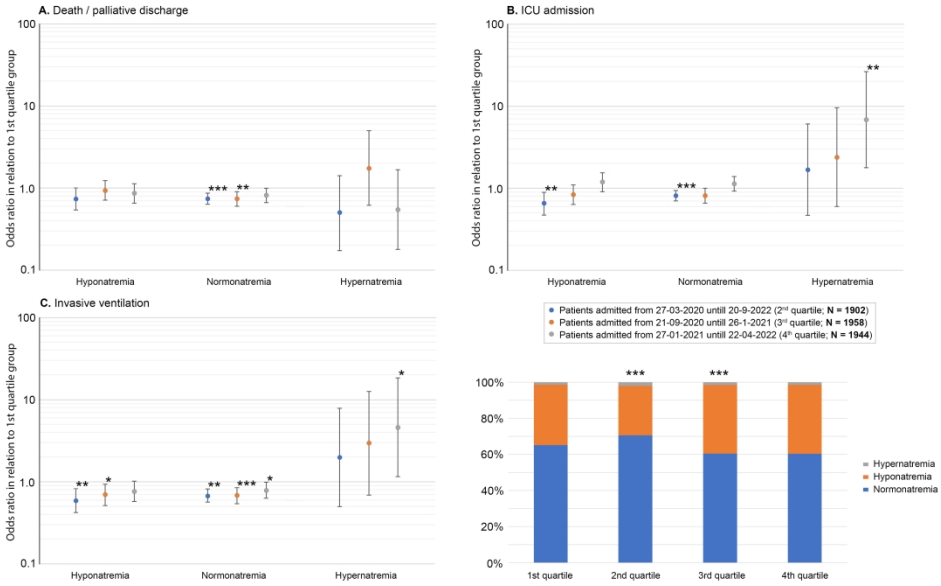

Figure 2. Odds ratio for adverse outcomes (death / palliative discharge (A), intensive care unit admission (B) invasive ventilation (C)) in each quartile compared to patients in the first quartile (admitted before 27-03-2020; N = 2002) for patients with hypo-, hyper-, or normonatremia at admission. * Indicates a p-value <0.05, ** indicates a p-value < 0.01, *** indicates a p-value <0.001 for the odds ratio as calculated by binary logistic regression. (D) incidence of hypo-, normo-, and hypernatremia in each quartile, *** indicates a p-value <0.001 as compared to the first quartile for the chi-square statistic with Bonferroni post-hoc correction.

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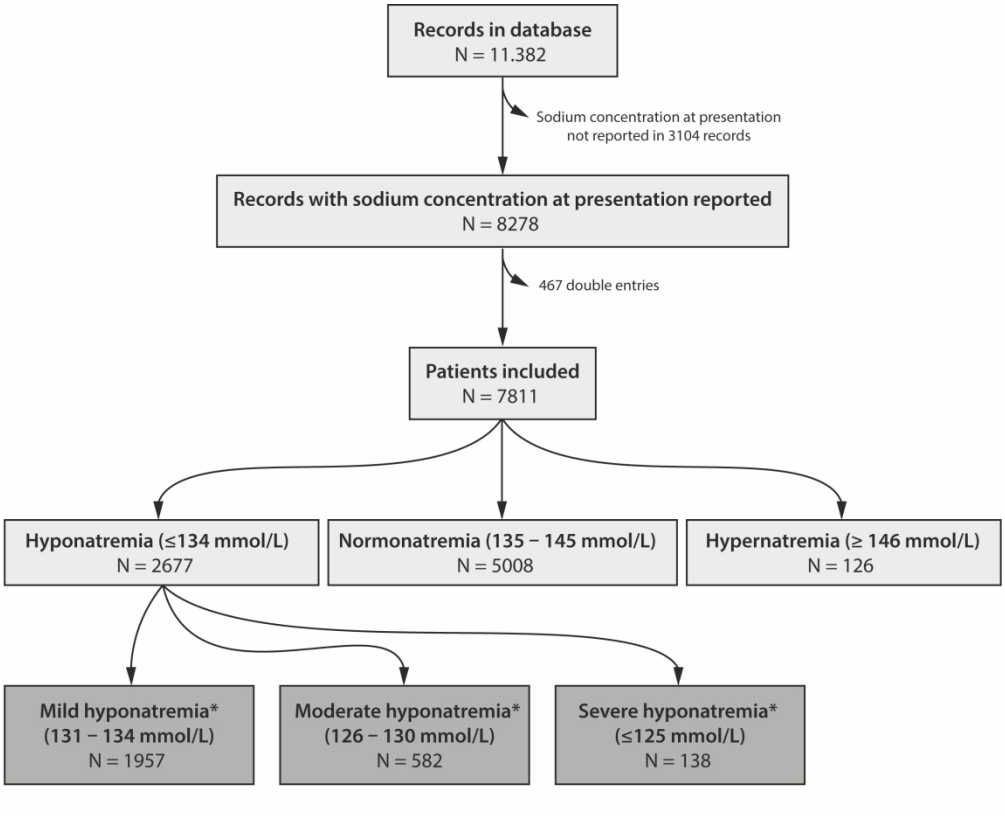

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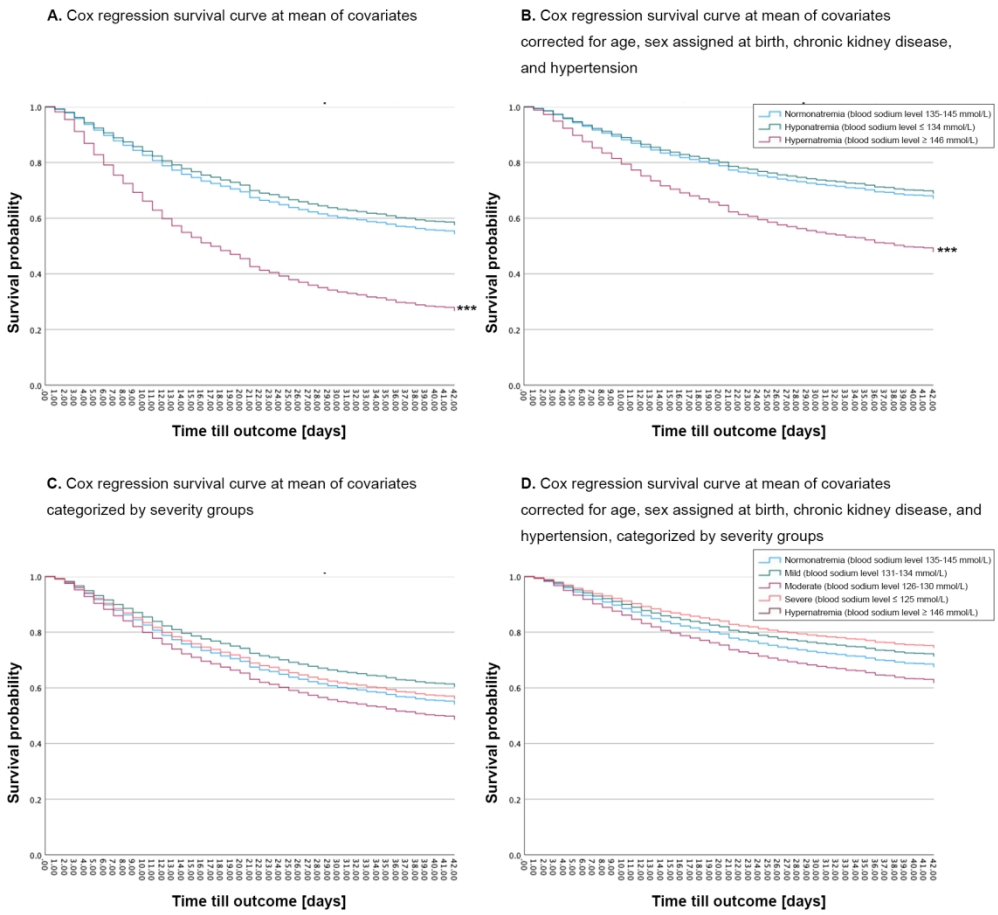

Supplemental Figure 2. Cox proportional survival curves at the mean of covariates for (A) unadjusted 6-week mortality categorized by normo-, hypo-, and hypernatremia, (B) 6-week mortality adjusted for age, sex assigned at birth, a history of chronic kidney disease, and a history of hypertension stratified in normo-, hypo-, and hypernatremia, (C) unadjusted 6-week mortality stratified in normo- and hypernatremia and mild, moderate, and severe hyponatremia, and (D)) 6-week mortality adjusted for age, sex assigned at birth, a history of chronic kidney disease, and a history of hypertension stratified in normo- and hypernatremia and mild, moderate, and severe hyponatremia. * Indicates a p-value <0.05, *** indicates a p-value <0.001

161x150mm (300 x 300 DPI)

Outcomes of COVID-19 patients presenting with dysnatremia: an observational study

Supplemental information

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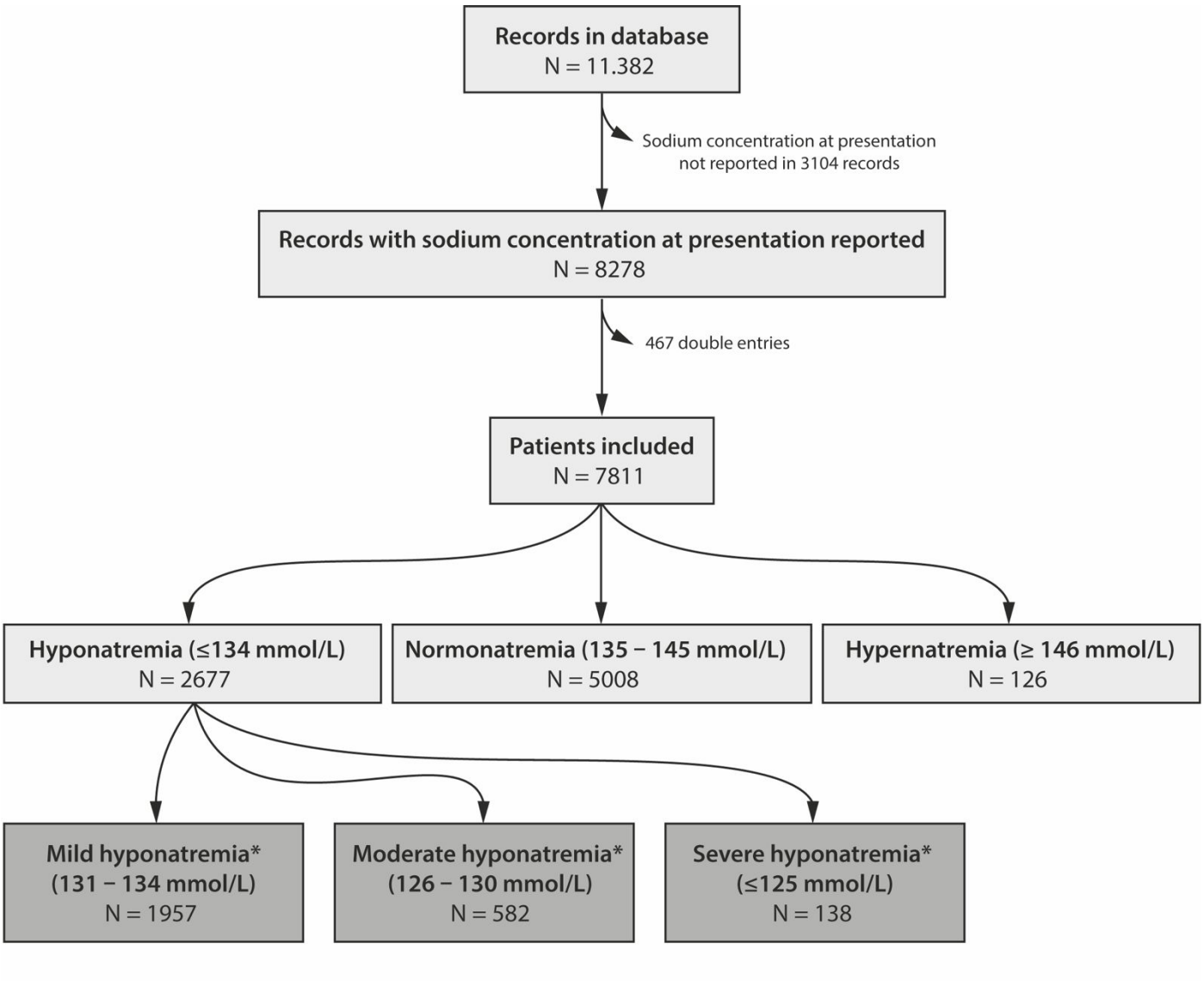


Supplemental Figure 1. Flow chart of included patients. Sodium concentrations indicate corrected serum sodium concentrations at hospital presentation * indicates the subgroup analysis as provided in the supplemental information.

Supplemental Table 1 – Subgroup analysis of patient characteristics

Comorbidity	**Included diseases**
Chronic pulmonary disease	Alpha-1 trypsin deficiency; asbestosis; cryptogenic organizing pneumonia; lymphangioeiomyomatosus; lung disease immuno-deficiency and chromosome breakage syndrome; bronchopulmonary dysplasia; primary ciliary dyskinesia; bronchiectasis; cystic fibrosis; chronic bronchitis or emphysema; lung fibrosis; sarcoidosis; obstructive sleep apnea; pulmonary hypertension
Chronic cardiac disease	**Chronical heart disease:** Myocardial infarction; Cardiac arrhythmias (AVNRT, atrial fibrillation, (supra)ventricular tachycardia, ventricular tachycardia, brugada syndrome, sick sinus syndrome, wolf parkinson white syndrome; decompensated heart failure, cardiomyopathy; valve disease (aortic valve stenosis, aortic valve insufficiency **Congential heart disease:** aortic valve insufficiency or aortic valve stenosis; Atrial septal defect or ventricular septal defect; hypoplastic left heart syndrome; Ebstein's anomaly; patent ductus arteriosis; tetralogy of Fallot; transposition of the great vessels
Chronic kidney disease	Acute tubulointerstitial nephritis; hemolytic uremic syndrome (HUS); amyloidosis; Anti-glomerular basement membrane disease; bartter syndrome; kidney damage due to medication, chronic bladder infections / kidney infections / diabetes, high blood pressure, arteriosclerosis; cryoglobulinemia, renal cystic disease; cystinosis; dense deposit disease (DDD); Focal segmental glomerulosclerosis (FSGS); Gitelman syndrome; glomerulonephritis; HNF1beta associated kidney disease; renal fusion (horseshoe kidney); IgA nephropathy; medullary sponge kidney; membranous nephropathy; minimal change disease; solitary kidney; Nail-patella syndrome (NPS); nephrogenic diabetes insipidus; nephroptosis; nephrotic syndrome; renal angiolipoma; renal cell carcinoma; primary hyperoxaluria; reflux nephropathy; atrophic kidney; scleroderma; lupus nephritis; Alport's syndrome; systemic vasculitis
Chronic liver disease	Liver disease that caused cirrhosis (e.g. Budd Chiari, hemochromatosis, hepatitis, Wilson's disease)

Supplemental Table 2 – *Subgroup analysis of patient characteristics*

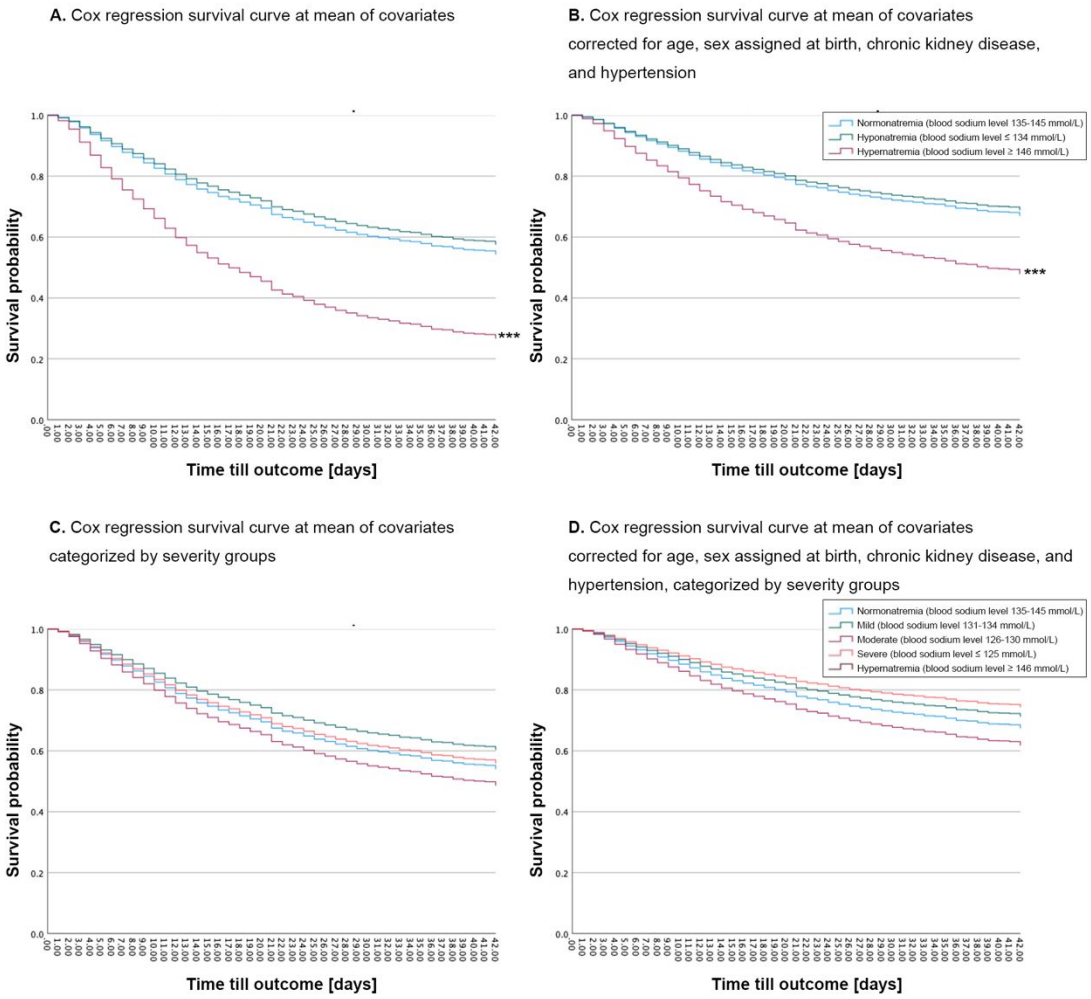
	Na 135 – 145 mmol/L N = 5008	Na 134 mmol/L N = 2677	Na 131 – 134 mmol/L N = 1957	Na 126 – 130 mmol/L N = 582	Na 125 mmol/L N = 138
Sex assigned at birth (N (%))	♂ 2946 (58.8 %) ♀ 2060 (41.2 %)	♂ 1673 (62.5%) ** ♀ 1003 (37.5%)	♂ 1249 (63.9%) *** ♀ 707 (36.1%)	♂ 363 (62.4%) ♀ 219 (37.6%)	♂ 61 (44.2%) *** ♀ 77 (55.8%)
Age (median age in years (IQR))	N = 5008 66.1 (55.0-76.0)	N = 2675 67.0 (58.0-77.0) **	N = 1956 67.0 (57.0 – 76.0)	N = 581 68.1 (60.0 – 78.0) ***	N =138 70.6 (62.0 – 79.3) ***
BMI (median BMI in kg/m^2 (IQR))	N = 3374 27.7 (24.6 – 31.6)	N = 1740 27.2 (24.2 – 31.1) **	N = 1271 27.4 (24.4 – 31.5)	N = 379 26.3 (23.4 – 30.3) ***	N = 90 26.9 (23.7 – 30.9)
Order 'Do not intubate' (N (%))	796 / 2469 (32.2 %)	440 / 1442 (30.5 %)	304 / 1043 (29.1 %)	108 / 322 (33.5 %)	28 / 77 (36.4 %)
Chronic cardiac disease (N (%))	1334 / 4982 (26.8 %)	760 / 2666 (28.5%)	541 / 1948 (27.8 %)	187 / 581 (32.2 %)	32 / 137 (23.4 %)
Hypertension (N (%))	1889 / 4586 (41.2 %)	**1055 / 2374 (44.4 %)** **	749 / 1735 (43.2 %)	240 / 520 (46.2 %)	**66 / 119 (55.5 %)** **
Chronic pulmonary disease (N (%))	844 / 4979 (17.0 %)	466 / 2662 (17.5 %)	328 /1945 (16.9 %)	111 / 580 (19.1 %)	27 / 137 (19.7 %)
Chronic kidney disease (N (%))	491 / 4587 (10.7 %)	329 / 2379 (13.8 %) ***	220 / 1738 (12.7 %)	92 / 522 (17.6 %) ***	17 / 119 (14.3 %)
Moderate to severe liver disease (N (%))	50 / 4972 (1.0 %)	30 / 2662 (1.1%)	25 / 1947 (1.3%)	3 / 579 (0.5 %)	2 / 136 (1.5%)
Diabetes (N (%))	1261 / 4972 (25.4 %)	664 / 2662 (24.9 %)	481 / 1946 (24.7 %)	148 / 579 (25.6 %)	35 / 137 (25.5 %)
Immunosuppressives (N (%))	295 / 4445 (6.6 %)	192 / 2283 (8.4 %) **	129 / 1669 (7.7 %)	56 / 497 (11.3 %) **	7 / 117 (6.0 %)
Thiazide diuretics (N (%))	394 / 4994 (7.9 %)	258 / 2671 (9.7 %) **	186 / 1953 (9.5 %)	55 / 580 (9.5 %)	17 / 138 (12.3 %)
Loop diuretics (N (%))	389 / 4994 (7.8 %)	187 / 2671 (7.0 %)	128 / 1953 (6.6 %)	50 / 580 (8.6 %)	9 / 138 (6.5 %)
SSRIs (N (%))	164 / 4994 (3.3 %)	78 / 2671 (2.9 %)	53 / 1953 (2.7%)	15 / 580 (2.6%)	10 / 138 (7.2 %)

*BMI = body mass index; IQR = interquartile range; % = percentage of patients in this group with indicated characteristic**;** SSRI = Selective Serotonin Reuptake inhibitor. SNRI = Selective Serotonin and Noradrenalin Reuptake inhibitor. Significance was assessed using a Kruskal Wallis test with post-hoc correction (for numerical data; non-normally distributed) or Chi-square test (for categorical data). p – values for all groups indicate the adjusted significance after post-hoc correction when compared to the normonatremia group.* * Indicates a p-value <0.05, ** indicates a p-value <0.01, *** indicates a p-value <0.001

Supplemental Table 3 – Subgroup analysis of signs and symptoms

Signs and symptoms	Na 135 – 145 mmol/L N = 3206	Na 134 mmol/L N = 1821	Na 131 – 134 mmol/L N = 1346	Na 126 – 130 mmol/L N = 383	Na 125 mmol/L N = 92
Nausea / vomiting (N (%))	1150 / 4129 (27.9 %)	679 / 2273 (29.9 %)	490 / 1663 (29.5 %)	151 / 499 (30.3 %)	38 / 111 (34.2%)
Diarrhea (N (%))	1146 / 4157 (27.6 %)	804 / 2298 (35.0%) ***	574 / 1686 (34.0 %) ***	180 / 501 (35.9%) ***	50 / 111 (45.0 %) ***
Anosmia (N (%))	352 / 3330 (10.6 %)	244 / 1904 (12.8 %)**	174 / 1395 (12.5 %)	62 / 420 (14.8 %)	8 / 89 (9.0 %)
Confusion (N (%))	651 / 4381 (14.9 %)	311 / 2319 (13.4%)	207 / 1688 (12.3 %)	78 / 511 (15.3 %)	26 / 120 (21.7 %)
Seizures (N (%))	31 / 3452 (0.9 %)	10 / 1977 (0.5%)	6 / 1448 (0.4 %)	2 / 434 (0.5 %)	2 / 95 (2.1 %)
FiO2 (median fraction (IQR))	N = 2084 0.36 (0.28 – 0.50)	N = 1159 0.36 (0.28 – 0.50)	N = 848 0.36 (0.28 – 0.48)	N = 258 0.36 (0.32 – 0.60)	N = 53 0.36 (0.31 – 0.75)
SBP (mean SBP in mmHg (SD))	N = 2648 132 (± 22)	N = 4971 135 (±23)***	N = 1934 132 (±22) ***	N = 578 132 (±22)**	N = 136 138 (±27)
HR (mean HR in BPM (SD))	N = 4965 91 (±20)	N = 2661 92 (±18) **	N = 1946 92 (±18) *	N = 580 92 (±18)	N = 135 90 (±19)
Disturbed capillary refill (N (%))	93 / 1369 (6.8 %)	81 / 863 (9.4 %)	51 / 614 (8.3 %)	27 / 206 (13.1 %)	3 / 43 (7.0 %)
Blood urea level (median level n mmol/L (IQR))	N = 4776 6.2 (4.5 – 9.2)	N = 2549 6.3 (4.5 – 9.3)	N = 1892 6.3 (4.6 – 9.1)	N = 559 6.2 (4.5 – 10.2)	N = 128 5.5 (4.2 – 9.8)
eGFR rate using 2021 CKD-epi creatinine equation in (median clearance in ml/min/1.73 m^3 (IQR))	N = 4983 68 (46 – 94)	N = 2656 64 (45 – 90) ***	N = 1944 64 (46 – 89) ***	N = 575 63 (41 – 90) ***	N = 137 79 (46 – 92)
CT-severity score (mean score (SD))	N = 1401 12.1 (±5.6)	N = 909 12.4 (±5.5)	N = 684 12.3 (±5.4)	N = 190 12.6 (±5.4)	N = 35 12.5 (±6.7)
Blood CRP level (median level in mg/L (IQR))	N = 4939 70.8 (28.0 – 131)	N = 2646 93.1 (49.0 – 154) ***	N = 1933 93.0 (48.2 – 151) ***	N = 577 103 (54.6 – 166) ***	N = 136 82.5 (36.0 – 145)
Blood LDH level (median level in U/L (IQR))	N = 4226 323 (247 – 426)	N = 2238 349 (268 – 471) ***	N = 1651 346 (269 – 467) ***	N = 479 361 (269 – 482) ***	N = 108 331 (240 – 543)
Modified early warning score (MEWS) (median score (IQR))	N = 4055 3.0 (2.0 – 4.0)	N = 2337 3.0 (2.0 – 4.0) ***	N = 1709 3.0 (2.0 – 4.0) ***	N = 509 3.0 (2.0 – 4.0)	N = 119 3.0 (2.0 – 4.0)
Quick sequential organ failure assessment (median score (IQR))	N = 4131 1.0 (0.0 – 1.0)	N = 2373 (0.0 – 1.0)	N = 1735 1.0 (0.0 – 1.0)	N = 517 1.0 (0.0 – 1.0)	N = 121 1.0 (0.0 – 1.0)

SBP = systolic blood pressure; HR = heart rate; CKD-epi = chronic kidney disease Epidemiology Collaboration BPM = beats per minute; IQR = interquartile range; SD = standard deviation; CRP = c-reactive protein; LDH = lactate dehydrogenase; % = percentage of patients in this group with indicated characteristic. Significance was assessed using a Kruskal wallis test with post-hoc correction (for numerical data) or Chi-square test (for categorical data). * Indicates a p-value <0.05, ** indicates a p-value <0.01, *** indicates a p-value <0.001



Supplemental Figure 2. Cox proportional survival curves at the mean of covariates for (A) unadjusted 6-week mortality categorized by normo-, hypo-, and hypernatremia, (B) 6-week mortality adjusted for age, sex assigned at birth, a history of chronic kidney disease, and a history of hypertension stratified in normo-, hypo-, and hypernatremia, (C) unadjusted 6-week mortality stratified in normo- and hypernatremia and mild, moderate, and severe hyponatremia, and (D)) 6-week mortality adjusted for age, sex assigned at birth, a history of chronic kidney disease, and a history of hypertension stratified in normo- and hypernatremia and mild, moderate, and severe hyponatremia. * Indicates a p-value <0.05, *** indicates a p-value <0.001

Supplemental Table 4 – Subgroup analysis of outcome and complications

Outcome	Na 135 – 145 mmol/L N = 3206	Na 134 mmol/L N = 1821	Na 131 – 134 mmol/L N = 1346	Na 126 – 130 mmol/L N = 383	Na 125 mmol/L N = 92
Death or palliative discharge (N (%))	729 / 4568 (16.0 %)	405 / 2360 (17.2 %) [A]OR 1.042 (0.906 – 1.200)	269 / 1723 (15.6 %)	115 / 518 (22.2 %)	21 / 119 (17.6 %)
ICU-admission (N (%), 'do not intubate' excluded	710 / 3778 (18.8 %)	439 / 1923 (22.8 %) [A]OR 1.274 (1.112 – 1.458)***	314 / 1422 (22.1 %) [A]OR 1.205 (1.036 – 1.401)*	104 / 410 (25.4 %) [A]OR 1.487 (1.170 – 1.889)***	21 / 91 (23.1 %) [A]OR 1.431 (0.868 – 2.360)
Invasive ventilation (N (%)), 'do not intubate' excluded	623 / 3706 (16.8 %)	352 / 1889 (18.6 %) [A]OR 1.122 (0.970 – 1.298)	250 / 1396 (17.9 %)	85 / 402 (21.1 %)	17 / 91 (18.7 %)
Discharge alive within 42 days; N indicating the number of non-censored cases	N = 2747	N = 1527 [A]HR 0.955 (0.897 – 1.017) p = 0.154	N = 1153	N = 302	N = 72
Complications	**Na 135 – 145 mmol/L N = 3206**	**Na 134 mmol/L N = 1821**	**Na 131 – 134 mmol/L N = 1346**	**Na 126 – 130 mmol/L N = 383**	**Na 125 mmol/L N = 92**
Bacterial pneumonia (N (%))	501 / 4307 (11.6 %)	289 / 2212 (13.1 %) [A]OR 1.123 (0.962 – 1.312)	207 / 1619 (12.8 %)	72 / 483 (14.9 %)	10 / 110 (9.1 %)
Aspergillosis pneumonia (N (%))	83 / 3456 (2.4 %)	67 / 1915 (3.5 %) [A]OR 1.436 (1.034 – 1.993)	49 / 1402 (3.5 %) [A]OR 1.426 (0.995 – 2.044)	14 / 417 (3.4 %) [A]OR 1.352 (0.759 – 2.410)	4 / 96 (4.2 %) [A]OR 1.839 (0.657 – 5.148)
ARDS (N (%))	404 / 4323 (9.3 %)	224 / 2223 (10.1 %) [A]OR 1.081 (0.909 – 1.286)	161 /1627 (9.9 %)	52 / 486 (10.7 %)	11 / 110 (10.0 %)
Treatment for septic shock (N (%)) &	135 / 4175 (3.2 %)	94 / 2153 (4.4 %) [A]OR 1.326 (1.013 – 1.737)*	66 / 1570 (4.2 %) [A]OR 1.274 (0.943 – 1.721)	25 / 478 (5.2 %) [A]OR 1.570 (1.012 – 2.438)*	3 / 105 (2.9%) [A]OR 0.920 (0.287 – 2.946
Congestive heart failure (N (%))	125 / 4352 (2.9 %)	64 / 2235 (2.9 %) [A]OR 0.946 (0.696 – 1.287)	34 / 1637 (2.1%)	23 / 488 (4.7 %)	7 / 110 (6.4 %)
Physical decline (N (%))	950 / 4126 (23.0 %)	576 / 2116 (27.2 %) [A]OR 1.221 (1.082 – 1.377)**	414 / 1544 (26.8 %) [A]OR 1.206 (1.054 – 1.380)**	136 / 468 (29.1 %) [A]OR 1.303 (1.053 – 1.614)*	26 / 104 (25.0 %) [A]OR 1.059 (0.674 – 1.666)
Delirium (N (%))	451 / 4146 (10.5 %)	237 / 2136 (11.1 %) [A]OR 0.987 (0.833 - 1.170)	157 / 1557 (10.1 %)	62 / 474 (13.1 %)	18 / 105 (17.1 %)

ICU = Intensive care unit; ARDS = acute respiratory distress syndrome. OR = odds ratio [A]OR = adjusted odds; odds ratio corrected for sex assigned at birth and age. [#]Uncorrected for sex assigned at birth and age [&] Treatment for septic shock was defined as the need for vasopressors in order to maintain mean arterial blood pressure >65 mmHg and blood lactate level >2 mmol/L, in the absence of other causes including hypovolemia. Significance was assessed using a Kruskal wallis test with post-hoc correction (time to discharge alive) or logistic regression (all other values). * Indicates a p-value <0.05, ** indicates a p-value <0.01, *** indicates a p-value <0.001

Supplemental Table 5 – Patient characteristics, signs and symptoms, outcome measures, and complications of patients with hyponatremia (Na ≤ 134 mmol/L) that did not use diuretics stratified based on their urinary sodium excretion.

02 **Patient characteristics**	**Urinary sodium excretion 30 mmol/L** % or IQR N = 72	**Urinary sodium excretion 30 mmol/L** % or IQR N = 73	**p - value**
Age (median age in years (IQR))	N = 72 67 (56 – 74)	N = 73 69 (59 – 76)	p = 0.47
Sex assigned at birth (N (%))	♂ 38 (53%) ♀ 34 (47%)	♂ 43 (59%) ♀ 30 (41%)	p = 0.51
Vomiting/nausea (N (%))	32 / 71 (45.1 %)	19 / 67 (28.4 %)	p = 0.05
Diarrhea (N (%))	26 / 67 (38.8 %)	28 / 68 (41.2 %)	p = 0.86
Heart rate (mean HR in BPM (SD))	N = 71 89.7 (± 16.3)	N = 72 93.1 (±18.9)	p = 0.20
Systolic blood pressure (mean SBP in mmHg (SD))	N = 70 135 (± 24.8)	N = 71 137 (±24.1)	p = 0.87
Disturbed capillary refill (N (%))	3 / 27 (11.1 %)	4 /31 (12.9 %)	p = 1.00
eGFR rate using 2021 CKD-epi creatinine equation in (median clearance in ml/min/1.73 m^3 (IQR))	N = 71 67 (49 – 90)	N = 73 71 (32 – 92)	p = 0.49
CRP (median level in mmol/L (IQR))	N = 70 111 (52.5 – 163)	N = 71 70 (35.0 – 154)	**p = 0.028**
LDH (median level in U/L (IQR))	N = 57 351 (270 – 491)	N = 61 273 (227 – 434)	**p = 0.021**
CT-severity score (median score (IQR))	N = 33 11.0 (7.0 – 15.0)	N = 40 12.0 (6.0 – 16.8)	p = 0.86
Outcome			
Death or palliative discharge (N (%))	14 / 72 (19.4%)	18 / 73 (24.7 %)	p = 0.55
ICU-admission (N (%), 'do not intubate' excluded	24 / 65 (36.9 %)	25 / 61 (41.0 %)	p = 0.72
Invasive ventilation (N (%)), 'do not intubate' excluded	18 / 64 (28.1 %)	23 / 60 (38.3 %)	p = 0.26

CRP = C-reactive protein; LDH = lactate dehydrogenase; CT = computed tomography; ICU = intensive care unit; eGFR = estimated glomerular filtration rate; CKD-epi = chronic kidney disease Epidemiology Collaboration. Significance was assessed using a Mann-Whitney test (for numerical data) or Chi-square test (for categorical data). p – values for all groups indicate the 2-tailed significance between the two groups.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6 and 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6 and 7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6 and 7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	FIG 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1, p 24
		(b) Indicate number of participants with missing data for each variable of interest	Table 1-4, p 24 to 29
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	FIG 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3, p 27-29
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8, 9, 11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

What is the etiology of dysnatremia in COVID-19 and how is this related to outcomes in patients admitted during earlier and later COVID-19 waves? A multicentre, retrospective observational study

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What is the etiology of dysnatremia in COVID-19 and how is this related to outcomes in patients admitted during earlier and later COVID-19 waves? A multicentre, retrospective observational study

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Abstract

Objectives

To evaluate the relation between dysnatremia at hospital presentation and duration of admission, risk of ICU-admission, and all-cause mortality and to assess the underlying pathophysiological mechanism of hyponatremia in COVID-19 patients. Our hypothesis is that both hypo- and hypernatremia at presentation are associated with adverse outcomes.

Design

Observational study

Setting

Secondary care; nine Dutch hospitals (2 university and 9 general hospitals)

Participants

An analysis was performed within the retrospective multicenter cohort study COVIDPredict. 7811 patients were included (60% males, 40% females) between February 24th 2020 and august 19th 2022. Patients who were ≥18 years with PCR-confirmed COVID-19, or CT with COVID-19 reporting and data system score ≥4 and alternative diagnosis were included. Patients were excluded when serum sodium levels at presentation were not registered in the database or when they had been transferred from another participating hospital.

Outcome measures

We studied demographics, medical history, symptoms, and outcomes. Patients were stratified according to serum sodium concentration and urinary sodium excretion.

Results

Hyponatremia was present in 2677 (34.2%) and hypernatremia in 126 (1.6%) patients. Patients with hyponatremia presented more frequently with diarrhea, lower blood pressure, and tachycardia. Hyponatremia was, despite a higher risk for ICU admission (OR 1.27 (1.11-1.46; p <0.001), not associated with mortality or the risk for intubation. Patients with hypernatremia had higher mortality rates

(OR 2.25 1.49 – 3.41; p <0.001) and were at risk for ICU-admission (OR 2.89 (1.83 – 4.58) and intubation (OR 2.95 (1.83 – 4.74).

Conclusions

Hypernatremia at presentation was associated with adverse outcomes in COVID-19 patients. Hypovolemic hyponatremia was found to be the most common etiology of hyponatremia. Hyponatremia of unknown etiology was associated with a higher risk for ICU admission and intubation and longer duration of admission.

Strengths and limitations of this study

- This study includes over 7000 patients from different COVID-19 waves and from multiple hospitals, resulting in an heterogenous patient population;
- This study relates the different presumed etiologies to clinical outcomes;
- A relative low number of urinary samples was available for patients with hyponatremia;
- Different treatment options that became available for COVID-19 during the ongoing pandemic were not taken into account in thus study, which may have influenced the outcome of patients.

1. Introduction

The coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic since February 2020. By the time of October 19th, 2022, there had been over 621 million reported cases and 2.9 million deaths attributed to coronavirus disease 19 (COVID-19), which is caused by SARS-COV-2-infection. Respiratory failure resulting from acute respiratory distress syndrome is the leading cause of death associated with SARS-CoV-2 infection[3 20 21].

Common signs and symptoms of COVID-19 infection vary widely, but fever, cough, and dyspnea are frequently present. Other less frequent symptoms include anosmia, nausea, vomiting, diarrhea, and general illness[3]. In addition to these clinical symptoms, certain laboratory markers can indicate COVID-19. Elevated lactate dehydrogenase (LDH) levels and lymphopenia are commonly observed[18 22]. Furthermore, electrolyte imbalances such as hypocalcemia, hypokalemia, and dysnatremia (hypo- or hypernatremia) are often present in COVID-19 patients upon hospital admission[15 18]. Hyponatremia, in particular, has been reported in 7% to 64% of COVID-19 cases[2 6 23-25], compared to 20-30% in all hospitalized patients[26]. It has been demonstrated that critically ill patients with COVID-19 more frequently develop hyponatremia during the first 72 hours of admission[7]. Hyponatremia is also frequently present in other infectious diseases, such as pneumonia, tuberculosis, meningitis, human immunodeficiency virus (HIV) infection, malaria, and leishmaniasis and has been linked to negative outcomes in these diseases and in COVID-19[2 4 19 23 25 27 28].On the other hand, hypernatremia is less common, occurring in less than 10% of the general population and in up to 38% of patients in intensive care units. Hypernatremia is also associated with adverse clinical outcomes[1 6 12 13 19].

The etiology of hyponatremia in infectious diseases, including COVID-19, can broadly be categorized into two groups based on urinary sodium excretion (USE). Low USE (<30 mmol/l) indicates an activation of the renin-angiotensin system (RAAS), e.g. due to hypovolemia resulting from inadequate dietary intake, vomiting or diarrhea. Conversely, high USE suggests RAAS inactivation, which could occur in patients with syndrome of inappropriate antidiuretic hormone secretion (SIADH) and in patients with critical illness-related corticoid deficiency, although diuretic usage can affect diagnostic accuracy[16 29]. In other infectious diseases, antidiuretic hormone (ADH) release has been linked to secretion of inflammatory marker interleukin-6[30]. Interleukin-6 is also enhanced in COVID-19 patients and is targeted

by off-label administration of interleukin-6-inhibitors, like tocilizumab and sarilumab[21 31]. Both etiologies (hypovolemic hyponatremia and inadequate ADH secretion) have been proposed to contribute to hyponatremia in COVID-19, although the exact mechanism is still unclear. Hypernatremia primarily occurs due to insufficient water intake, often caused by hypothalamic thirst center dysfunction or limited access to fluid intake. It can also result from diabetes insipidus, a condition characterized by ADH deficiency or resistance[32].

Previous studies have associated both hyponatremia and hypernatremia with worse clinical outcomes in COVID-19 patients during the early stages of the pandemic[1 2 4 23 25 28]. However, most of these studies were conducted before interleukin-6 inhibitors were administered and before the registration of Sars-CoV-2 vaccines[1 21 23 25 33-36]. Additionally, they lacked data on clinical parameters at presentation and how they differed between patients with or without dysnatremia, making it difficult to determine the underlying cause of the hyponatremia and to relate this cause to clinical outcomes[19 34 37-39].

This study reports the incidence rates of hypo- and hypernatremia upon admission in COVID-19 patients from a large multi-center cohort study in The Netherlands, encompassing multiple COVID-19 waves. We hypothesize that both hyponatremia and hypernatremia can predict adverse outcomes, including ICU admission, the need for invasive ventilation, and mortality rates among hospitalized COVID-19 patients. Furthermore, we seek to investigate potential pathophysiological mechanisms underlying these conditions based on clinical features and laboratory values at presentation.

2. Methods

2.1 Patient recruitment and public involvement

We utilized data from the ongoing retrospective multicenter COVIDPredict Clinical Course Cohort, containing over 6500 patients with COVID-19, recruited between February 24th, 2020, and August 9th, 2022, in nine Dutch hospitals (two university and nine general hospitals). Inclusion criteria for the database required patients to be 18 years or older and either had a positive polymerase chain reaction (PCR) test for SARS-CoV-2 or had a COVID-19 reporting data system (CO-RADS) score of 4 (indicating abnormalities suspicious for COVID-19) or 5 (indicating typical COVID-19) on thoracic computed tomography (CT)-scan in the absence of an alternative diagnosis[40]. A waiver for the use of hospital data was obtained from the Medical Ethical Committees of the participating centers (Amsterdam UMC; 20.131) to utilize the hospital data. Patients were given the opportunity to opt out. To avoid duplicate entries, patients transferred from one participating hospital to another were excluded, resulting in a total 297 exclusions.

2.2 Study design

The included patients were categorized into three groups based on their serum sodium concentration upon admission to the participating hospital. The serum sodium concentration was adjusted for serum glucose concentration, whenever available, following the method described by Hillier, et al. [41]. The sodium concentrations were stratified as follows: 'normonatremia' (corrected serum sodium concentration (Na) 135-145 mmol/L), hyponatremia (corrected serum sodium concentration (Na) <135 mmol/L), further subcategorized as 'mild' (corrected serum sodium concentration Na 131-134 mmol/L), 'moderate' (corrected serum sodium concentration Na 126-130 mmol/L), and 'severe' (corrected serum sodium concentration Na $\leq$ 125 mmol/L) (Supplemental information). 'Hypernatremia' referred to corrected serum sodium concentration Na $\geq$ 146 mmol/L. Throughout the text, serum sodium concentrations and sodium groups refer to the corrected sodium values unless otherwise specified.

Demographic information such as ethnicity, sex at birth, and age, as well as co-morbidities categorized according to predetermined groups (additional information in the Supplemental Information), home medication, and presenting signs and symptoms were compared between the

groups and between normonatremia and different severity categories of hyponatremia (Supplemental information). Serum concentrations of creatinine, urea, C-reactive protein (CRP), and LDH were measured at the time of first presentation in the participating hospital. The estimated glomerular filtration rate (eGFR) was calculated using the 2021 Chronic kidney disease Epidemiology Collaboration (CKD-epi) formula based on serum creatinine levels[42]. The Modified Early Warning Score (MEWS) and Quick Sequential Organ Failure Assessment (qSOFA) were calculated based in clinical values obtained at presentation.

The following clinical outcome measures were compared between the groups and across different severity categories: duration of hospitalization, admission to intensive care unit, invasive ventilation, duration of ICU admission, discharge alive, death, and the administration of tocilizumab, sarilumab, or anakinra. Additionally, the incidence of complications was compared between the groups.

2.3 Statistical analysis

All data were analyzed using SPSS version 27. Comparisons were conducted between hyper-, normo-, and hyponatremia (Main Text) and between the normonatremia, mild, moderate, and severe hyponatremia groups (Supplemental Information). Baseline numerical data were presented as median and interquartile range, and the Kruskal Wallis test was used for analysis when the data were not normally distributed. For normally distributed data, baseline numerical data were presented as mean and standard deviation, and one-way ANOVA was employed for analysis. Baseline categorical data were displayed as absolute number and percentage of patients with the specific condition, and the Chi-square test was used for analysis.

Outcome data (risk for ICU-admission, intubation, mortality rates, use of tocilizumab, sarilumab, or anakinra, and complications) were assessed using a binary logistic regression model. The odds ratios were calculated and adjusted for age, sex assigned at birth (categorized as male or female based on genotype and internal and external anatomy at birth), a history of chronic kidney disease, and a history of hypertension. The duration of hospital and ICU admission were evaluated using a Kruskal Wallis test. Survival analysis over a 6-week period from hospital admission was conducted using Cox proportional hazard regression analysis to estimate cumulative mortality rates and cumulative rates for being

discharged alive for patients with and without dysnatremia. The hazard ratios were adjusted for age, sex assigned at birth, a history of chronic kidney disease, and a history of hypertension.

A p-value of ≤ 0.05 was considered statistically significant for all statistical tests. Patients who did not have data available for the specific variable being tested were excluded from the corresponding analysis.

2.4 Patients and public involvement

This study was largely conducted during the first waves of the COVID-19 pandemic. As a result, it was not feasible to directly involve patients in the design of the study. Patients received information about the CovidPredict database via pamphlets and verbal communication. Additionally, information was available on the websites of participating hospitals and through various media channels. Details regarding the study design and dissemination plans are available on our website www.covidpredict.org.

3. Results

3.1 Incidence of dysnatremia at presentation

At the time of August 9th, 2022, the database contained a total of 11.382 records. Serum sodium concentrations at admission were available for 8278 (73%) admissions from 7811 patients (170 duplicate entries due to readmission and 297 patients had been transferred from or previously admitted to another participating hospital and transfer records were therefore excluded). Patients were included based on two criteria: a positive result for SARS-CoV-2 PCR (6673 patients) and or a CO-RADS score 4 or 5 in the absence of an alternative diagnosis (1138 patients). In cases where patients were readmitted, the admission with the abnormal sodium level at presentation (in case of hyponatremia or hypernatremia) or the first admission (in case sodium concentrations were normal for both presentations) was included in the analysis.

Of the 7811 included patients with COVID-19, 2677 (34.3%) presented with hyponatremia (corrected blood serum Na <135 mmol/L), and 126 (1.6%) presented with hypernatremia (corrected blood serum Na $\geq$ 146 mmol/L). Among the patients presenting with hyponatremia, 1957 (25.1%) presented with blood serum Na ranging 131-134 mmol/L (considered 'mild'), 582 (7.5%) presented with blood serum Na ranging 126-130 mmol/L (considered 'moderate'), and 138 (1.8%) with blood serum Na $\leq$ 125 mmol/L (considered 'severe') (see Supplemental Figure 1). A total of 1888 patients were included after the start of the SARS-CoV-19 vaccination campaign in the Netherlands on January 6th, 2021, of whom 445 were vaccinated (319 had received two or more doses). A total of 6183 patients (79.2%) started having symptoms prior to the seventh week of 2021, when the initial SARS-CoV-2 variants were most prevalent. 747 patients (9.6%) developed symptoms from the seventh to twenty-fifth week of 2021, when alpha-variants dominated in the Netherlands. 686 patients (8.8%) started having symptoms when delta variants dominated (twenty-sixth to fifty-first week of 2021), and 118 patients (1.5%) when the omicron variants dominated (after the fifty-second week of 2021)[17].

3.2 Patient characteristics of patients presenting with dysnatremia

Table 1 shows the characteristics of patients with hyponatremia and hypernatremia compared to patients presenting with normal sodium concentrations at presentation. Both hypo- and hypernatremia occurred more often in males than in females (Table 1), except for 'severe' hyponatremia (Supplemental Table 1). The mean age of patients with and without hyponatremia differed slightly, with patients presenting with 'moderate' or 'severe' hyponatremia being significantly older (median age 68.1 and 70.6 years, respectively). Patients with hypernatremia were also older, with a mean age of 72.5 years. The body mass index (BMI) of patients presenting with hyponatremia tended to be slightly lower compared to those with normal sodium levels and was also lower in patients presenting with hypernatremia. Abnormal sodium levels at presentation were associated with chronic kidney disease. Patients with hyponatremia, particularly those with severe hyponatremia, more frequently had a history of hypertension, but this difference was not statistically significant for the subgroup of patients who did not use diuretics (36.4% (normonatremia) vs. 39.1% (hyponatremia); p = 0.003; determined by a Chi-square test). The presence of hypo- or hypernatremia was not associated with a history of chronic heart, pulmonary, or liver disease (refer to Supplemental Table 2 for definitions). Regarding medication use, the use of thiazide diuretics was higher in patients with hyponatremia (Table 1), but the overall use of diuretics or the use of loop diuretics did not differ between the groups. Similarly, the use of selective serotonin (and noradrenalin) reuptake inhibitors (SSRIs/SNRIs) did not show significant differences between the groups. The use of immunosuppressives was more common in patients presenting with hyponatremia as compared to those with normal sodium concentration at presentation.

3.3 Signs and symptoms of patients presenting with dysnatremia

Patients with hyponatremia more frequently presented with diarrhea and anosmia compared to patients without hyponatremia (Table 2 and Supplemental Table 3). The presence of vomiting or nausea as presenting symptoms was not associated with hyponatremia. In the hypernatremia group, confusion was more frequently observed compared to patients with normal sodium levels. A prolonged capillary refill time of ≥3s, which may indicate dehydration, was more often present in the hypernatremia group.

Patients with hypernatremia also had a slightly higher heart rate. Hyponatremia was associated with a slightly higher heart rate and a slightly lower systolic blood pressure, although these differences were not clinically significant. Both patients with hypernatremia and hyponatremia had a lower eGFR, with a more pronounced effect observed in the hypernatremia group (Table 2). A lower eGFR was associated with slightly higher mortality rates (unadjusted HR 1.008, 95% CI 1.007 – 1.008); p = 0.001, analyzed using a Cox proportional hazard regression analysis), regardless of sodium levels at presentation or exclusion of patients with chronic kidney disease. Enhanced blood urea concentration was only associated with hypernatremia.

Patients with hyponatremia had higher blood CRP and LDH concentrations compared to those with normal sodium levels (Table 2). However, the fraction of supplemented oxygen (FiO2) and CT-severity scores did not differ significantly between the groups. The clinical score systems MEWS and qSOFA[43] (Table 2) also showed significant differences between the groups, but these differences were not clinically relevant.

Furthermore, patients with hyponatremia had a slightly longer duration of complaints compared to those with normonatremia (8.8 days for hyponatremia vs. 8.6 days for; p = 0.010; assessed using a Kruskal-Wallis test), although this difference was not clinically relevant.

3.4 Clinical outcomes in patients presenting with dysnatriemia

Hypernatremia was associated with higher mortality rates or palliative discharge rates compared to the normo- and hyponatremia groups (Table 3, Figure 1, and Supplemental Figure 2). Additionally, patients with hypernatremia had a higher risk of ICU-admission and invasive ventilation. However, hyponatremia was not associated with increased mortality or palliative discharge rates (Table 3). Although there was a trend towards increased mortality in patients with severe hyponatremia, these results did not reach statistical significance due to the low number of patients that presented with sodium levels ≤ 125 mmol/L (Supplemental Table 4). After excluding patients with a 'do not intubate' order hyponatremia was associated with a higher likelihood of ICU-admission, but not with the need for invasive ventilation. The duration of ICU admission was similar for patients with hypo-, normo-, and hypernatremia (Table 3). Based on the additional details provided in Supplemental Table 5, patients with the order 'do not intubate' are considered frailer and thus had limited live expectancy.

Hyponatremia corrected for glucose was used for all statistical testing. However, as some other studies used uncorrected hyponatremia[37 44], we also examined the association of uncorrected hyponatremia with different outcomes. Without correction for serum glucose concentration, hyponatremia was still associated with a slightly higher rate of ICU admission (adjusted odds ratio (^{A}OR) 1.40 (1.23 – 1.60); $p < 0.001$) and with the need for intubation (^{A}OR 1.26 (1.10 – 1.46); $p = 0.001$), but not with death or palliative discharge rates (^{A}OR 1.11 (0.97 – 1.28); $p = 0.13$).

Despite the correlation with ICU admission in patients with hyponatremia, the duration of admission was not significantly longer in this group. Similar outcomes were observed for patients with confirmed COVID-19 (SARS-CoV-2 PCR positive; 6673 patients) only, although in this subgroup, the higher risk for ICU admission for patients with hyponatremia no longer reached statistical significance.

As the COVID-19 pandemic progressed, the incidence of adverse outcomes was significantly lower in patients with normo-, and hyponatremia at presentation that were admitted after September 20th 2020 (2nd to 4th quartile) as compared to those admitted before September 20th, 2020 (1st quartile; Figure 2). However, hypernatremia was associated with a higher risk for ICU admission and invasive ventilation for patients admitted after 26-01-2022 (4th quartile; compared to patients admitted in the 1st quartile). The use of tocilizumab, sarilumab (interleukin-6 receptor agonists) and anakinra (interleukin-1 receptor agonist) did not differ between the groups. Administration of COVID-19 vaccination was not reported frequently enough to draw conclusions about its possible effects on outcome measures.

3.5 Complications associated with hyponatremia upon admission

After adjusting for sex assigned at birth, age, and a history of chronic kidney disease and hypertension, the course of disease of patients with hyponatremia was more often complicated by an aspergillosis pneumonia (almost exclusively in patients that needed invasive ventilation and more frequently in patients treated with dexamethasone, antibiotics, tocilizumab, sarilumab, or anakinra) and physical decline (the latter was scored when explicitly documented in the patients' medical records, when the patient suffered from 'ICU-acquired weakness', or when the patient was referred for medical rehabilitation).

Patients with hypernatremia, on the other hand, were more likely to experience acute respiratory distress syndrome and receive treatment for septic shock (defined as the need for vasopressors in order

to maintain mean arterial blood pressure >65 mmHg and blood lactate level >2 mmol/L, in the absence of other causes including hypovolemia). They also had a higher incidence of delirium. It should be noted that excessive fluid resuscitation for the management of hypo- or hypernatremia could potentially lead to congestive heart failure, but the occurrence of this complication was rare and did not occur more frequently in patients with abnormal sodium values at presentation.

3.6 Urinary sodium excretion related to patients' characteristics and outcomes

USE was measured in 185 (6.9%) patients with hyponatremia of whom 145 (78%) did not use diuretics. Among these patients were 48 with 'mild', 67 with 'moderate', and 30 with 'severe' hyponatremia. The range of USE was 5.0 to 239 mmol/L, with a median of 30.0 mmol/L. Urinary osmolarity (UOL) was measured in 81 (3.0%) patients who did not use diuretics, including 26 with 'mild', 37 with 'moderate', and 18 with 'severe' hyponatremia. The range of UOL values was 8 - 1007 mOsmol/kg, with a median of 496 mOsmol/kg. Among patients in whom both USE and UOL were measured, 12 patients (15% of the total) met the definition of SIADH (USE ≥ 30 mmol/L and UOL $\geq$ 100 mOsmol/kg in the absence of diuretic use and signs of hypovolemia (systolic blood pressure < 90 mmHg or heart rate $\geq$ 100 BPM)).

Patients were divided in two groups based on USE. Out of urinary sodium measurements, 72 patients (49.7%) had low USE (< 30 mmol/L), indicating activation of the RAAS, while 73 patients (50.3%) had high USE (≥ 30 mmol/L), indicating activation of the RAAS (Supplemental Table 6). A low USE was associated with a higher levels of CRP (111 (52.5 – 163) mmol/L vs. 70 (35.0 – 154) mmol/L; p = 0.028) and LDH (351 (270 – 491) U/L vs. 273 (227- 434) U/L; p = 0.021) at presentation (Supplemental Table 6), but was not associated with symptoms such as nausea / vomiting or clinical signs of hypovolemia, such as tachycardia or hypotension. There were no significant differences in outcome measures, such as duration of admission, ICU admission, or death/palliative discharge, between patients with a low and high USE.

3.7 Etiology related to outcomes

Among the patients who presented with hyponatremia, 983 patients (36.7%) reported a history of gastrointestinal symptoms, such as nausea, vomiting, or diarrhea, and did not use diuretics or met the criteria for SIADH. 271 patients (10.1%) used diuretics in the absence of gastrointestinal symptoms and 12 (0.5%) who did not use diuretics complied to the definition of SIADH, of whom 5 also had gastro-intestinal symptoms. Another group of 201 patients (7.5) had a history of nausea, vomiting, or diarrhea and used diuretics. However, the largest portion of patients (1210 patients, 45.2%) had an unknown etiology for hyponatremia, as they did not have a history of gastrointestinal symptoms, did not use diuretics, and did not meet the criteria for SIADH.

Figure 1D illustrates a cox proportional hazard curve, with separate lines representing each proposed etiology. It was observed that patients with a history of gastrointestinal symptoms had lower mortality rates compared to those with normal sodium levels (unadjusted hazard ratio (HR) 0.739, 95% confidence interval (CI) 0.611 – 0.894; p = 0.002), despite higher CRP (mean 95 mg/L, IQR 47.5 – 151 mg/L) and LDH levels (mean 350 U/L, IQR 271 – 470 U/L) compared to normonatremia (p <0.001; assessed using a Kruskal-Wallis test). Patients with hyponatremia of unknown etiology had a higher risk of ICU admission (unadjusted OR 1.299, 95% CI 1.091 – 1.549; p = 0.003; linear regression) and were at risk for intubation (unadjusted OR 1.313, 95% CI 1.109 – 1.554; p = 0.002; linear regression), which was in line with higher CRP levels (mean 98 mg/L, IQR 53 – 166 mg/L) and LDH levels (mean 353 U/L, IQR 270 – 479 U/L) in this group compared to normonatremia (p < 0.001; assessed using a Kruskal-Wallis test). However, the duration of ICU admission did not differ significantly among the different groups. It was found that patients with hyponatremia of unknown etiology had a slightly longer duration of hospital admission (8 days, interquartile range 4 – 17 days) compared to other groups (p = 0.005; assessed using the Kruskal-Wallis test).

4. Discussion

This large multicenter observational cohort study examined 7811 patients with COVID-19 over an extended period and multiple phases of the COVID-pandemic. We found that hyponatremia was highly prevalent but not associated with higher mortality rates. Although less prevalent, hypernatremia was associated with a three-to-four-fold increased risk of worse outcomes, including increased risk of ICU-admission, intubation, and mortality. Hyponatremia was also associated with a higher risk for ICU-admission, but not for intubation.

Patients with hyponatremia experienced more complications such as aspergillosis pneumonia and physical decline, while those with hypernatremia were more prone to sepsis and delirium. Similar to previous studies, hypo- and hypernatremia were more prevalent in males than in females, in elderly patients, those with chronic kidney disease, and a lower BMI[4 6 28 33 35-37 44]. In contrast to others, we did not find an association between hyponatremia and diabetes, which possibly relates to the fact that we corrected sodium levels for serum glucose[4 6 28 33 37]. Among COVID-19 patients, hyponatremia appeared to have multiple etiologies, but hypovolemic hyponatremia was found to be predominant.

The incidence of hyponatremia among COVID-19 patients in this study was 34.3%, which is higher than the pooled prevalence of hyponatremia in previous systematic reviews which included studies conducted during the earlier COVID-19-waves 24% to 25.8%[23 25]. However, it aligns with Tezcan, et al. [39] Voets, et al. [45], and Sarvazad, et al. [38], who reported rates of 34%, 35.8% and 38%, respectively (the latter study included only patients without underlying disease), although even higher incidences have been reported[5 8 9 24 35]. The incidence of hyponatremia in COVID-19 was also found to be higher compared to hyponatremia in other types of pneumonia: 5.4% - 28%[6 7 27 45 46]. Hyponatremia is most common in pneumonias caused by viral pathogens (e.g. rhinovirus, respiratory syncytial virus, (para)influenza virus, and adenovirus) with a incidence reported of 17.6%, as compared to 13.8% in patients with bacterial pneumonias[46]. Patients presenting with hyponatremia in this study were significantly older compared to patients with normonatremia, potentially due to age-related tubular atrophy and subsequent decreased urine concentrating capacity and sodium reabsorption[47]. The fact that previous studies have identified various other underlying conditions as risk factors for hyponatremia, including cardiac[28], pulmonary[28], and liver diseases[28] possibly relates to the older age of patients with

hyponatremia included (median age was 67 years in our study versus a mean age of 74.3 years in Chan, et al. [28] and a median age of 70 years in Ruiz-Sánchez, et al. [44]).

Hypernatremia is less common among COVID-19 patients compared to other pneumonias. We found an incidence of 1.6% among COVID-19 patients. This number is lower than the incidences reported in previous studies (2.9% - 38%)[19 45] and lower than the incidence of hypernatremia (5.3%) reported in patients with a community acquired pneumonia[48]. Patients with hypernatremia were found to be older than patients with normo- or hyponatremia. These age differences were in line with the expected age-related impairment of the thirst mechanism and potential barriers to accessible fluids (e.g. due to immobilization or dementia) which could contribute to inadequate fluid intake with subsequent development of hypernatremia[32].

Hyponatremia in infectious diseases can have multiple etiologies, of which SIADH, hypovolemia, and the use of diuretics are the most common, but critical illness-related corticoid insufficiency is also reported[16 27]. In this study we showed that multiple etiologies seem to play a role in COVID-19 patients. Among patients with hyponatremia a higher incidence of diarrhea and anosmia was observed. These symptoms could contribute to decreased appetite and subsequently lower dietary intake. Clinical investigations revealed an increased heart rate and slightly decreased systolic blood pressure, which suggests a possible hypovolemic state as an underlying cause for hyponatremia. Correspondingly, eGFR was lower in this group, despite comparable blood urea levels, which have been employed by others as measure to differentiate euvolemic from hypovolemic hyponatremia[36]. This hypovolemia could result from both reduced dietary intake and dehydration due to diarrhea. The low median USE (30 mmol/L) in a proportion of patients also points to extrarenal sodium loss and a hypovolemic status[49]. However, due to the limited number of patients with USE measurements, these findings should be interpreted as supportive rather than definitive evidence.

Moreover, patients presenting with hyponatremia had higher serum concentrations of LDH and CRP. A relationship between serum CRP and sodium concentration has been observed in other infectious diseases and has also been demonstrated in COVID-19 patients[5 28 35]. This phenomenon has been attributed to release of cytokines such as interleukin-6 and interleukin-1β[50], which can affect the secretion of ADH and potentially contribute to the development of SIADH[10 30]. In COVID-19 patients, elevated levels of interleukin-6 and interleukin-1β have been noted[37 51 52]. Furthermore, a negative correlation between interleukin-6 and sodium levels has been demonstrated, implying a similar

mechanism in the development of hyponatremia[21 36]. It is important to note that although administration of interleukin-6 receptor antagonists (tocilizumab and sarilumab) and interleukin-1 receptor antagonist (anakinra) was similar between groups, this observation does not undermine the aforementioned hypothesis, as these agents were administered based on indirect markers of interleukin release such as disease severity and CRP levels. Additionally, most patients in the study were included before registration of these agents for COVID-19 treatment, and the sample sizes of the groups might have been too small to draw definitive conclusions on the relationship between cytokine levels and hyponatremia in COVID-19 patients.

Contrary to previous studies and in contrast to patients with community acquired pneumonia, we did not find SIADH as frequent cause of hyponatremia in COVID-19 patients[2 25 37 53]. In our study, only a small proportion of USE + UOL samples complied with the definition of SIADH, and a correlation between low urinary sodium excretion and serum CRP concentration was found, which is in contrast to the theory that interleukin-6 induces ADH release (Supplemental Table 6). The overall incidence of SIADH in our study suggests that SIADH is a less frequent cause of hyponatremia among COVID-19 patients, compared to hyponatremia in patients with other pneumonias. This is possibly because COVID-19 more often causes diarrhea thereby also leading to other causes of hyponatremia. Frontera, et al. [37] reported a prevalence of 36% of SIADH among COVID-19 patients that presented with a serum sodium level ≤120 mmol/L. However, in our study population, less than 1% presented with a sodium level this low, and mild and severe hyponatremia differ in pathophysiology. Previous studies that identified SIADH as a frequent underlying mechanism of hyponatremia in COVID-19 patients based their information mostly on case reports, which likely focused on more severe cases[25]. The fact that in our study urinary investigation was not performed in all patients with hyponatremia may suggest that hyponatremia was not persistent or was otherwise not found to be severe enough to do so. This could also contribute to the lower incidence of confirmed SIADH cases in our study.

The association between thiazide diuretics and hyponatremia is well-established. Thiazide diuretics are known to increase the risk of developing hyponatremia due to their effects on renal sodium and water excretion[54]. Therefore, it is not surprising that patients with hyponatremia more frequently used thiazide diuretics. The use of immunosuppressive medications, such as glucocorticoids, was also related to hyponatremia. Glucocorticoids can potentially affect the body's water and electrolyte imbalance, including sodium levels. The development of iatrogenic adrenal insufficiency, resulting from

the (prior) prescription of steroids, can contribute to relative glucocorticoid efficiency and potentially lead to hyponatremia[55 56].

We did not find a significant association between hyponatremia and the risk of mortality or intubation, although ICU admission rates were higher in the hyponatremia group. These results are in line with Machiraju, et al. [5], who also demonstrated a higher need for ICU admission in COVID-19 patients presenting with hyponatremia but could not relate hyponatremia to mortality nor the length of hospital stay. Consistent with our results, Tzoulis, et al. [36] found no significant association between hyponatremia and mortality but did relate hyponatremia to invasive ventilation and the length of hospital admission. The higher serum CRP and LDH concentrations in hyponatremic patients in our study indicate that these patients might be more ill compared to those with normal sodium levels, which is not in line with the similar mortality rates[57 58]. We speculate that dehydration accompanied by hyponatremia, along with elevated LDH and CRP levels were reasons for hospital admission. However, other pathophysiologic mechanisms leading to worse outcomes were absent in these patients, favoring a relatively good outcome.

Our findings are in contrast with previous studies, in which the presence of hyponatremia at presentation was independently associated with disease severity and prolonged hospital stay [28 46] and was thought to be an independent predictor of hospital mortality[2 4 23 25 28]. These studies suggest that hyponatremia, especially when not corrected for serum glucose concentration[59], is a significant factor in determining the prognosis of patients. The observed trend towards increased mortality in patients with severe hyponatremia was also demonstrated by Ruiz-Sánchez, et al. [44], Chan, et al. [28], and Frontera, et al. [37]. However, the latter study obtained statistically significant results with a lower number of patients (36 out of 4645, representing 1% of the population, stratified as having severe hyponatremia based on sodium levels $\leq$ 120 mmol/L) compared to 1.8% in our study, which could not be confirmed by our study.

There are several potential explanations for the difference in outcomes between our study and previous studies. First, previous studies only included patients that were admitted during 2020 and the spring of 2021, the beginning of the COVID-19 pandemic[2 4 19 23 25]. In large previous studies, mortality rates between 22.6-28.9% have been reported[6 59]. In contrast, our study included patients from the beginning of the COVID-19 pandemic until August 2022 and the overall mortality in our study was 16.7%. Moreover, we observed significant variations in mortality, ICU-admission, and intubation rates in the

normo- and hyponatremia groups differed significantly between patients that were included during the initial wave in the spring of 2020 (when original SARS-CoV-2 variants dominated) and those included in subsequent COVID-19 waves (with alpha, delta, and omicron variants dominating in the last quartile of patients included). These differences in outcomes are likely attributed to increased knowledge about the disease, the development of new treatments such as dexamethasone and tocilizumab, and the commencement of widespread vaccination campaigns starting in January 2021. It is important to note that a study by Chan, et al. [28] included patients from late 2021 and early 2022 and still found an association between hyponatremia and adverse outcomes. However, these results may not be directly comparable to our study due to potential differences in vaccine efficacy and COVID-19 policies between Hong-Kong and Western countries[60]. These variations in patient cohorts and treatment strategies could influence outcomes and thus could lead to different results as compared to other studies. We speculate that the absence of a higher risk of adverse outcomes in COVID-19 patients presenting with hyponatremia, contrary to previous studies, could be partly attributed to the overall decrease in mortality as the pandemic progressed.

Second, previous studies examined uncorrected sodium concentration at presentation as a prognostic factor and found increased mortality rates in patients with hyponatremia[4 24 25 33 35 37 39 44 61]. However, other studies that corrected for serum glucose concentration when these exceeded 10 mmol/L, found no significant association between hyponatremia and mortality[36]. Hirsch, et al. [59] demonstrated that the association between hyponatremia and mortality was only evident prior to correction for serum glucose concentration, and the association disappeared after correcting for glucose levels. These findings are similar to studies conducted outside the context of COVID-19[62]. In our study, uncorrected hyponatremia was associated with an elevated risk of ICU admission and intubation, whereas corrected hyponatremia did not show an association between hyponatremia and intubation. This suggests that a similar effect related to the correction of sodium levels for glucose concentration could explain the discrepancies between our study and previous studies[37 44].

The association between ICU admission and hyponatremia was most pronounced in patients with a hyponatremia of unknown etiology. However, it is important to consider that this group may include mild presentations of SIADH due to the limited number of urinary samples available. These findings align with the higher CRP and LDH levels observed in this group. Patients that had a history of gastro-intestinal symptoms had a lower risk of ICU admission, despite having higher levels of CRP and

LDH levels. The higher CRP and LDH levels in this group could not be related to the SARS-CoV-2 variants, as the highest CRP levels were observed in patients that developed symptoms during a period in which the delta variant dominated. Notably, this group also had the lowest prevalence of gastro-intestinal symptoms (data not shown).

In contrast to the findings in patients with hyponatremia, our study revealed a significant association between hypernatremia and adverse outcomes such as ICU-admission, intubation, and death. While there were no significant differences in serum CRP and LDH concentration, as well as CT-severity scores at admission, between hypernatremic and normonatremic patients, higher MEWS and qSOFA scores indicated that a greater extent of lung tissue in hypernatremic patients. Furthermore, elevated serum urea concentration, lower eGFR, and a prolonged capillary refill time suggested dehydration in this group of patients. These findings collectively point towards a more severely ill patient population, which could account for the worse clinical outcomes observed. The association between hypernatremia and worse clinical outcomes has been previously documented in COVID-19[1 4] and other type of pneumonias[48].

Our study on hyponatremia in COVID-19 is characterized by its large size, including over 7000 patients from various hospitals across Netherlands. A notable strength of our study lies in the inclusion of patients from different waves of the COVID-19 and from multiple hospitals, both university and general. This approach resulted in a diverse patient population, making our findings applicable to the current situation. Furthermore, our study benefitted from the availability of a large amount of clinical data being available for each patient. This allowed us to analyze the associations we discovered in conjunction with relevant patient background details. For instance, we had access to vital signs recorded at admission, providing us with a more comprehensive understanding of the patients' condition upon admission compared to previous studies[37 44]. Consequently, we were able to offer more substantiated insights into the presumed underlying etiology and how the different etiologies were related to clinical outcomes.

This study has several limitations that should be acknowledged. Firstly, the availability of urinary samples of patients with hyponatremia (185 out of the total) limits the generalizability of our findings. Additionally, information on the duration of hyponatremia in participating patients was not provided. Exploring these aspects would have been valuable, as a previous study by de La Flor, et al. [14] demonstrated that persistent hyponatremia (72 – 96h after admission) was associated with higher

mortality in COVID-19 patients. Secondly, the variability in treatment protocols among the participating hospital may have influenced outcome of patients in our study. Lastly, we were unable to study specific treatment options for hyponatremia in patients.

Our results suggest that while hyponatremia is commonly observed among COVID-19 patients, it is not associated with adverse clinical outcome. However, the presence of hypernatremia should be of concern to clinicians, as it is indicative of a poorer prognosis. To enhance our understanding of the etiology of hyponatremia in COVID-19, future studies should focus on monitoring the clinical course of hyponatremia during hospitalization, documenting the duration of hyponatremia, and recording the treatment administered. It is crucial to obtain urinary samples from all patients presenting with COVID-19 and hyponatremia to further elucidate the underlying causes. Moreover, further research is warranted to investigate the incidence and potential mechanisms of SIADH in relation to disease severity and inflammation. More specifically, studies examining the relationship with interleukin-6 would be valuable, given that the interleukin-6 antagonist tocilizumab is used in the treatment of patients with moderate to severe COVID-19.

5. Conclusion

Hyponatremia is a common electrolyte disorder found in one third of patients hospitalized with COVID-19. Several risk factors have been identified, including male sex assigned at birth, a slightly lower BMI, pre-existing conditions like chronic kidney disease, hypertension, as well as the use of certain medications such as the use of thiazide diuretics and immunosuppressives. We found that hyponatremia was not associated with a higher need for invasive ventilation nor with mortality. In contrast, hypernatremia was associated with worse outcomes as compared to normonatremia. Regarding the underlying pathophysiological mechanisms, hypovolemic hyponatremia appeared to be the predominant mechanism in COVID-19 patients. Other causes of hyponatremia, such as SIADH, were less commonly observed in our study population.

Contributorship Statement

LRdH, MtW, and RAD conceptualized and designed the study, and were responsible for the planning, conduct, data analysis and interpretation. LRdH drafted the article supervised by MtW, and RAD. Figures and tables were designed by LRdH. LRdH, MtW, RAD, MB, RHOE, BA, EKHH, DR, NCGvdO, SS, NP, JPvdB, CEW, MdK, TD, HM, NB, and KB were responsible for the inclusion of patients and data entry in the COVID-PREDICT database in their respective centers on behalf of the COVID-PREDICT study group. MB, RHOE, BA, EKHH, DR, NCGvdO, SS, NP, JPvdB, CEW, MdK, TD, HM, NB, and KB critically revised the manuscript and supplemental material. All authors provided final approval of the manuscript and accepted responsibility for the integrity and accuracy of the work. They also ensued that any inquiries regarding the work's integrity or accuracy would be thoroughly investigated and resolved.

Competing of interest

The authors declare that there is no conflict of interest.

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Data sharing statement

No data are available. Not all patients provided active informed consent, and therefore sharing data is not possible.

Ethics approval

The ethical board of the Amsterdam University Medical Centers (20.131) approved the study protocol.

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Figure legends

Figure 1. Hazard ratios of cox proportional survival curves for survival probability for each sodium value adjusted for age, sex assigned at birth, a history of chronic kidney disease, and a history of hypertension. The grey area indicates the normonatremia. Table shows hazard ratios for covariates and sodium as a continuous variable (**A**). Cox proportional survival curves at the mean of covariates for (**B**) unadjusted 6-week mortality stratified by normo-, hypo-, and hypernatremia, (**C**) 6-week mortality adjusted for age, sex assigned at birth, a history of chronic kidney disease, and a history of hypertension stratified in normo-, hypo-, and hypernatremia, (**D**) Unadjusted 6-week mortality stratified by etiology. ** indicates a p-value <0.01, *** indicates a p-value <0.001

Figure 2. Odds ratio for adverse outcomes (death / palliative discharge (**A**), intensive care unit admission (**B**) invasive ventilation (**C**)) in each quartile compared to patients in the first quartile (admitted before 27-03-2020; N = 2002) for patients with hypo-, hyper-, or normonatremia at admission. * Indicates a p-value <0.05, ** indicates a p-value < 0.01, *** indicates a p-value <0.001 for the odds ratio as calculated by binary logistic regression. (**D**) incidence of hypo-, normo-, and hypernatremia in each quartile, *** indicates a p-value <0.001 as compared to the first quartile for the chi-square statistic with Bonferroni post-hoc correction.

Table 1 – Comparison of patient characteristics between COVID-19 patients with hypo-, normo-, and hypernatremia

	Hyponatremia Na 134 mmol/L N = 2677	**Normonatremia** Na 136 – 145 mmo/L N = 5008	**Hypernatremia** Na 146 mmol/L N = 126
Sex assigned at birth (N (%))	♂ 1673 (62.5%) ♀ 1003 (37.5%) p = 0.002	♂ 2946 (58.8 %) ♀ 2060 (41.2 %)	♂ 84 (66.7%) ♀ 42 (33.3%)
Age (median age in years (IQR))	N = 2675 67.0 (58.0-77.0) p < 0.001	N = 5008 66.1 (55.0-76.0)	N = 126 72.5 (62.8 – 80.3) p < 0.001
BMI (median BMI in kg/m^2 (IQR))	N = 1740 27.2 (24.2 – 31.1) p = 0.009	N = 3374 27.7 (24.6 – 31.6)	N = 91 25.0 (22.2 – 29.1) p < 0.001
Order 'Do not intubate' (N (%))	440 / 1442 (30.5 %)	796 / 2469 (32.2 %)	39 / 77 (50.6 %) p = 0.004
Chronic cardiac disease (N (%))	760 / 2666 (28.5%) p = 0.07	1334 / 4982 (26.8 %)	42 / 123 (34.1 %) p = 0.07
Hypertension (N (%))	1055 / 2374 (44.4 %) p = 0.002	1889 / 4586 (41.2 %)	64 / 120 (53.3 %)
Chronic pulmonary disease (N (%))	466 / 2662 (17.5 %) p = 0.75	844 / 4979 (17.0 %)	19 / 122 (15.6 %) p = 0.75
Chronic kidney disease (N (%))	329 / 2379 (13.8 %) p < 0.001	491 / 4587 (10.7 %)	26 / 121 (21.5 %) p < 0.001
Moderate to severe liver disease (N (%))	30 / 2662 (1.1 %) p = 0.46	50 / 4972 (1.0 %)	0 / 123 (0.0 %) p = 0.46
Diabetes (N (%))	664 / 2662 (24.9 %) p = 0.39	1261 / 4972 (25.4 %)	38 / 125 (30.4 %) p = 0.39
Immunosuppressives (N (%))	192 / 2283 (8.4 %) p = 0.002	295 / 4445 (6.6 %)	2 / 118 (1.7 %)
Thiazide diuretics (N (%))	258 / 2671 (9.7 %) p = 0.015	394 / 4994 (7.9 %)	7 / 125 (5.6 %)
Loop diuretics (N (%))	187 / 2671 (7.0 %) p = 0.22	389 / 4994 (7.8 %)	13 / 125 (10.4 %) p = 0.22
SSRIs / SNRIs (N (%))	78 / 2671 (2.9 %) p = 0.69	164 / 4994 (3.3 %)	4 / 125 (3.2 %) p = 0.69

BMI = body mass index; IQR = interquartile range; % = percentage of patients in this group with indicated characteristic; SSRI = Selective Serotonin Reuptake inhibitor; SNRI = Selective Serotonin and Noradrenalin Reuptake inhibitor. Significance was assessed using a Kruskal-Wallis test with post-hoc correction (for numerical data; non-normally distributed) or Chi-square test (for categorical data). p – values for all groups indicate the adjusted significance after post-hoc correction when compared to the normonatremia group. When no p – value was provided there was no significant difference compared to the normonatremia group. Subgroup analyses for hyponatremia is provided in the supplemental information.

Table 2 – Comparison of signs and symptoms at presentation between COVID-19 patients with hypo-, normo-, and hypernatremia

Signs and symptoms	**Hyponatremia** Na 134 mmol/L N = 2677	**Normonatremia** Na 136 – 145 mmol/L N = 5008	**Hypernatremia** Na 146 mmol/L N = 126
Nausea / vomiting (N (%))	679 / 2273 (29.9 %) p = 0.04	1150 / 4129 (27.9 %)	16 / 83 (19.3 %) p = 0.04
Diarrhea (N (%))	804 / 2298 (35.0%) p < 0.001	1146 / 4157 (27.6 %)	15 / 82 (18.3 %)
Anosmia (N (%))	244 / 1904 (12.8 %) p = 0.002	352 / 3330 (10.6 %)	1 / 66 (1.5 %)
Confusion (N (%))	311 / 2319 (13.4%)	651 / 4381 (14.9 %)	45 / 105 (42.9 %) p < 0.001
Seizures (N (%))	10 / 1977 (0.5%) p = 0.20	31 / 3452 (0.9 %)	0 / 80 (0.0 %) p = 0.20
FiO2 (median fraction (IQR))	N = 1159 0.36 (0.28-0.50) p = 0.05	N = 2084 0.36 (0.28 – 0.50)	N = 67 0.44 (0.30 – 0.80) p = 0.05
SBP (mean SBP in mmHg (SD))	N = 2648 132 (± 22) p < 0.001	N = 4971 135 (±23)	N = 120 135 (± 25) p = 1.00
HR (mean HR in BPM (SD))	N = 2661 92 (±18) p = 0.003	N = 4965 91 (±20)	N = 123 95 (±25) p = 0.034
Capillary refill ≥3 s (N (%))	81 / 863 (9.4 %)	93 / 1369 (6.8 %)	6 / 33 (18.2 %) p = 0.008
Blood urea level (median level n mmol/L (IQR))	N = 2549 6.3 (4.5 – 9.3) p = 0.87	N = 4776 6.2 (4.5 – 9.2)	N = 115 12.6 (7.9 – 25.3) p < 0.000
eGFR rate using 2021 CKD-epi creatinine equation in (median clearance in ml/min/1.73 m^3 (IQR))	N = 2656 64 (45 – 90) p < 0.001	N = 4983 68 (46 – 94)	N = 125 41 (24 – 71) p < 0.001
CT-severity score (mean score (SD))	N = 909 12.4 (±5.5) p = 0.58	N = 1401 12.1 (±5.6)	N = 30 14.5 (±7.2) p = 0.06
Blood CRP level (median level in mg/L (IQR))	N = 2646 93.1 (49.0 – 154) p < 0.001	N = 4939 70.8 (28.0 – 131)	N = 123 75.0 (29.0 – 148) P = 1.00
Blood LDH level (median level in U/L (IQR))	N = 2238 349 (268 – 471) p < 0.001	N = 4226 323 (247 – 426)	N = 89 363 (255 – 447) p = 0.52

MEWS (median score (IQR))	N = 2337 3.0 (2.0 – 4.0) p < 0.001	N = 4055 3.0 (2.0 – 4.0)	N = 103 4.0 (2.0 – 5.0) p < 0.001
qSOFA (median score (IQR))	N = 2373 1.0 (0.0 – 1.0) p = 1.00	N = 4131 1.0 (0.0 – 1.0)	N = 104 1.0 (1.0 – 1.0) p < 0.001

SBP = systolic blood pressure; HR = heart rate; eGFR = estimated glomerular filtration rate; CKD-epi = chronic kidney disease Epidemiology Collaboration; CT = computed tomography; BPM = beats per minute; IQR = interquartile range; SD = standard deviation; CRP = c-reactive protein; LDH = lactate dehydrogenase; MEWS = modified early warning score; qSOFA = quick sequential organ failure assessment. % = percentage of patients in this group with indicated characteristic. Significance was assessed using a Kruskal-Wallis test with post-hoc correction (for numerical data) or Chi-square test (for categorical data). p – values for all groups indicate significance when compared to the normonatremia group. When no p – value was provided there was no significant difference to the normonatremia group. Subgroup analyses for hyponatremia is provided in the supplemental information.

Table 3 – Comparison of clinical outcomes between COVID-19 patients with hypo-, normo-, and hypernatremia

Outcome	**Hyponatremia** Na 134 mmol/L N = 2677	**Normonatremia** Na 136 – 145 mmo/L N = 5008	**Hypernatremia** Na 146 mmol/L N = 126
Duration of admission (median days (IQR))	N = 2372 7 (4 – 16) p < 0.001	N = 4116 7 (3 – 14)	N = 103 8 (4 – 15) P = 0.998
Death or palliative discharge (N (%))	405 / 2360 (17.2 %) [A]OR 1.04 (0.91 – 1.20) p = 0.56	729 / 4568 (16.0 %)	42 / 119 (35.3 %) [A]OR 2.25 (1.49 – 3.41) p < 0.001
ICU-admission (N (%)), 'do not intubate' excluded	439 / 1923 (22.8 %) [A]OR 1.27 (1.11 – 1.46) p < 0.001	710 / 3778 (18.8 %)	32 / 80 (40.0%) [A]OR 2.89 (1.83 – 4.58) p < 0.001
Duration of ICU-admission (days (IQR)) 'do not intubate' excluded	N = 299 8 (3 - 19) p = 0.356	N = 437 10 (4 – 19)	N = 25 11 (3.5 – 19) p = 0.356
Invasive ventilation (N (%)), 'do not intubate' excluded	352 / 1889 (18.6 %) [A]OR 1.12 (0.97 – 1.30) p = 0.121	623 / 3706 (16.8 %)	29 / 77 (37.7 %) [A]OR 2.95 (1.83 – 4.74) p < 0.001
Discharge alive within 42 days; N indicating the number of non-censored cases	N = 1527 [A]HR 0.96 (0.90 – 1.02) p = 0.15	N = 2747	N = 52 [A]HR 0.78 (0.59 – 1.03) p = 0.08
Use of tocilizumab, sarilumab, or anakinra (N (%))	134 / 688 (19.5%) [A]OR 1.256 (0.984 – 1.604) p = 0.068	199 / 1245 (16.0%)	3 / 34 (8.8%) [A]OR 0.550 (0.165 – 1.830) p = 0.330
Complications	Na 134 mmol/L N = 1821	Na 136 – 145 mmo/L N = 3206	Na 146 mmol/L N = 82
Bacterial pneumonia (N (%))	289 / 2212 (13.1 %) [A]OR 1.12 (0.96 – 1.31) p = 0.14	501 / 4307 (11.6 %)	18 / 109 (16.5 %) [A]OR 1.44 (0.85 – 2.40) p = 0.17

Aspergillosis pneumonia (N (%))	67 / 1915 (3.5 %) [A]OR 1.44 (1.03 – 1.99) p = 0.031	83 / 3442 (2.4 %)	5 / 90 (5.6 %) [A]OR 2.26 (0.89 – 5.74) p = 0.084
ARDS (N (%))	224 / 2223 (10.1 %) [A]OR 1.08 (0.91 – 1.29) p = 0.377	404 / 4323 (9.3 %)	17 / 110 (15.5 %) [A]OR 1.78 (1.05– 3.04) p = 0.033
Treatment for septic shock (N (%)) *	94 / 2153 (4.4 %) [A]OR 1.33 (1.01 – 1.74) p = 0.04	135 / 4175 (3.2 %)	12 / 109 (11.0 %) [A]OR 3.37 (1.80 – 6.33) p < 0.001
Congestive heart failure (N (%))	64 / 2235 (2.9 %) [A]OR 0.95 (0.70 – 1.29) p = 0.73	125 / 4352 (2.9 %)	2 / 111 (1.8 %) [A]OR 0.48 (0.12 – 1.96) p = 0.31
Physical decline (N (%))	576 / 2116 (27.2 %) [A]OR 1.22 (1.08 – 1.38) p < 0.001	950 / 4126 (23.0 %)	30 / 106 (28.3 %) [A]OR 1.18 (0.77 – 1.82) p = 0.44
Delirium (N (%))	237 / 2136 (11.1 %) [A]OR 0.99 (0.83 - 1.17) p = 0.88	451 / 4146 (10.5 %)	27 / 107 (25.7 %) [A]OR 2.25 (1.42 – 3.56) p < 0.001

*ICU = Intensive care unit; ARDS = acute respiratory distress syndrome. [A]OR = adjusted odds ratio; odds ratio adjusted for sex assigned at birth, age, a history of chronic kidney disease, and a history of hypertension. [A]HR = adjusted hazard ratio; hazard ratio adjusted for sex assigned at birth, age, a history of chronic kidney disease, and a history of hypertension * Treatment for septic shock was defined as the need for vasopressors in order to maintain mean arterial blood pressure >65 mmHg and blood lactate level >2 mmol/L, in the absence of other causes including hypovolemia. Significance was assessed using a cox proportional-hazard model at the mean of the covariates (discharge alive) or logistic regression (all other values). p – values for all groups indicate significance when compared to the normonatremia group.*

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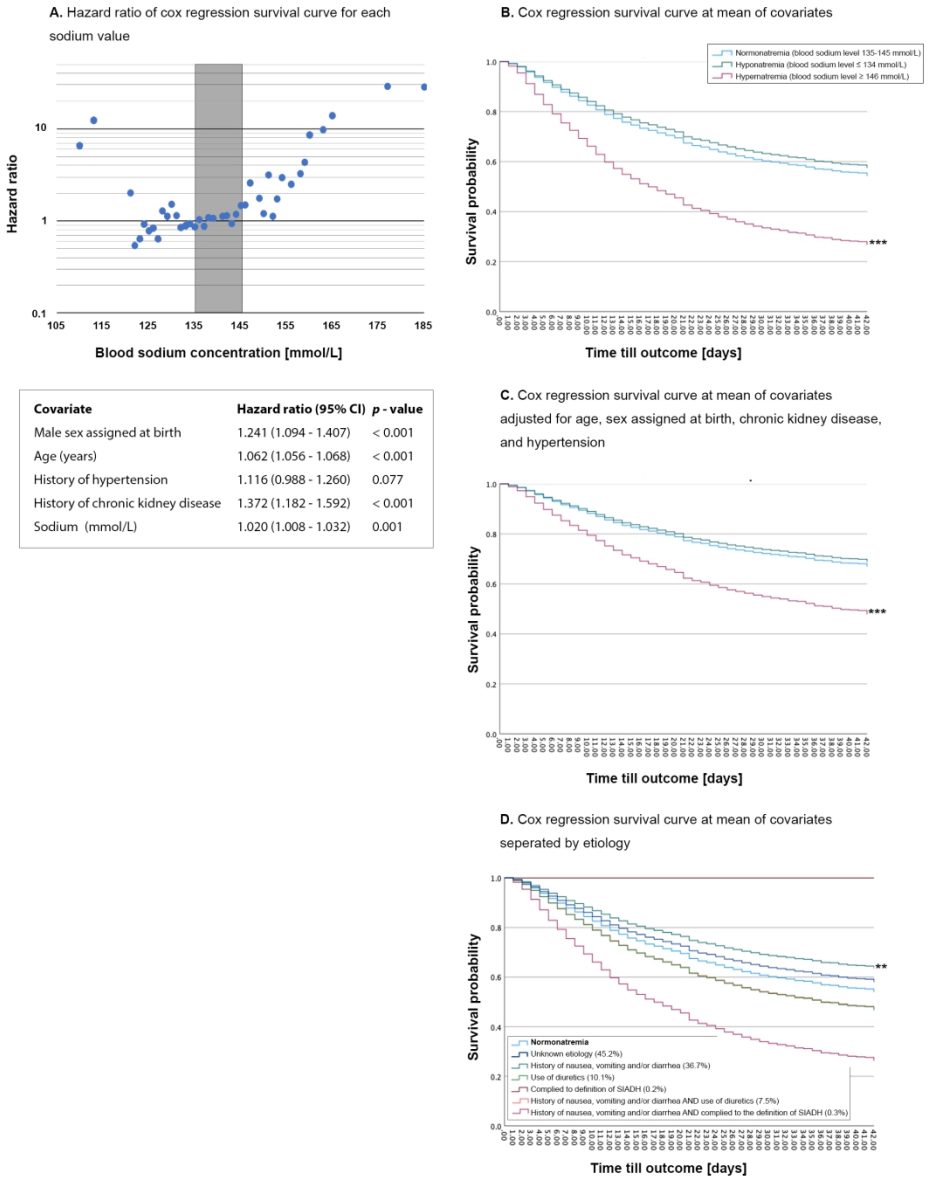

Covariate	Hazard ratio (95% CI)	*p* - value
Male sex assigned at birth	1.241 (1.094 - 1.407)	< 0.001
Age (years)	1.062 (1.056 - 1.068)	< 0.001
History of hypertension	1.116 (0.988 - 1.260)	0.077
History of chronic kidney disease	1.372 (1.182 - 1.592)	< 0.001
Sodium (mmol/L)	1.020 (1.008 - 1.032)	0.001

Figure 1. Hazard ratios of cox proportional survival curves for survival probability for each sodium value adjusted for age, sex assigned at birth, a history of chronic kidney disease, and a history of hypertension. The grey area indicates the normonatremia. Table shows hazard ratios for covariates and sodium as a continuous variable (A). Cox proportional survival curves at the mean of covariates for (B) unadjusted 6-week mortality stratified by normo-, hypo-, and hypernatremia, (C) 6-week mortality adjusted for age, sex assigned at birth, a history of chronic kidney disease, and a history of hypertension stratified in normo-, hypo-, and hypernatremia, (D) Unadjusted 6-week mortality stratified by etiology. ** indicates a p-value <0.01, *** indicates a p-value <0.001

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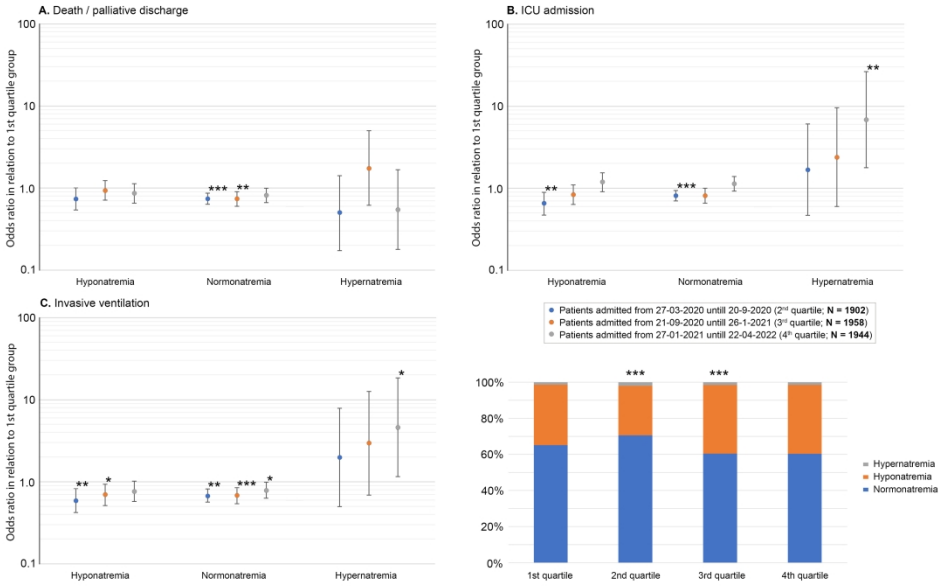

Figure 2. Odds ratio for adverse outcomes (death / palliative discharge (A), intensive care unit admission (B) invasive ventilation (C)) in each quartile compared to patients in the first quartile (admitted before 27-03-2020; N = 2002) for patients with hypo-, hyper-, or normonatremia at admission. * Indicates a p-value <0.05, ** indicates a p-value < 0.01, *** indicates a p-value <0.001 for the odds ratio as calculated by binary logistic regression. (D) incidence of hypo-, normo-, and hypernatremia in each quartile, *** indicates a p-value <0.001 as compared to the first quartile for the chi-square statistic with Bonferroni post-hoc correction.

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Outcomes of COVID-19 patients presenting with dysnatremia: an observational study

Supplemental information

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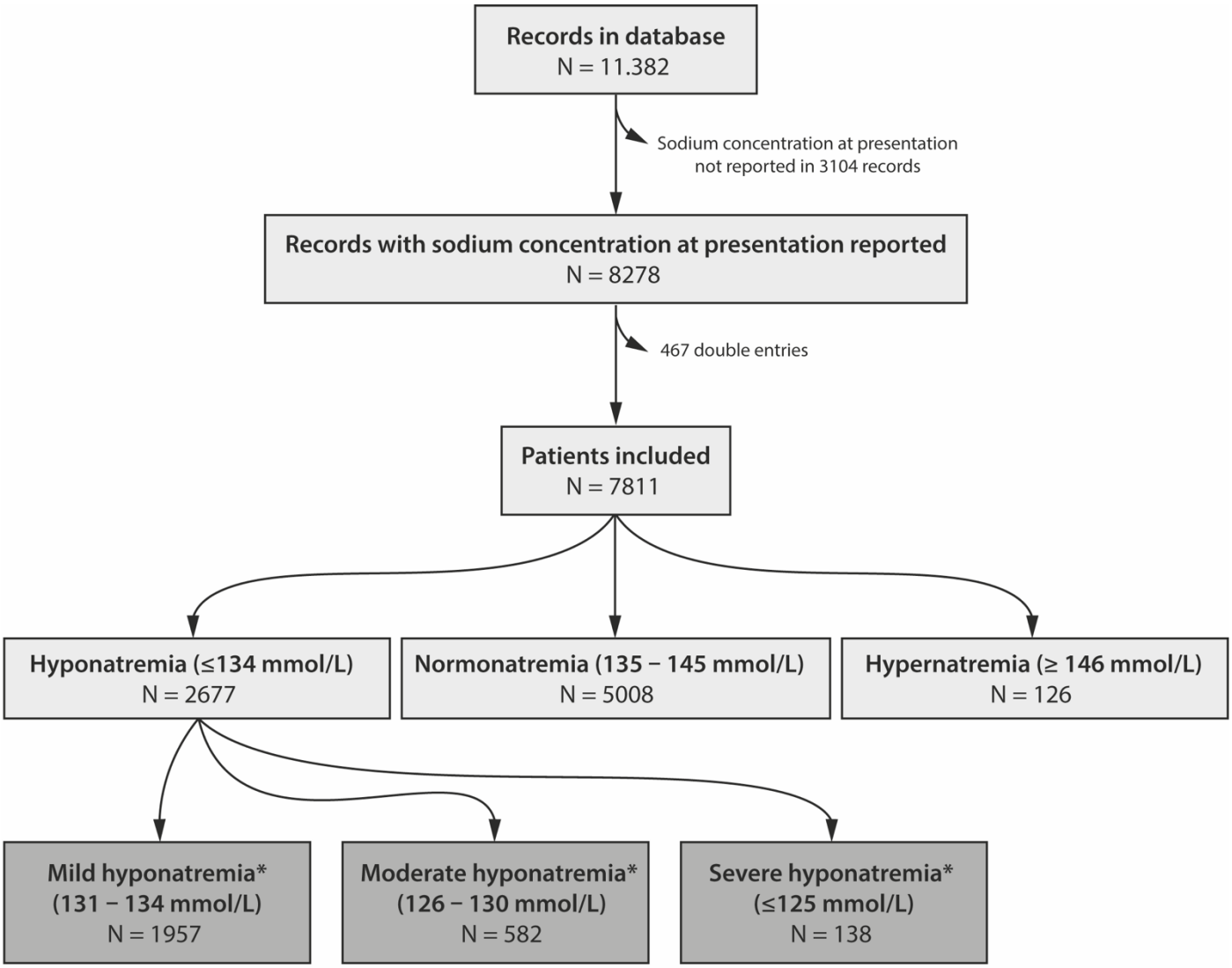


Supplemental Figure 1. Flow chart of included patients. Sodium concentrations indicate corrected serum sodium concentrations at hospital presentation * indicates the subgroup analysis as provided in the supplemental information.

Supplemental Table 1 – Subgroup analysis of patient characteristics

	Na 135 – 145 mmol/L N = 5008	Na ≤134 mmol/L N = 2677	Na 131 – 134 mmol/L N = 1957	Na 126 – 130 mmol/L N = 582	Na ≤125 mmol/L N = 138
Sex assigned at birth (N (%))	♂ 2946 (58.8 %) ♀ 2060 (41.2 %)	♂ 1673 (62.5%) ** ♀ 1003 (37.5%)	♂ 1249 (63.9%) *** ♀ 707 (36.1%)	♂ 363 (62.4%) ♀ 219 (37.6%)	♂ 61 (44.2%) *** ♀ 77 (55.8%)
Age (median age in years (IQR))	N = 5008 66.1 (55.0-76.0)	N = 2675 67.0 (58.0-77.0) **	N = 1956 67.0 (57.0 – 76.0)	N = 581 68.1 (60.0 – 78.0) ***	N =138 70.6 (62.0 – 79.3) ***
BMI (median BMI in kg/m^2 (IQR))	N = 3374 27.7 (24.6 – 31.6)	N = 1740 27.2 (24.2 – 31.1) **	N = 1271 27.4 (24.4 – 31.5)	N = 379 26.3 (23.4 – 30.3) ***	N = 90 26.9 (23.7 – 30.9)
Order 'Do not intubate' (N (%))	796 / 2469 (32.2 %)	440 / 1442 (30.5 %)	304 / 1043 (29.1 %)	108 / 322 (33.5 %)	28 / 77 (36.4 %)
Chronic cardiac disease (N (%))	1334 / 4982 (26.8 %)	760 / 2666 (28.5%)	541 / 1948 (27.8 %)	187 / 581 (32.2 %)	32 / 137 (23.4 %)
Hypertension (N (%))	1889 / 4586 (41.2 %)	**1055 / 2374 (44.4 %) ** **	749 / 1735 (43.2 %)	240 / 520 (46.2 %)	**66 / 119 (55.5 %) ** **
Chronic pulmonary disease (N (%))	844 / 4979 (17.0 %)	466 / 2662 (17.5 %)	328 /1945 (16.9 %)	111 / 580 (19.1 %)	27 / 137 (19.7 %)
Chronic kidney disease (N (%))	491 / 4587 (10.7 %)	329 / 2379 (13.8 %) ***	220 / 1738 (12.7 %)	92 / 522 (17.6 %) ***	17 / 119 (14.3 %)
Moderate to severe liver disease (N (%))	50 / 4972 (1.0 %)	30 / 2662 (1.1%)	25 / 1947 (1.3%)	3 / 579 (0.5 %)	2 / 136 (1.5%)
Diabetes (N (%))	1261 / 4972 (25.4 %)	664 / 2662 (24.9 %)	481 / 1946 (24.7 %)	148 / 579 (25.6 %)	35 / 137 (25.5 %)
Immunosuppressives (N (%))	295 / 4445 (6.6 %)	192 / 2283 (8.4 %) **	129 / 1669 (7.7 %)	56 / 497 (11.3 %) **	7 / 117 (6.0 %)
Thiazide diuretics (N (%))	394 / 4994 (7.9 %)	258 / 2671 (9.7 %) **	186 / 1953 (9.5 %)	55 / 580 (9.5 %)	17 / 138 (12.3 %)
Loop diuretics (N (%))	389 / 4994 (7.8 %)	187 / 2671 (7.0 %)	128 / 1953 (6.6 %)	50 / 580 (8.6 %)	9 / 138 (6.5 %)
SSRIs (N (%))	164 / 4994 (3.3 %)	78 / 2671 (2.9 %)	53 / 1953 (2.7%)	15 / 580 (2.6%)	10 / 138 (7.2 %)

*BMI = body mass index; IQR = interquartile range; % = percentage of patients in this group with indicated characteristic; SSRI = Selective Serotonin Reuptake inhibitor. SNRI = Selective Serotonin and Noradrenalin Reuptake inhibitor. Significance was assessed using a Kruskal-Wallis test with post-hoc correction (for numerical data; non-normally distributed) or Chi-square test (for categorical data). p – values for all groups indicate the adjusted significance after post-hoc correction when compared to the normonatremia group. * Indicates a p-value <0.05, ** indicates a p-value <0.01, *** indicates a p-value <0.001*

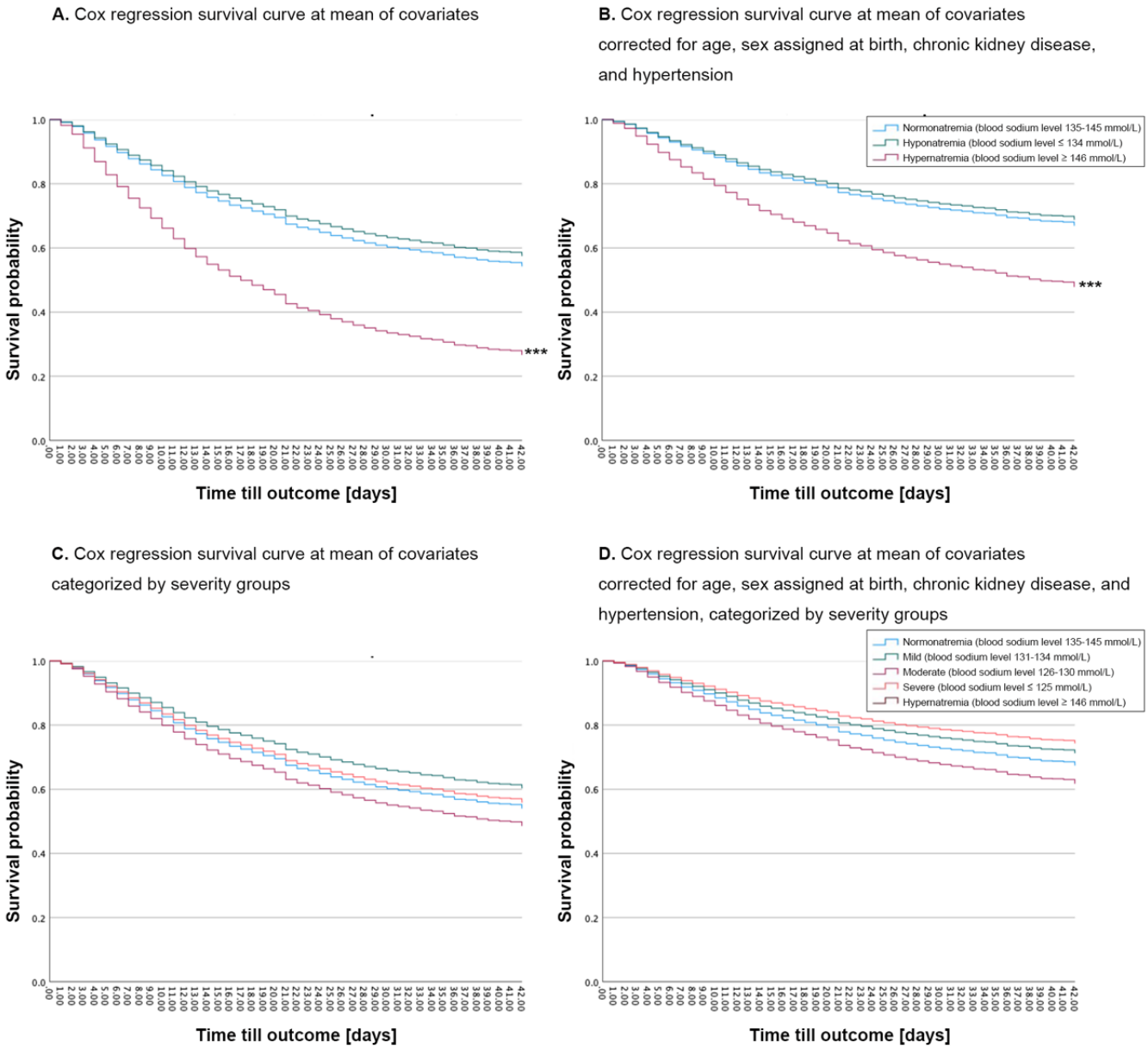
Supplemental Table 2 – Definitions for comorbidities

Comorbidity	Included diseases
Chronic pulmonary disease	Alpha-1 trypsin deficiency; asbestosis; cryptogenic organizing pneumonia; lymphangioeiomyomatosus; lung disease immuno-deficiency and chromosome breakage syndrome; bronchopulmonary dysplasia; primary ciliary dyskinesia; bronchiectasis; cystic fibrosis; chronic bronchitis or emphysema; lung fibrosis; sarcoidosis; obstructive sleep apnea; pulmonary hypertension
Chronic cardiac disease	**Chronical heart disease:** Myocardial infarction; Cardiac arrhythmias (AVNRT, atrial fibrillation, (supra)ventricular tachycardia, ventricular tachycardia, brugada syndrome, sick sinus syndrome, wolf parkinson white syndrome; decompensated heart failure, cardiomyopathy; valve disease (aortic valve stenosis, aortic valve insufficiency **Congential heart disease:** aortic valve insufficiency or aortic valve stenosis; Atrial septal defect or ventricular septal defect; hypoplastic left heart syndrome; Ebstein's anomaly; patent ductus arteriosis; tetralogy of Fallot; transposition of the great vessels
Chronic kidney disease	Acute tubulointerstitial nephritis; hemolytic uremic syndrome (HUS); amyloidosis; Anti-glomerular basement membrane disease; bartter syndrome; kidney damage due to medication, chronic bladder infections / kidney infections / diabetes, high blood pressure, arteriosclerosis; cryoglobulinemia, renal cystic disease; cystinosis; dense deposit disease (DDD); Focal segmental glomerulosclerosis (FSGS); Gitelman syndrome; glomerulonephritis; HNF1beta associated kidney disease; renal fusion (horseshoe kidney); IgA nephropathy; medullary sponge kidney; membranous nephropathy; minimal change disease; solitary kidney; Nail-patella syndrome (NPS); nephrogenic diabetes insipidus; nephroptosis; nephrotic syndrome; renal angiolipoma; renal cell carcinoma; primary hyperoxaluria; reflux nephropathy; atrophic kidney; scleroderma; lupus nephritis; Alport's syndrome; systemic vasculitis
Moderate to severe liver disease	Liver disease that caused cirrhosis (e.g. Budd Chiari, hemochromatosis, hepatitis, Wilson's disease)

Supplemental Table 3 – Subgroup analysis of signs and symptoms

Signs and symptoms	Na 135 – 145 mmol/L N = 3206	Na ≤134 mmol/L N = 1821	Na 131 – 134 mmol/L N = 1346	Na 126 – 130 mmol/L N = 383	Na ≤125 mmol/L N = 92
Nausea / vomiting (N (%))	1150 / 4129 (27.9 %)	679 / 2273 (29.9 %)	490 / 1663 (29.5 %)	151 / 499 (30.3 %)	38 / 111 (34.2%)
Diarrhea (N (%))	1146 / 4157 (27.6 %)	804 / 2298 (35.0%) ***	574 / 1686 (34.0 %) ***	180 / 501 (35.9%) ***	50 / 111 (45.0 %) ***
Anosmia (N (%))	352 / 3330 (10.6 %)	244 / 1904 (12.8 %)**	174 / 1395 (12.5 %)	62 / 420 (14.8 %)	8 / 89 (9.0 %)
Confusion (N (%))	651 / 4381 (14.9 %)	311 / 2319 (13.4%)	207 / 1688 (12.3 %)	78 / 511 (15.3 %)	26 / 120 (21.7 %)
Seizures (N (%))	31 / 3452 (0.9 %)	10 / 1977 (0.5%)	6 / 1448 (0.4 %)	2 / 434 (0.5 %)	2 / 95 (2.1 %)
FiO2 (median fraction (IQR))	N = 2084 0.36 (0.28 – 0.50)	N = 1159 0.36 (0.28 – 0.50)	N = 848 0.36 (0.28 – 0.48)	N = 258 0.36 (0.32 – 0.60)	N = 53 0.36 (0.31 – 0.75)
SBP (mean SBP in mmHg (SD))	N = 2648 132 (± 22)	N = 4971 135 (±23)***	N = 1934 132 (±22) ***	N = 578 132 (±22)**	N = 136 138 (±27)
HR (mean HR in BPM (SD))	N = 4965 91 (±20)	N = 2661 92 (±18) **	N = 1946 92 (±18) *	N = 580 92 (±18)	N = 135 90 (±19)
Disturbed capillary refill (N (%))	93 / 1369 (6.8 %)	81 / 863 (9.4 %)	51 / 614 (8.3 %)	27 / 206 (13.1 %)	3 / 43 (7.0 %)
Blood urea level (median level n mmol/L (IQR))	N = 4776 6.2 (4.5 – 9.2)	N = 2549 6.3 (4.5 – 9.3)	N = 1892 6.3 (4.6 – 9.1)	N = 559 6.2 (4.5 – 10.2)	N = 128 5.5 (4.2 – 9.8)
eGFR rate using 2021 CKD-epi creatinine equation in (median clearance in ml/min/1.73 m^3 (IQR))	N = 4983 68 (46 – 94)	N = 2656 64 (45 – 90) ***	N = 1944 64 (46 – 89) ***	N = 575 63 (41 – 90) ***	N = 137 79 (46 – 92)
CT-severity score (mean score (SD))	N = 1401 12.1 (±5.6)	N = 909 12.4 (±5.5)	N = 684 12.3 (±5.4)	N = 190 12.6 (±5.4)	N = 35 12.5 (±6.7)
Blood CRP level (median level in mg/L (IQR))	N = 4939 70.8 (28.0 – 131)	N = 2646 93.1 (49.0 – 154) ***	N = 1933 93.0 (48.2 – 151) ***	N = 577 103 (54.6 – 166) ***	N = 136 82.5 (36.0 – 145)
Blood LDH level (median level in U/L (IQR))	N = 4226 323 (247 – 426)	N = 2238 349 (268 – 471) ***	N = 1651 346 (269 – 467) ***	N = 479 361 (269 – 482) ***	N = 108 331 (240 – 543)
Modified early warning score (MEWS) (median score (IQR))	N = 4055 3.0 (2.0 – 4.0)	N = 2337 3.0 (2.0 – 4.0) ***	N = 1709 3.0 (2.0 – 4.0) ***	N = 509 3.0 (2.0 – 4.0)	N = 119 3.0 (2.0 – 4.0)
Quick sequential organ failure assessment (median score (IQR))	N = 4131 1.0 (0.0 – 1.0)	N = 2373 (0.0 – 1.0)	N = 1735 1.0 (0.0 – 1.0)	N = 517 1.0 (0.0 – 1.0)	N = 121 1.0 (0.0 – 1.0)

*SBP = systolic blood pressure; HR = heart rate; CKD-epi = chronic kidney disease Epidemiology Collaboration BPM = beats per minute; IQR = interquartile range; SD = standard deviation; CRP = c-reactive protein; LDH = lactate dehydrogenase; % = percentage of patients in this group with indicated characteristic. Significance was assessed using a Kruskal wallis test with post-hoc correction (for numerical data) or Chi-square test (for categorical data). * Indicates a p-value <0.05, ** indicates a p-value <0.01, *** indicates a p-value <0.001*



Supplemental Figure 2. Cox proportional survival curves at the mean of covariates for (A) unadjusted 6-week mortality categorized by normo-, hypo-, and hypernatremia, (B) 6-week mortality adjusted for age, sex assigned at birth, a history of chronic kidney disease, and a history of hypertension stratified in normo-, hypo-, and hypernatremia, (C) unadjusted 6-week mortality stratified in normo- and hypernatremia and mild, moderate, and severe hyponatremia, and (D)) 6-week mortality adjusted for age, sex assigned at birth, a history of chronic kidney disease, and a history of hypertension stratified in normo- and hypernatremia and mild, moderate, and severe hyponatremia. * Indicates a p-value <0.05, *** indicates a p-value <0.001

Supplemental Table 4 – Subgroup analysis of outcome and complications

Outcome	Na 135 – 145 mmol/L N = 3206	Na ≤134 mmol/L N = 1821	Na 131 – 134 mmol/L N = 1346	Na 126 – 130 mmol/L N = 383	Na ≤125 mmol/L N = 92
Duration of admission (median days (IQR))	N = 4116 7 (3 – 14)	N = 2372 7 (4 – 16) ***	N = 1735 7 (4 –15) **	N = 514 8 (4 – 18)*	N123 8 (3 – 18)
Death or palliative discharge (N (%))	729 / 4568 (16.0 %)	405 / 2360 (17.2 %) [A]OR 1.042 (0.906 – 1.200)	269 / 1723 (15.6 %)	115 / 518 (22.2 %)	21 / 119 (17.6 %)
ICU-admission (N (%), 'do not intubate' excluded	710 / 3778 (18.8 %)	439 / 1923 (22.8 %) [A]OR 1.274 (1.112 – 1.458)***	314 / 1422 (22.1 %) [A]OR 1.205 (1.036 – 1.401)*	104 / 410 (25.4 %) [A]OR 1.487 (1.170 – 1.889)***	21 / 91 (23.1 %) [A]OR 1.431 (0.868 – 2.360)
Duration of ICU-admission (days (IQR)) 'do not intubate' excluded	N = 437 10 (4 – 19)	N = 299 8 (3 - 19) p = 0.356	N = 215 8 (3 – 20)	N = 68 8 (4 – 18)	N = 16 9 (4 – 21)
Invasive ventilation (N (%)), 'do not intubate' excluded	623 / 3706 (16.8 %)	352 / 1889 (18.6 %) [A]OR 1.122 (0.970 – 1.298)	250 / 1396 (17.9 %)	85 / 402 (21.1 %)	17 / 91 (18.7 %)
Discharge alive within 42 days; N indicating the number of non-censored cases	N = 2747	N = 1527 [A]HR 0.955 (0.897 – 1.017) p = 0.154	N = 1153	N = 302	N = 72
Use of tocilizumab, sarilumab, or anakinra (N (%))	199 / 1245 (16.0%)	134 / 688 (19.5%) [A]OR 1.256 (0.984 – 1.604) p = 0.068	91 / 480 (19.0 %)	36 / 169 (21.3 %)	7 / 39 (17.9%)
Complications	**Na 135 – 145 mmol/L N = 3206**	**Na ≤134 mmol/L N = 1821**	**Na 131 – 134 mmol/L N = 1346**	**Na 126 – 130 mmol/L N = 383**	**Na ≤125 mmol/L N = 92**
Bacterial pneumonia (N (%))	501 / 4307 (11.6 %)	289 / 2212 (13.1 %) [A]OR 1.123 (0.962 – 1.312)	207 / 1619 (12.8 %)	72 / 483 (14.9 %)	10 / 110 (9.1 %)
Aspergillosis pneumonia (N (%))	83 / 3456 (2.4 %)	67 / 1915 (3.5 %) [A]OR 1.436 (1.034 – 1.993)	49 / 1402 (3.5 %) [A]OR 1.426 (0.995 – 2.044)	14 / 417 (3.4 %) [A]OR 1.352 (0.759 – 2.410)	4 / 96 (4.2 %) [A]OR 1.839 (0.657 – 5.148)
ARDS (N (%))	404 / 4323 (9.3 %)	224 / 2223 (10.1 %) [A]OR 1.081 (0.909 – 1.286)	161 /1627 (9.9 %)	52 / 486 (10.7 %)	11 / 110 (10.0 %)
Treatment for septic shock (N (%)) [&]	135 / 4175 (3.2 %)	94 / 2153 (4.4 %) [A]OR 1.326 (1.013 – 1.737)*	66 / 1570 (4.2 %) [A]OR 1.274 (0.943 – 1.721)	25 / 478 (5.2 %) [A]OR 1.570 (1.012 – 2.438)*	3 / 105 (2.9%) [A]OR 0.920 (0.287 – 2.946
Congestive heart failure (N (%))	125 / 4352 (2.9 %)	64 / 2235 (2.9 %) [A]OR 0.946 (0.696 – 1.287)	34 / 1637 (2.1%)	23 / 488 (4.7 %)	7 / 110 (6.4 %)
Physical decline (N (%))	950 / 4126 (23.0 %)	576 / 2116 (27.2 %) [A]OR 1.221 (1.082 – 1.377)**	414 / 1544 (26.8 %) [A]OR 1.206 (1.054 – 1.380)**	136 / 468 (29.1 %) [A]OR 1.303 (1.053 – 1.614)*	26 / 104 (25.0 %) [A]OR 1.059 (0.674 – 1.666)

Delirium (N (%))	451 / 4146 (10.5 %)	237 / 2136 (11.1 %) [A]OR 0.987 (0.833 - 1.170)	157 / 1557 (10.1 %)	62 / 474 (13.1 %)	18 / 105 (17.1 %)

*ICU = Intensive care unit; ARDS = acute respiratory distress syndrome. OR = odds ratio [A]OR = adjusted odds ratio; odds ratio corrected for sex assigned at birth and age. [#]Uncorrected for sex assigned at birth and age [&] Treatment for septic shock was defined as the need for vasopressors in order to maintain mean arterial blood pressure >65 mmHg and blood lactate level >2 mmol/L, in the absence of other causes including hypovolemia. Significance was assessed using a Kruskal wallis test with post-hoc correction (time to discharge alive) or logistic regression (all other values). * Indicates a p-value <0.05, ** indicates a p-value <0.01, *** indicates a p-value <0.001*

Supplemental Table 5 – Characteristics of patients with the order 'do not intubate'

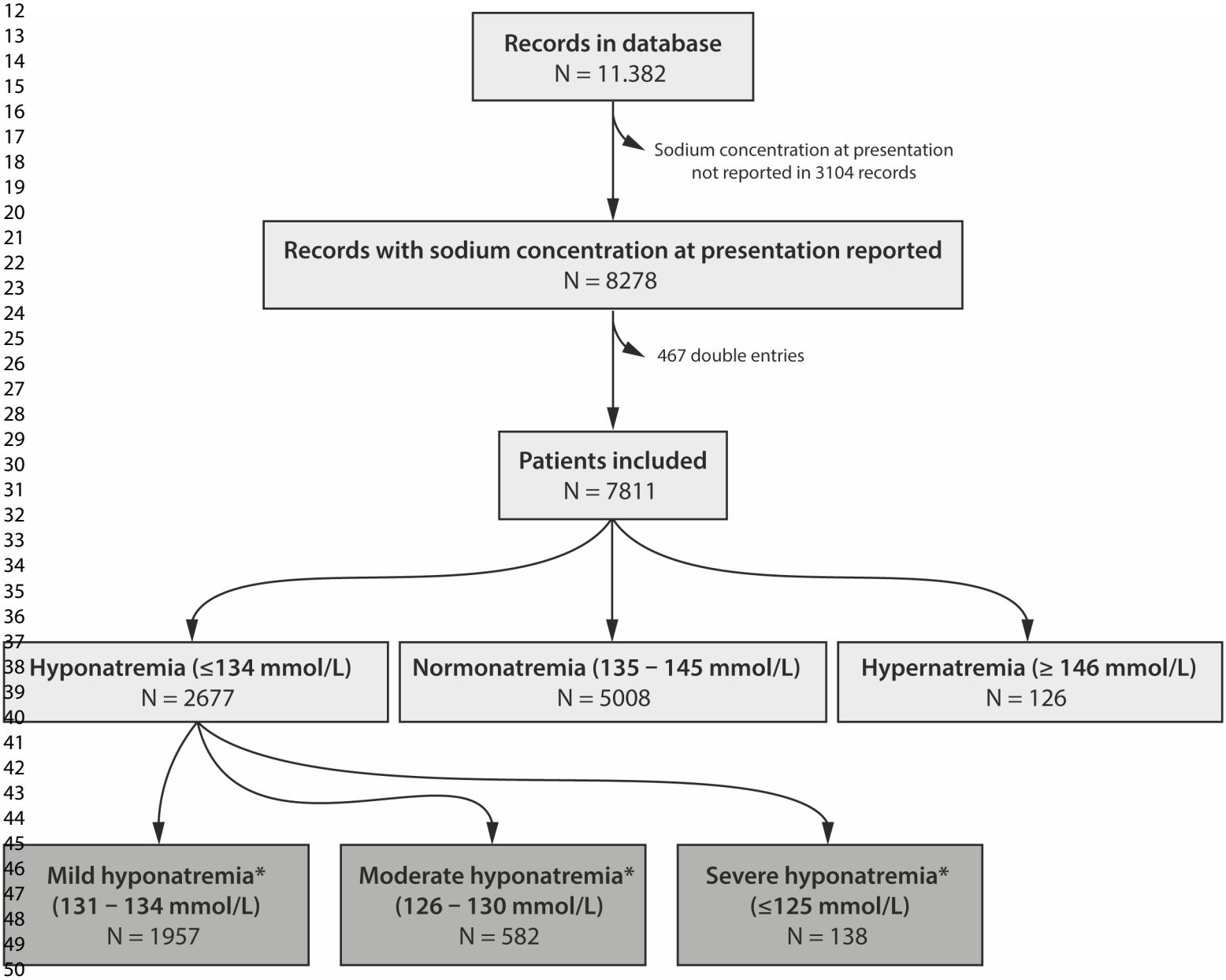
	Order 'do not intubate'	**No order 'do not intubate'**	**p-value**
Sex assigned at birth (N (%))	♀ 531/ 1576 (33.7 %) ♂ 743 / 2388 (31.1 %)	♀ 1045 / 1576 (66.3 %) ♂ 1645 / 2388 (68.9 %)	p = 0.095
Age (median age in years (IQR))	79 (73 – 84)	62 (53 -71)	p < 0.001
BMI (median BMI in kg/m^2 (IQR))	26.2 (23.1 – 30.1)	27.9 (25.0 – 31.9)	p < 0.001
Chronic pulmonary disease (N (%))	361 / 1270 (28.4 %)	359 / 2680 (13.4%)	p < 0.001
Asthma (N (%))	95 / 1269 (7.5 %)	256 / 2678 (9.6%)	p = 0.036
Chronic obstructive pulmonary disease (N (%))	125 / 267 (46.8 %)	80 / 293 (27.3 %)	p < 0.001
Chronic kidney disease (N (%))	259 / 1270 (20.4 %)	250 / 2681 (9.3%)	p < 0.001
Chronic cardiac disease (N (%))	637 / 1266 (50.3 %)	564 / 2683 (21.0%)	p < 0.001
Hypertension (N (%))	755 / 1270 (59.4 %)	1051 / 2685 (39.1 %)	p < 0.001
Moderate to severe liver disease (N (%))	21 / 1267 (1.7 %)	28 / 2680 (1.0 %)	p = 0.123
Diabetes (N (%))	457 / 1270 (36.0 %)	679 / 2680 (25.3 %)	p < 0.001
Neoplasm (N (%))	156 / 1273 (12.3 %)	130 / 2682 (4.8 %)	p < 0.001

BMI = Body Mass Index. Significance was assessed using a Mann-Whitney test (for numerical data) or Chi-square test (for categorical data). p – values for all groups indicate the 2-tailed significance between the two groups.

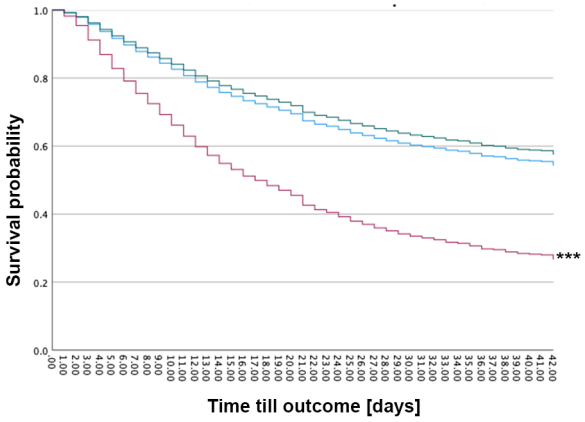
Supplemental Table 6 – Patient characteristics, signs and symptoms, outcome measures, and complications of patients with hyponatremia (Na ≤ 134 mmol/L) that did not use diuretics stratified based on their urinary sodium excretion.

Patient characteristics	**Urinary sodium excretion < 30 mmol/L** % or IQR N = 72	**Urinary sodium excretion ≥ 30 mmol/L** % or IQR N = 73	**p - value**
Age (median age in years (IQR))	N = 72 67 (56 – 74)	N = 73 69 (59 – 76)	p = 0.47
Sex assigned at birth (N (%))	♂ 38 (53%) ♀ 34 (47%)	♂ 43 (59%) ♀ 30 (41%)	p = 0.51
Vomiting/nausea (N (%))	32 / 71 (45.1 %)	19 / 67 (28.4 %)	p = 0.05
Diarrhea (N (%))	26 / 67 (38.8 %)	28 / 68 (41.2 %)	p = 0.86
Heart rate (mean HR in BPM (SD))	N = 71 89.7 (± 16.3)	N = 72 93.1 (±18.9)	p = 0.20
Systolic blood pressure (mean SBP in mmHg (SD))	N = 70 135 (± 24.8)	N = 71 137 (±24.1)	p = 0.87
Disturbed capillary refill (N (%))	3 / 27 (11.1 %)	4 /31 (12.9 %)	p = 1.00
eGFR rate using 2021 CKD-epi creatinine equation in (median clearance in ml/min/1.73 m^3 (IQR))	N = 71 67 (49 – 90)	N = 73 71 (32 – 92)	p = 0.49
CRP (median level in mmol/L (IQR))	N = 70 111 (52.5 – 163)	N = 71 70 (35.0 – 154)	**p = 0.028**
LDH (median level in U/L (IQR))	N = 57 351 (270 – 491)	N = 61 273 (227 – 434)	**p = 0.021**
CT-severity score (median score (IQR))	N = 33 11.0 (7.0 – 15.0)	N = 40 12.0 (6.0 – 16.8)	p = 0.86
Outcome			
Death or palliative discharge (N (%))	14 / 72 (19.4%)	18 / 73 (24.7 %)	p = 0.55
ICU-admission (N (%), ‘do not intubate’ excluded	24 / 65 (36.9 %)	25 / 61 (41.0 %)	p = 0.72
Invasive ventilation (N (%)), ‘do not intubate’ excluded	18 / 64 (28.1 %)	23 / 60 (38.3 %)	p = 0.26

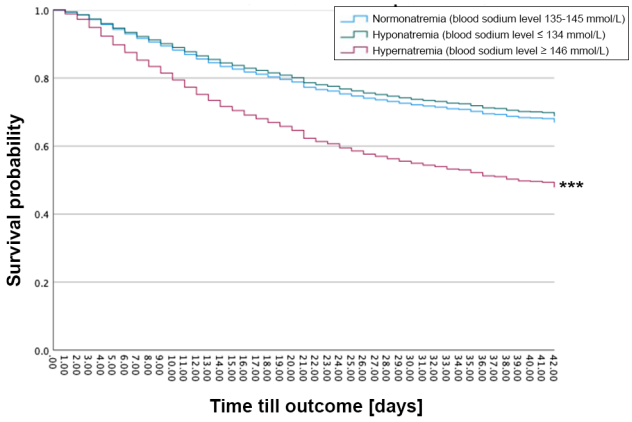
CRP = C-reactive protein; LDH = lactate dehydrogenase; CT = computed tomography; ICU = intensive care unit; eGFR = estimated glomerular filtration rate; CKD-epi = chronic kidney disease Epidemiology Collaboration. Significance was assessed using a Mann-Whitney test (for numerical data) or Chi-square test (for categorical data). p – values for all groups indicate the 2-tailed significance between the two groups.


Records in database
N = 11.382
Sodium concentration at presentation not reported in 3104 records
Records with sodium concentration at presentation reported
N = 8278
467 double entries
Patients included
N = 7811
Hyponatremia (≤134 mmol/L)
N = 2677
Normonatremia (135 – 145 mmol/L)
N = 5008
Hypernatremia (≥ 146 mmol/L)
N = 126
Mild hyponatremia*
(131 – 134 mmol/L)
N = 1957
Moderate hyponatremia*
(126 – 130 mmol/L)
N = 582
Severe hyponatremia*
(≤125 mmol/L)
N = 138

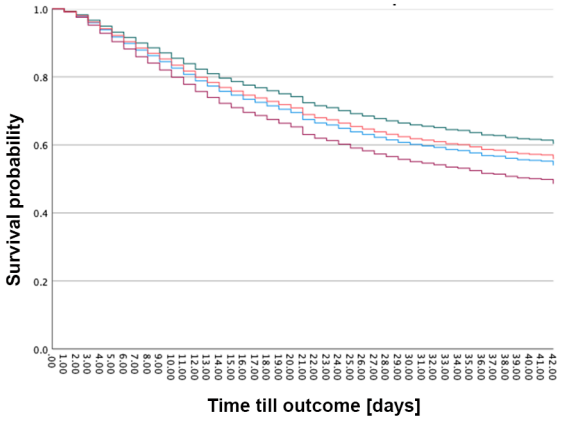
A. Cox regression survival curve at mean of covariates



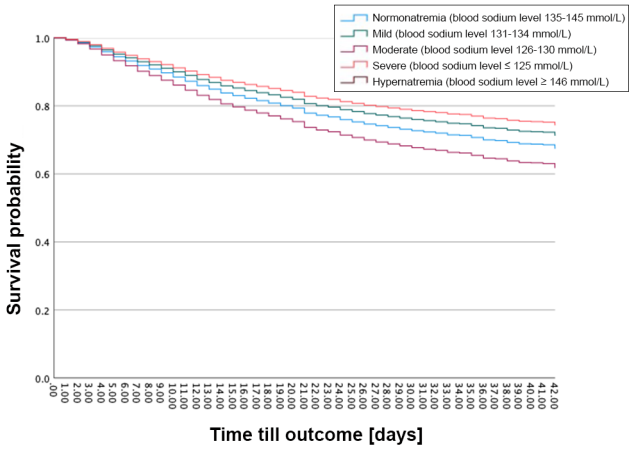
B. Cox regression survival curve at mean of covariates corrected for age, sex assigned at birth, chronic kidney disease, and hypertension



C. Cox regression survival curve at mean of covariates categorized by severity groups



D. Cox regression survival curve at mean of covariates corrected for age, sex assigned at birth, chronic kidney disease, and hypertension, categorized by severity groups



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6 and 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6 and 7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6 and 7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	FIG 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1, p 24
		(b) Indicate number of participants with missing data for each variable of interest	Table 1-4, p 24 to 29
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	FIG 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3, p 27-29
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8, 9, 11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

What is the etiology of dysnatremia in COVID-19 and how is this related to outcomes in patients admitted during earlier and later COVID-19 waves? A multicentre, retrospective observational study in eleven Dutch hospitals

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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Renal medicine, Respiratory medicine
Keywords:	INTERNAL MEDICINE, COVID-19, INFECTIOUS DISEASES

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What is the etiology of dysnatremia in COVID-19 and how is this related to outcomes in patients admitted during earlier and later COVID-19 waves? A multicentre, retrospective observational study in eleven Dutch hospitals

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Abstract

Objectives

To evaluate the relation between dysnatremia at hospital presentation and duration of admission, risk of ICU-admission, and all-cause mortality and to assess the underlying pathophysiological mechanism of hyponatremia in COVID-19 patients. Our hypothesis is that both hypo- and hypernatremia at presentation are associated with adverse outcomes.

Design

Observational study

Setting

Secondary care; eleven Dutch hospitals (2 university and 9 general hospitals)

Participants

An analysis was performed within the retrospective multicenter cohort study COVIDPredict. 7811 patients were included (60% males, 40% females) between February 24th 2020 and august 19th 2022. Patients who were ≥18 years with PCR-confirmed COVID-19, or CT with COVID-19 reporting and data system score ≥4 and alternative diagnosis were included. Patients were excluded when serum sodium levels at presentation were not registered in the database or when they had been transferred from another participating hospital.

Outcome measures

We studied demographics, medical history, symptoms, and outcomes. Patients were stratified according to serum sodium concentration and urinary sodium excretion.

Results

Hyponatremia was present in 2677 (34.2%) and hypernatremia in 126 (1.6%) patients. Patients with hyponatremia presented more frequently with diarrhea, lower blood pressure, and tachycardia.

Hyponatremia was, despite a higher risk for ICU admission (OR 1.27 (1.11-1.46; p <0.001), not associated with mortality or the risk for intubation. Patients with hypernatremia had higher mortality rates (OR 2.25 1.49 – 3.41; p <0.001) and were at risk for ICU-admission (OR 2.89 (1.83 – 4.58) and intubation (OR 2.95 (1.83 – 4.74).

Conclusions

Hypernatremia at presentation was associated with adverse outcomes in COVID-19 patients. Hypovolemic hyponatremia was found to be the most common etiology of hyponatremia. Hyponatremia of unknown etiology was associated with a higher risk for ICU admission and intubation and longer duration of admission.

Strengths and limitations of this study

- This study includes over 7000 patients from different COVID-19 waves and from multiple hospitals, resulting in an heterogenous patient population;
- This study relates the different presumed etiologies to clinical outcomes;
- A relative low number of urinary samples was available for patients with hyponatremia;
- Different treatment options that became available for COVID-19 during the ongoing pandemic were not taken into account in thus study, which may have influenced the outcome of patients.

1. Introduction

The coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic since February 2020. By the time of October 19th, 2022, there had been over 621 million reported cases and 2.9 million deaths attributed to coronavirus disease 19 (COVID-19), which is caused by SARS-COV-2-infection. Respiratory failure resulting from acute respiratory distress syndrome is the leading cause of death associated with SARS-CoV-2 infection[1-3].

Common signs and symptoms of COVID-19 infection vary widely, but fever, cough, and dyspnea are frequently present. Other less frequent symptoms include anosmia, nausea, vomiting, diarrhea, and general illness[1]. In addition to these clinical symptoms, certain laboratory markers can indicate COVID-19. Elevated lactate dehydrogenase (LDH) levels and lymphopenia are commonly observed[4,5]. Furthermore, electrolyte imbalances such as hypocalcemia, hypokalemia, and dysnatremia (hypo- or hypernatremia) are often present in COVID-19 patients upon hospital admission[4,6]. Hyponatremia, in particular, has been reported in 7% to 64% of COVID-19 cases[7-11], compared to 20-30% in all hospitalized patients[12]. It has been demonstrated that critically ill patients with COVID-19 more frequently develop hyponatremia during the first 72 hours of admission[13]. Hyponatremia is also frequently present in other infectious diseases, such as pneumonia, tuberculosis, meningitis, human immunodeficiency virus (HIV) infection, malaria, and leishmaniasis and has been linked to negative outcomes in these diseases and in COVID-19[7,8,11,14-17].On the other hand, hypernatremia is less common, occurring in less than 10% of the general population and in up to 38% of patients in intensive care units. Hypernatremia is also associated with adverse clinical outcomes[9,16,18-20].

The etiology of hyponatremia in infectious diseases, including COVID-19, can broadly be categorized into two groups based on urinary sodium excretion (USE). Low USE (<30 mmol/l) indicates an activation of the renin-angiotensin system (RAAS), e.g. due to hypovolemia resulting from inadequate dietary intake, vomiting or diarrhea. Conversely, high USE suggests RAAS inactivation, which could occur in patients with syndrome of inappropriate antidiuretic hormone secretion (SIADH) and in patients with critical illness-related corticoid deficiency, although diuretic usage can affect diagnostic accuracy[21,22]. In other infectious diseases, antidiuretic hormone (ADH) release has been linked to secretion of inflammatory marker interleukin-6[23]. Interleukin-6 is also enhanced in COVID-19 patients and is targeted by off-label administration of interleukin-6-inhibitors, like tocilizumab and

sarilumab[3,24]. Both etiologies (hypovolemic hyponatremia and inadequate ADH secretion) have been proposed to contribute to hyponatremia in COVID-19, although the exact mechanism is still unclear. Hypernatremia primarily occurs due to insufficient water intake, often caused by hypothalamic thirst center dysfunction or limited access to fluid intake. It can also result from diabetes insipidus, a condition characterized by ADH deficiency or resistance[25].

Previous studies have associated both hyponatremia and hypernatremia with worse clinical outcomes in COVID-19 patients during the early stages of the pandemic[7,8,11,15,17,19]. However, most of these studies were conducted before interleukin-6 inhibitors were administered and before the registration of Sars-CoV-2 vaccines[3,7,11,19,26-29]. Additionally, they lacked data on clinical parameters at presentation and how they differed between patients with or without dysnatremia, making it difficult to determine the underlying cause of the hyponatremia and to relate this cause to clinical outcomes[16,27,30-32].

This study reports the incidence rates of hypo- and hypernatremia upon admission in COVID-19 patients from a large multi-center cohort study in The Netherlands, encompassing multiple COVID-19 waves. We hypothesize that both hyponatremia and hypernatremia can predict adverse outcomes, including ICU admission, the need for invasive ventilation, and mortality rates among hospitalized COVID-19 patients. Furthermore, we seek to investigate potential pathophysiological mechanisms underlying these conditions based on clinical features and laboratory values at presentation.

2. Methods

2.1 Patient recruitment

We utilized data from the ongoing retrospective multicenter COVIDPredict Clinical Course Cohort, containing over 10,000 patients with COVID-19, recruited between February 24th, 2020, and August 9th, 2022, in eleven Dutch hospitals (two university and nine general hospitals). Inclusion criteria for the database required patients to be 18 years or older and either had a positive polymerase chain reaction (PCR) test for SARS-CoV-2 or had a COVID-19 reporting data system (CO-RADS) score of 4 (indicating abnormalities suspicious for COVID-19) or 5 (indicating typical COVID-19) on thoracic computed tomography (CT)-scan in the absence of an alternative diagnosis[33]. A waiver for the use of hospital data was obtained from the Medical Ethical Committees of the participating centers (Amsterdam UMC; 20.131) to utilize the hospital data. Patients were given the opportunity to opt out. To avoid duplicate entries, patients transferred from one participating hospital to another were excluded, resulting in a total 297 exclusions.

2.2 Study design

The included patients were categorized into three groups based on their serum sodium concentration upon admission to the participating hospital. The serum sodium concentration was adjusted for serum glucose concentration, whenever available, following the method described by Hillier, et al. [34]. The sodium concentrations were stratified as follows: 'normonatremia' (corrected serum sodium concentration (Na) 135-145 mmol/L), hyponatremia (corrected serum sodium concentration (Na) <135 mmol/L), further subcategorized as 'mild' (corrected serum sodium concentration Na 131-134 mmol/L), 'moderate' (corrected serum sodium concentration Na 126-130 mmol/L), and 'severe' (corrected serum sodium concentration Na $\leq$ 125 mmol/L) (Supplemental information). 'Hypernatremia' referred to corrected serum sodium concentration Na $\geq$ 146 mmol/L. Throughout the text, serum sodium concentrations and sodium groups refer to the corrected sodium values unless otherwise specified.

Demographic information such as ethnicity, sex at birth, and age, as well as co-morbidities categorized according to predetermined groups (additional information in the Supplemental Information), home medication, and presenting signs and symptoms were compared between the

groups and between normonatremia and different severity categories of hyponatremia (Supplemental information). Serum concentrations of creatinine, urea, C-reactive protein (CRP), and LDH were measured at the time of first presentation in the participating hospital. The estimated glomerular filtration rate (eGFR) was calculated using the 2021 Chronic kidney disease Epidemiology Collaboration (CKD-epi) formula based on serum creatinine levels[35]. The Modified Early Warning Score (MEWS) and Quick Sequential Organ Failure Assessment (qSOFA) were calculated based in clinical values obtained at presentation.

The following clinical outcome measures were compared between the groups and across different severity categories: duration of hospitalization, admission to intensive care unit, invasive ventilation, duration of ICU admission, discharge alive, death, and the administration of tocilizumab, sarilumab, or anakinra. Additionally, the incidence of complications was compared between the groups.

2.3 Statistical analysis

All data were analyzed using SPSS version 27. Comparisons were conducted between hyper-, normo-, and hyponatremia (Main Text) and between the normonatremia, mild, moderate, and severe hyponatremia groups (Supplemental Information). Baseline numerical data were presented as median and interquartile range, and the Kruskal Wallis test was used for analysis when the data were not normally distributed. For normally distributed data, baseline numerical data were presented as mean and standard deviation, and one-way ANOVA was employed for analysis. Baseline categorical data were displayed as absolute number and percentage of patients with the specific condition, and the Chi-square test was used for analysis.

Outcome data (risk for ICU-admission, intubation, mortality rates, use of tocilizumab, sarilumab, or anakinra, and complications) were assessed using a binary logistic regression model. The odds ratios were calculated and adjusted for age, sex assigned at birth (categorized as male or female based on genotype and internal and external anatomy at birth), a history of chronic kidney disease, and a history of hypertension. The duration of hospital and ICU admission were evaluated using a Kruskal Wallis test. Survival analysis over a 6-week period from hospital admission was conducted using Cox proportional hazard regression analysis to estimate cumulative mortality rates and cumulative rates for being

discharged alive for patients with and without dysnatremia. The hazard ratios were adjusted for age, sex assigned at birth, a history of chronic kidney disease, and a history of hypertension.

A p-value of ≤ 0.05 was considered statistically significant for all statistical tests. Patients who did not have data available for the specific variable being tested were excluded from the corresponding analysis.

2.4 Patients and public involvement

This study was largely conducted during the first waves of the COVID-19 pandemic. As a result, it was not feasible to directly involve patients in the design of the study. Patients received information about the CovidPredict database via pamphlets and verbal communication. Additionally, information was available on the websites of participating hospitals and through various media channels. Details regarding the study design and dissemination plans are available on our website www.covidpredict.org.

3. Results

3.1 Incidence of dysnatremia at presentation

At the time of August 9th, 2022, the database contained a total of 11.382 records. Serum sodium concentrations at admission were available for 8278 (73%) admissions from 7811 patients (170 duplicate entries due to readmission and 297 patients had been transferred from or previously admitted to another participating hospital and transfer records were therefore excluded). Patients were included based on two criteria: a positive result for SARS-CoV-2 PCR (6673 patients) and or a CO-RADS score 4 or 5 in the absence of an alternative diagnosis (1138 patients). In cases where patients were readmitted, the admission with the abnormal sodium level at presentation (in case of hyponatremia or hypernatremia) or the first admission (in case sodium concentrations were normal for both presentations) was included in the analysis.

Of the 7811 included patients with COVID-19, 2677 (34.3%) presented with hyponatremia (corrected blood serum Na <135 mmol/L), and 126 (1.6%) presented with hypernatremia (corrected blood serum Na $\geq$ 146 mmol/L). Among the patients presenting with hyponatremia, 1957 (25.1%) presented with blood serum Na ranging 131-134 mmol/L (considered 'mild'), 582 (7.5%) presented with blood serum Na ranging 126-130 mmol/L (considered 'moderate'), and 138 (1.8%) with blood serum Na $\leq$ 125 mmol/L (considered 'severe') (see Supplemental Figure 1). A total of 1888 patients were included after the start of the SARS-CoV-19 vaccination campaign in the Netherlands on January 6th, 2021, of whom 445 were vaccinated (319 had received two or more doses). A total of 6186 patients (79.2%) started having symptoms prior to the seventh week of 2021, when the initial SARS-CoV-2 variants were most prevalent. 800 patients (10.2%) developed symptoms from the seventh to twenty-fifth week of 2021, when alpha-variants dominated in the Netherlands. 700 patients (9.0%) started having symptoms when delta variants dominated (twenty-sixth to fifty-first week of 2021), and 122 patients (1.6%) when the omicron variants dominated (after the fifty-second week of 2021)[36].

3.2 Patient characteristics of patients presenting with dysnatremia

Table 1 shows the characteristics of patients with hyponatremia and hypernatremia compared to patients presenting with normal sodium concentrations at presentation. Both hypo- and hypernatremia occurred more often in males than in females (Table 1), except for 'severe' hyponatremia (Supplemental Table 1). The mean age of patients with and without hyponatremia differed slightly, with patients presenting with 'moderate' or 'severe' hyponatremia being significantly older (median age 68.1 and 70.6 years, respectively). Patients with hypernatremia were also older, with a mean age of 72.5 years. The body mass index (BMI) of patients presenting with hyponatremia tended to be slightly lower compared to those with normal sodium levels and was also lower in patients presenting with hypernatremia. Abnormal sodium levels at presentation were associated with chronic kidney disease. Patients with hyponatremia, particularly those with severe hyponatremia, more frequently had a history of hypertension, but this difference was not statistically significant for the subgroup of patients who did not use diuretics (36.4% (normonatremia) vs. 39.1% (hyponatremia); p = 0.003; determined by a Chi-square test). The presence of hypo- or hypernatremia was not associated with a history of chronic heart, pulmonary, or liver disease (refer to Supplemental Table 2 for definitions). Regarding medication use, the use of thiazide diuretics was higher in patients with hyponatremia (Table 1), but the overall use of diuretics or the use of loop diuretics did not differ between the groups. Similarly, the use of selective serotonin (and noradrenalin) reuptake inhibitors (SSRIs/SNRIs) did not show significant differences between the groups. The use of immunosuppressives was more common in patients presenting with hyponatremia as compared to those with normal sodium concentration at presentation.

3.3 Signs and symptoms of patients presenting with dysnatremia

Patients with hyponatremia more frequently presented with diarrhea and anosmia compared to patients without hyponatremia (Table 2 and Supplemental Table 3). The presence of vomiting or nausea as presenting symptoms was not associated with hyponatremia. In the hypernatremia group, confusion was more frequently observed compared to patients with normal sodium levels. A prolonged capillary refill time of ≥3s, which may indicate dehydration, was more often present in the hypernatremia group.

Patients with hypernatremia also had a slightly higher heart rate. Hyponatremia was associated with a slightly higher heart rate and a slightly lower systolic blood pressure, although these differences were not clinically significant. Both patients with hypernatremia and hyponatremia had a lower eGFR, with a more pronounced effect observed in the hypernatremia group (Table 2). A lower eGFR was associated with slightly higher mortality rates (unadjusted HR 1.008, 95% CI 1.007 – 1.008); p = 0.001, analyzed using a Cox proportional hazard regression analysis), regardless of sodium levels at presentation or exclusion of patients with chronic kidney disease. Enhanced blood urea concentration was only associated with hypernatremia.

Patients with hyponatremia had higher blood CRP and LDH concentrations compared to those with normal sodium levels (Table 2). However, the fraction of supplemented oxygen (FiO2) and CT-severity scores did not differ significantly between the groups. The clinical score systems MEWS and qSOFA[37] (Table 2) also showed significant differences between the groups, but these differences were not clinically relevant.

Furthermore, patients with hyponatremia had a slightly longer duration of complaints compared to those with normonatremia (8.8 days for hyponatremia vs. 8.6 days for normonatremia; p = 0.010; assessed using a Kruskal-Wallis test), although this difference was not clinically relevant.

3.4 Clinical outcomes in patients presenting with dysnatriemia

Hypernatremia was associated with higher mortality rates or palliative discharge rates compared to the normo- and hyponatremia groups (Table 3, Figure 1, and Supplemental Figure 2). Additionally, patients with hypernatremia had a higher risk of ICU-admission and invasive ventilation. However, hyponatremia was not associated with increased mortality or palliative discharge rates (Table 3). Although there was a trend towards increased mortality in patients with severe hyponatremia, these results did not reach statistical significance due to the low number of patients that presented with sodium levels $\leq$ 125 mmol/L (Supplemental Table 4). After excluding patients with a 'do not intubate' order hyponatremia was associated with a higher likelihood of ICU-admission, but not with the need for invasive ventilation. Off all hyponatremic patients to admitted to the ICU (N = 486), 62 (12.8%) did not receive any form of ventilatory support ((non-)invasive ventilation or high flow nasal therapy). This percentage was similar (10.5 %; p = 0.403) among patients with normonatremia admitted to the ICU. The duration of ICU

admission was similar for patients with hypo-, normo-, and hypernatremia (Table 3). Based on the additional details provided in Supplemental Table 5, patients with the order 'do not intubate' are considered frailer and thus had limited live expectancy.

Hyponatremia corrected for glucose was used for all statistical testing. However, as some other studies used uncorrected hyponatremia[30,38], we also examined the association of uncorrected hyponatremia with different outcomes. Without correction for serum glucose concentration, hyponatremia was still associated with a slightly higher rate of ICU admission (adjusted odds ratio (^{A}OR) 1.40 (1.23 – 1.60); $p < 0.001$) and with the need for intubation (^{A}OR 1.26 (1.10 – 1.46); $p = 0.001$), but not with death or palliative discharge rates (^{A}OR 1.11 (0.97 – 1.28); $p = 0.13$).

Despite the correlation with ICU admission in patients with hyponatremia, the duration of admission was not significantly longer in this group. Similar outcomes were observed for patients with confirmed COVID-19 (SARS-CoV-2 PCR positive; 6673 patients) only, although in this subgroup, the higher risk for ICU admission for patients with hyponatremia no longer reached statistical significance.

As the COVID-19 pandemic progressed, the incidence of adverse outcomes was significantly higher for patients with normo-, and hyponatremia at presentation that started having complaints when delta variants dominated as compared to those admitted during the earlier COVID-19 waves when the initial variants dominated (Figure 2). The use of tocilizumab, sarilumab (interleukin-6 receptor agonists) and anakinra (interleukin-1 receptor agonist) did not differ between the groups. Administration of COVID-19 vaccination was not reported frequently enough to draw conclusions about its possible effects on outcome measures.

3.5 Complications associated with hyponatremia upon admission

After adjusting for sex assigned at birth, age, and a history of chronic kidney disease and hypertension, the course of disease of patients with hyponatremia was more often complicated by an aspergillosis pneumonia (almost exclusively in patients that needed invasive ventilation and more frequently in patients treated with dexamethasone, antibiotics, tocilizumab, sarilumab, or anakinra) and physical decline (the latter was scored when explicitly documented in the patients' medical records, when the patient suffered from 'ICU-acquired weakness', or when the patient was referred for medical rehabilitation).

Patients with hypernatremia, on the other hand, were more likely to experience acute respiratory distress syndrome and receive treatment for septic shock (defined as the need for vasopressors in order to maintain mean arterial blood pressure >65 mmHg and blood lactate level >2 mmol/L, in the absence of other causes including hypovolemia). They also had a higher incidence of delirium. It should be noted that excessive fluid resuscitation for the management of hypo- or hypernatremia could potentially lead to congestive heart failure, but the occurrence of this complication was rare and did not occur more frequently in patients with abnormal sodium values at presentation.

3.6 Urinary sodium excretion related to patients' characteristics and outcomes

USE was measured in 185 (6.9%) patients with hyponatremia of whom 145 (78%) did not use diuretics. Among these patients were 48 with 'mild', 67 with 'moderate', and 30 with 'severe' hyponatremia. The range of USE was 5.0 to 239 mmol/L, with a median of 30.0 mmol/L. Urinary osmolarity (UOL) was measured in 81 (3.0%) patients who did not use diuretics, including 26 with 'mild', 37 with 'moderate', and 18 with 'severe' hyponatremia. The range of UOL values was 8 - 1007 mOsmol/kg, with a median of 496 mOsmol/kg. Among patients in whom both USE and UOL were measured, 12 patients (15% of the total) met the definition of SIADH (USE ≥ 30 mmol/L and UOL $\geq$ 100 mOsmol/kg in the absence of diuretic use and signs of hypovolemia (systolic blood pressure < 90 mmHg or heart rate $\geq$ 100 BPM)).

Patients were divided in two groups based on USE. Out of urinary sodium measurements, 72 patients (49.7%) had low USE (< 30 mmol/L), indicating activation of the RAAS, while 73 patients (50.3%) had high USE (≥ 30 mmol/L), indicating activation of the RAAS (Supplemental Table 6). A low USE was associated with a higher levels of CRP (111 (52.5 – 163) mmol/L vs. 70 (35.0 – 154) mmol/L; p = 0.028) and LDH (351 (270 – 491) U/L vs. 273 (227- 434) U/L; p = 0.021) at presentation (Supplemental Table 6), but was not associated with symptoms such as nausea / vomiting or clinical signs of hypovolemia, such as tachycardia or hypotension. There were no significant differences in outcome measures, such as duration of admission, ICU admission, or death/palliative discharge, between patients with a low and high USE.

3.7 Etiology related to outcomes

Among the patients who presented with hyponatremia, 983 patients (36.7%) reported a history of gastrointestinal symptoms, such as nausea, vomiting, or diarrhea, and did not use diuretics or met the criteria for SIADH. The prevalence of gastrointestinal symptoms was highest when delta variants dominated (Supplemental Table 7). 271 patients (10.1%) used diuretics in the absence of gastrointestinal symptoms and this percentage was higher for patients that started having symptoms during the omicron wave (Supplemental Table 7). 12 (0.5%) who did not use diuretics complied to the definition of SIADH, of whom 5 also had gastro-intestinal symptoms. All patients that complied to the definition of SIADH started having symptoms when the initial COVID-19 variants dominated (Supplemental Table 7). Another group of 201 patients (7.5) had a history of nausea, vomiting, or diarrhea and used diuretics. However, the largest portion of patients (1210 patients, 45.2%) had an unknown etiology for hyponatremia, as they did not have a history of gastrointestinal symptoms, did not use diuretics, and did not meet the criteria for SIADH.

Figure 1D illustrates a cox proportional hazard curve, with separate lines representing each proposed etiology. It was observed that patients with a history of gastrointestinal symptoms had lower mortality rates compared to those with normal sodium levels (unadjusted hazard ratio (HR) 0.739, 95% confidence interval (CI) 0.611 – 0.894; p = 0.002), despite higher CRP (mean 95 mg/L, IQR 47.5 – 151 mg/L) and LDH levels (mean 350 U/L, IQR 271 – 470 U/L) compared to normonatremia (p <0.001; assessed using a Kruskal-Wallis test). Patients with hyponatremia of unknown etiology had a higher risk of ICU admission (unadjusted OR 1.299, 95% CI 1.091 – 1.549; p = 0.003; linear regression) and were at risk for intubation (unadjusted OR 1.313, 95% CI 1.109 – 1.554; p = 0.002; linear regression), which was in line with higher CRP levels (mean 98 mg/L, IQR 53 – 166 mg/L) and LDH levels (mean 353 U/L, IQR 270 – 479 U/L) in this group compared to normonatremia (p < 0.001; assessed using a Kruskal-Wallis test). However, the duration of ICU admission did not differ significantly among the different groups. It was found that patients with hyponatremia of unknown etiology had a slightly longer duration of hospital admission (8 days, interquartile range 4 – 17 days) compared to other groups (p = 0.005; assessed using the Kruskal-Wallis test).

4. Discussion

This large multicenter observational cohort study examined 7811 patients with COVID-19 over an extended period and multiple phases of the COVID-pandemic. We found that hyponatremia was highly prevalent but not associated with higher mortality rates. Although less prevalent, hypernatremia was associated with a three-to-four-fold increased risk of worse outcomes, including increased risk of ICU-admission, intubation, and mortality. Hyponatremia was also associated with a higher risk for ICU-admission, but not for intubation.

Patients with hyponatremia experienced more complications such as aspergillosis pneumonia and physical decline, while those with hypernatremia were more prone to sepsis and delirium. Similar to previous studies, hypo- and hypernatremia were more prevalent in males than in females, in elderly patients, those with chronic kidney disease, and a lower BMI[9,15,17,26,28-30,38]. In contrast to others, we did not find an association between hyponatremia and diabetes, which possibly relates to the fact that we corrected sodium levels for serum glucose[9,15,17,26,30]. Among COVID-19 patients, hyponatremia appeared to have multiple etiologies, but hypovolemic hyponatremia was found to be predominant.

The incidence of hyponatremia among COVID-19 patients in this study was 34.3%, which is higher than the pooled prevalence of hyponatremia in previous systematic reviews which included studies conducted during the earlier COVID-19-waves 24% to 25.8%[7,11]. However, it aligns with Tezcan, et al. [32],Voets, et al. [39], and Sarvazad, et al. [31], who reported rates of 34%, 35.8% and 38%, respectively (the latter study included only patients without underlying disease), although even higher incidences have been reported[10,28,40-42]. The incidence of hyponatremia in COVID-19 was also found to be higher compared to hyponatremia in other types of pneumonia: 5.4% - 28%[9,13,14,39,43]. Hyponatremia is most common in pneumonias caused by viral pathogens (e.g. rhinovirus, respiratory syncytial virus, (para)influenza virus, and adenovirus) with a incidence reported of 17.6%, as compared to 13.8% in patients with bacterial pneumonias[43]. Patients presenting with hyponatremia in this study were significantly older compared to patients with normonatremia, potentially due to age-related tubular atrophy and subsequent decreased urine concentrating capacity and sodium reabsorption[44]. The fact that previous studies have identified various other underlying conditions as risk factors for hyponatremia, including cardiac[17], pulmonary[17], and liver diseases[17] possibly relates to the older age of patients with hyponatremia included (median age was 67 years in our study

versus a mean age of 74.3 years in Chan, et al. [17] and a median age of 70 years in Ruiz-Sánchez, et al. [38]).

Hypernatremia is less common among COVID-19 patients compared to other pneumonias. We found an incidence of 1.6% among COVID-19 patients. This number is lower than the incidences reported in previous studies (2.9% - 38%)[16,39] and lower than the incidence of hypernatremia (5.3%) reported in patients with a community acquired pneumonia[45]. Patients with hypernatremia were found to be older than patients with normo- or hyponatremia. These age differences were in line with the expected age-related impairment of the thirst mechanism and potential barriers to accessible fluids (e.g. due to immobilization or dementia) which could contribute to inadequate fluid intake with subsequent development of hypernatremia[25].

Hyponatremia in infectious diseases can have multiple etiologies, of which SIADH, hypovolemia, and the use of diuretics are the most common, but critical illness-related corticoid insufficiency is also reported[14,22]. In this study we showed that multiple etiologies seem to play a role in COVID-19 patients. Among patients with hyponatremia a higher incidence of diarrhea and anosmia was observed. These symptoms could contribute to decreased appetite and subsequently lower dietary intake. Clinical investigations revealed an increased heart rate and slightly decreased systolic blood pressure, which suggests a possible hypovolemic state as an underlying cause for hyponatremia. Correspondingly, eGFR was lower in this group, despite comparable blood urea levels, which have been employed by others as measure to differentiate euvolemic from hypovolemic hyponatremia[29]. This hypovolemia could result from both reduced dietary intake and dehydration due to diarrhea. The low median USE (30 mmol/L) in a proportion of patients also points to extrarenal sodium loss and a hypovolemic status[46]. However, due to the limited number of patients with USE measurements, these findings should be interpreted as supportive rather than definitive evidence.

Moreover, patients presenting with hyponatremia had higher serum concentrations of LDH and CRP. A relationship between serum CRP and sodium concentration has been observed in other infectious diseases and has also been demonstrated in COVID-19 patients[17,28,41]. This phenomenon has been attributed to release of cytokines such as interleukin-6 and interleukin-1β[47], which can affect the secretion of ADH and potentially contribute to the development of SIADH[23,48]. In COVID-19 patients, elevated levels of interleukin-6 and interleukin-1β have been noted[30,49,50]. Furthermore, a negative correlation between interleukin-6 and sodium levels has been demonstrated, implying a similar

mechanism in the development of hyponatremia[3,29]. It is important to note that although administration of interleukin-6 receptor antagonists (tocilizumab and sarilumab) and interleukin-1 receptor antagonist (anakinra) was similar between groups, this observation does not undermine the aforementioned hypothesis, as these agents were administered based on indirect markers of interleukin release such as disease severity and CRP levels. Additionally, most patients in the study were included before registration of these agents for COVID-19 treatment, and the sample sizes of the groups might have been too small to draw definitive conclusions on the relationship between cytokine levels and hyponatremia in COVID-19 patients.

Contrary to previous studies and in contrast to patients with community acquired pneumonia, we did not find SIADH as frequent cause of hyponatremia in COVID-19 patients[8,11,30,51]. In our study, only a small proportion of USE + UOL samples complied with the definition of SIADH, and a correlation between low urinary sodium excretion and serum CRP concentration was found, which is in contrast to the theory that interleukin-6 induces ADH release (Supplemental Table 6). The overall incidence of SIADH in our study suggests that SIADH is a less frequent cause of hyponatremia among COVID-19 patients, compared to hyponatremia in patients with other pneumonias. This is possibly because COVID-19 more often causes diarrhea thereby also leading to other causes of hyponatremia. Frontera, et al. [30] reported a prevalence of 36% of SIADH among COVID-19 patients that presented with a serum sodium level ≤120 mmol/L. However, in our study population, less than 1% presented with a sodium level this low, and mild and severe hyponatremia differ in pathophysiology. Previous studies that identified SIADH as a frequent underlying mechanism of hyponatremia in COVID-19 patients based their information mostly on case reports, which likely focused on more severe cases[11]. The fact that in our study urinary investigation was not performed in all patients with hyponatremia may suggest that hyponatremia was not persistent or was otherwise not found to be severe enough to do so. This could also contribute to the lower incidence of confirmed SIADH cases in our study.

The association between thiazide diuretics and hyponatremia is well-established. Thiazide diuretics are known to increase the risk of developing hyponatremia due to their effects on renal sodium and water excretion[52]. Therefore, it is not surprising that patients with hyponatremia more frequently used thiazide diuretics. The use of immunosuppressive medications, such as glucocorticoids, was also related to hyponatremia. Glucocorticoids can potentially affect the body's water and electrolyte imbalance, including sodium levels. The development of iatrogenic adrenal insufficiency, resulting from

the (prior) prescription of steroids, can contribute to relative glucocorticoid efficiency and potentially lead to hyponatremia[53,54].

We did not find a significant association between hyponatremia and the risk of mortality or intubation, although ICU admission rates were higher in the hyponatremia group. These results are in line with Machiraju, et al. [41], who also demonstrated a higher need for ICU admission in COVID-19 patients presenting with hyponatremia but could not relate hyponatremia to mortality nor the length of hospital stay. Consistent with our results, Tzoulis, et al. [29] found no significant association between hyponatremia and mortality but did relate hyponatremia to invasive ventilation and the length of hospital admission. The higher serum CRP and LDH concentrations in hyponatremic patients in our study indicate that these patients might be more ill compared to those with normal sodium levels, which is not in line with the similar mortality rates[55,56]. Moreover, 13% of all patients admitted to the ICU did not receive any form of ventilatory support, suggesting that there were reasons other than respiratory failure for ICU admission. The fact that this percentage was similar among patients with normonatremia suggests that hyponatremia was not a frequent reason for ICU admission. We speculate that dehydration accompanied by hyponatremia, along with elevated LDH and CRP levels were reasons for hospital admission. However, other pathophysiologic mechanisms leading to worse outcomes were absent in these patients, favoring a relatively good outcome.

Our findings are in contrast with previous studies, in which the presence of hyponatremia at presentation was independently associated with disease severity and prolonged hospital stay [17,43] and was thought to be an independent predictor of hospital mortality[7,8,11,15,17]. These studies suggest that hyponatremia, especially when not corrected for serum glucose concentration[57], is a significant factor in determining the prognosis of patients. The observed trend towards increased mortality in patients with severe hyponatremia was also demonstrated by Ruiz-Sánchez, et al. [38], Chan, et al. [17], and Frontera, et al. [30]. However, the latter study obtained statistically significant results with a lower number of patients (36 out of 4645, representing 1% of the population, stratified as having severe hyponatremia based on sodium levels $\leq$ 120 mmol/L) compared to 1.8% in our study, which could not be confirmed by our study.

There are several potential explanations for the difference in outcomes between our study and previous studies. First, previous studies only included patients that were admitted during 2020 and the spring of 2021, the beginning of the COVID-19 pandemic[7,8,11,15,16]. In large previous studies,

mortality rates between 22.6-28.9% have been reported[9,57]. In contrast, our study included patients from the beginning of the COVID-19 pandemic until August 2022 and the overall mortality in our study was 16.7% (despite an increased risk for ICU admission and intubation for hyponatremic patients that started having complaints when the delta variant dominated). These differences in outcomes are likely attributed to increased knowledge about the disease, the development of new treatments such as dexamethasone and tocilizumab, and the commencement of widespread vaccination campaigns starting in January 2021. It is important to note that a study by Chan, et al. [17] included patients from late 2021 and early 2022 and still found an association between hyponatremia and adverse outcomes. However, these results may not be directly comparable to our study due to potential differences in vaccine efficacy and COVID-19 policies between Hong-Kong and Western countries[58]. These variations in patient cohorts and treatment strategies could influence outcomes and thus could lead to different results as compared to other studies. We speculate that the absence of a higher risk of adverse outcomes in COVID-19 patients presenting with hyponatremia, contrary to previous studies, could be partly attributed to the overall decrease in mortality as the pandemic progressed.

Second, previous studies examined uncorrected sodium concentration at presentation as a prognostic factor and found increased mortality rates in patients with hyponatremia[10,11,15,26,28,30,32,38,59]. However, other studies that corrected for serum glucose concentration when these exceeded 10 mmol/L, found no significant association between hyponatremia and mortality[29]. Hirsch, et al. [57] demonstrated that the association between hyponatremia and mortality was only evident prior to correction for serum glucose concentration, and the association disappeared after correcting for glucose levels. These findings are similar to studies conducted outside the context of COVID-19[60]. In our study, uncorrected hyponatremia was associated with an elevated risk of ICU admission and intubation, whereas corrected hyponatremia did not show an association between hyponatremia and intubation. This suggests that a similar effect related to the correction of sodium levels for glucose concentration could explain the discrepancies between our study and previous studies[30,38].

The association between ICU admission and hyponatremia was most pronounced in patients with a hyponatremia of unknown etiology. However, it is important to consider that this group may include mild presentations of SIADH due to the limited number of urinary samples available. These findings align with the higher CRP and LDH levels observed in this group. Patients that had a history of

gastro-intestinal symptoms had a lower risk of ICU admission, despite having higher levels of CRP and LDH levels. The higher CRP and LDH levels in this group could not be related to the SARS-CoV-2 variants, as the highest CRP levels were observed in patients that developed symptoms during a period in which the delta variant dominated. Notably, this group also had the lowest prevalence of gastro-intestinal symptoms (data not shown). We suggest that the prevalence of SIADH in our study group was very low for two reasons. Firstly, we included patients during later COVID-19 waves (when alpha, delta, and omicron variants dominated), whereas patients with hyponatremia due to SIADH that was severe enough to perform urinary analysis presented mostly during the period where initial variants dominated. This could have resulted in a lower prevalence that studies that only included patients during the first COVID-19 wave. Secondly, SIADH can only be diagnosed based on urinary sodium excretion and urinary osmolarity, but only a limited number of urinary samples was available, so we were not able to provide a precise estimate.

In contrast to the findings in patients with hyponatremia, our study revealed a significant association between hypernatremia and adverse outcomes such as ICU-admission, intubation, and death. While there were no significant differences in serum CRP and LDH concentration, as well as CT-severity scores at admission, between hypernatremic and normonatremic patients, higher MEWS and qSOFA scores indicated that a greater extent of lung tissue in hypernatremic patients. Furthermore, elevated serum urea concentration, lower eGFR, and a prolonged capillary refill time suggested dehydration in this group of patients. These findings collectively point towards a more severely ill patient population, which could account for the worse clinical outcomes observed. The association between hypernatremia and worse clinical outcomes has been previously documented in COVID-19[15,19] and other type of pneumonias[45].

Our study on hyponatremia in COVID-19 is characterized by its large size, including over 7000 patients from various hospitals across Netherlands. A notable strength of our study lies in the inclusion of patients from different waves of the COVID-19 and from multiple hospitals, both university and general. This approach resulted in a diverse patient population, making our findings applicable to the current situation. Furthermore, our study benefitted from the availability of a large amount of clinical data being available for each patient. This allowed us to analyze the associations we discovered in conjunction with relevant patient background details. For instance, we had access to vital signs recorded at admission, providing us with a more comprehensive understanding of the patients' condition upon

admission compared to previous studies[30,38]. Consequently, we were able to offer more substantiated insights into the presumed underlying etiology and how the different etiologies were related to clinical outcomes.

This study has several limitations that should be acknowledged. Firstly, the availability of urinary samples of patients with hyponatremia (185 out of the total) limits the generalizability of our findings. Additionally, information on the duration of hyponatremia in participating patients was not provided. Exploring these aspects would have been valuable, as a previous study by de La Flor, et al. [61] demonstrated that persistent hyponatremia (72 – 96h after admission) was associated with higher mortality in COVID-19 patients. Secondly, the variability in treatment protocols among the participating hospital may have influenced outcome of patients in our study. Lastly, we were unable to study specific treatment options for hyponatremia in patients.

Our results suggest that while hyponatremia is commonly observed among COVID-19 patients, it is not associated with adverse clinical outcome. However, the presence of hypernatremia should be of concern to clinicians, as it is indicative of a poorer prognosis. To enhance our understanding of the etiology of hyponatremia in COVID-19, future studies should focus on monitoring the clinical course of hyponatremia during hospitalization, documenting the duration of hyponatremia, and recording the treatment administered. It is crucial to obtain urinary samples from all patients presenting with COVID-19 and hyponatremia to further elucidate the underlying causes. Moreover, further research is warranted to investigate the incidence and potential mechanisms of SIADH in relation to disease severity and inflammation. More specifically, studies examining the relationship with interleukin-6 would be valuable, given that the interleukin-6 antagonist tocilizumab is used in the treatment of patients with moderate to severe COVID-19.

5. Conclusion

Hyponatremia is a common electrolyte disorder found in one third of patients hospitalized with COVID-19. Several risk factors have been identified, including male sex assigned at birth, a slightly lower BMI, pre-existing conditions like chronic kidney disease, hypertension, as well as the use of certain medications such as the use of thiazide diuretics and immunosuppressives. We found that hyponatremia was not associated with a higher need for invasive ventilation nor with mortality. In contrast, hypernatremia was associated with worse outcomes as compared to normonatremia. Regarding the underlying pathophysiological mechanisms, hypovolemic hyponatremia appeared to be the predominant mechanism in COVID-19 patients. Other causes of hyponatremia, such as SIADH, were less commonly observed in our study population.

Contributorship Statement

LRdH, MtW, and RAD conceptualized and designed the study, and were responsible for the planning, conduct, data analysis and interpretation. LRdH drafted the article supervised by MtW, and RAD. Figures and tables were designed by LRdH. LRdH, MtW, RAD, MB, RHOE, BA, EKHH, DR, NCGvdO, SS, NP, JPvdB, CEW, MdK, TD, HM, NB, and KB were responsible for the inclusion of patients and data entry in the COVID-PREDICT database in their respective centers on behalf of the COVID-PREDICT study group. MB, RHOE, BA, EKHH, DR, NCGvdO, SS, NP, JPvdB, CEW, MdK, TD, HM, NB, and KB critically revised the manuscript and supplemental material. All authors provided final approval of the manuscript and accepted responsibility for the integrity and accuracy of the work. They also ensued that any inquiries regarding the work's integrity or accuracy would be thoroughly investigated and resolved.

Competing of interest

The authors declare that there is no conflict of interest.

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Data sharing statement

No data are available. Not all patients provided active informed consent, and therefore sharing data is not possible.

Ethics approval

The ethical board of the Amsterdam University Medical Centers (20.131) approved the study protocol.

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Figure legends

Figure 1. Hazard ratios of cox proportional survival curves for survival probability for each sodium value adjusted for age, sex assigned at birth, a history of chronic kidney disease, and a history of hypertension. The grey area indicates the normonatremia. Table shows hazard ratios for covariates and sodium as a continuous variable (**A**). Cox proportional survival curves at the mean of covariates for (**B**) unadjusted 6-week mortality stratified by normo-, hypo-, and hypernatremia, (**C**) 6-week mortality adjusted for age, sex assigned at birth, a history of chronic kidney disease, and a history of hypertension stratified in normo-, hypo-, and hypernatremia, (**D**) Unadjusted 6-week mortality stratified by etiology. ** indicates a p-value <0.01, *** indicates a p-value <0.001

Figure 2. Odds ratio for adverse outcomes (death / palliative discharge (**A**), intensive care unit admission (**B**) invasive ventilation (**C**)) for each SARS-CoV-2 variant compared to patients in that started having symptoms when the initial variants for patients with hypo-, hyper-, or normonatremia at admission. *** indicates a p-value <0.001 for the odds ratio as calculated by binary logistic regression. (**D**) incidence of hypo-, normo-, and hypernatremia for each variant, * indicates a p-value <0.05 as compared to the first quartile for the chi-square statistic with Bonferroni post-hoc correction.

Table 1 – Comparison of patient characteristics between COVID-19 patients with hypo-, normo-, and hypernatremia

	Hyponatremia Na 134 mmol/L N = 2677	**Normonatremia** Na 136 – 145 mmo/L N = 5008	**Hypernatremia** Na 146 mmol/L N = 126
Sex assigned at birth (N (%))	♂ 1673 (62.5%) ♀ 1003 (37.5%) p = 0.002	♂ 2946 (58.8 %) ♀ 2060 (41.2 %)	♂ 84 (66.7%) ♀ 42 (33.3%)
Age (median age in years (IQR))	N = 2675 67.0 (58.0-77.0) p < 0.001	N = 5008 66.1 (55.0-76.0)	N = 126 72.5 (62.8 – 80.3) p < 0.001
BMI (median BMI in kg/m^2 (IQR))	N = 1740 27.2 (24.2 – 31.1) p = 0.009	N = 3374 27.7 (24.6 – 31.6)	N = 91 25.0 (22.2 – 29.1) p < 0.001
Order 'Do not intubate' (N (%))	440 / 1442 (30.5 %)	796 / 2469 (32.2 %)	39 / 77 (50.6 %) p = 0.004
Chronic cardiac disease (N (%))	760 / 2666 (28.5%) p = 0.07	1334 / 4982 (26.8 %)	42 / 123 (34.1 %) p = 0.07
Hypertension (N (%))	1055 / 2374 (44.4 %) p = 0.002	1889 / 4586 (41.2 %)	64 / 120 (53.3 %)
Chronic pulmonary disease (N (%))	466 / 2662 (17.5 %) p = 0.75	844 / 4979 (17.0 %)	19 / 122 (15.6 %) p = 0.75
Chronic kidney disease (N (%))	329 / 2379 (13.8 %) p < 0.001	491 / 4587 (10.7 %)	26 / 121 (21.5 %) p < 0.001
Moderate to severe liver disease (N (%))	30 / 2662 (1.1 %) p = 0.46	50 / 4972 (1.0 %)	0 / 123 (0.0 %) p = 0.46
Diabetes (N (%))	664 / 2662 (24.9 %) p = 0.39	1261 / 4972 (25.4 %)	38 / 125 (30.4 %) p = 0.39
Immunosuppressives (N (%))	192 / 2283 (8.4 %) p = 0.002	295 / 4445 (6.6 %)	2 / 118 (1.7 %)
Thiazide diuretics (N (%))	258 / 2671 (9.7 %) p = 0.015	394 / 4994 (7.9 %)	7 / 125 (5.6 %)
Loop diuretics (N (%))	187 / 2671 (7.0 %) p = 0.22	389 / 4994 (7.8 %)	13 / 125 (10.4 %) p = 0.22
SSRIs / SNRIs (N (%))	78 / 2671 (2.9 %) p = 0.69	164 / 4994 (3.3 %)	4 / 125 (3.2 %) p = 0.69

BMI = body mass index; IQR = interquartile range; % = percentage of patients in this group with indicated characteristic; SSRI = Selective Serotonin Reuptake inhibitor; SNRI = Selective Serotonin and Noradrenalin Reuptake inhibitor. Significance was assessed using a Kruskal-Wallis test with post-hoc correction (for numerical data; non-normally distributed) or Chi-square test (for categorical data). p – values for all groups indicate the adjusted significance after post-hoc correction when compared to the normonatremia group. When no p – value was provided there was no significant difference compared to the normonatremia group. Subgroup analyses for hyponatremia is provided in the supplemental information.

Table 2 – Comparison of signs and symptoms at presentation between COVID-19 patients with hypo-, normo-, and hypernatremia

Signs and symptoms	**Hyponatremia** Na 134 mmol/L N = 2677	**Normonatremia** Na 136 – 145 mmol/L N = 5008	**Hypernatremia** Na 146 mmol/L N = 126
Nausea / vomiting (N (%))	679 / 2273 (29.9 %) p = 0.04	1150 / 4129 (27.9 %)	16 / 83 (19.3 %) p = 0.04
Diarrhea (N (%))	804 / 2298 (35.0%) p < 0.001	1146 / 4157 (27.6 %)	15 / 82 (18.3 %)
Anosmia (N (%))	244 / 1904 (12.8 %) p = 0.002	352 / 3330 (10.6 %)	1 / 66 (1.5 %)
Confusion (N (%))	311 / 2319 (13.4%)	651 / 4381 (14.9 %)	45 / 105 (42.9 %) p < 0.001
Seizures (N (%))	10 / 1977 (0.5%) p = 0.20	31 / 3452 (0.9 %)	0 / 80 (0.0 %) p = 0.20
FiO2 (median fraction (IQR))	N = 1159 0.36 (0.28-0.50) p = 0.05	N = 2084 0.36 (0.28 – 0.50)	N = 67 0.44 (0.30 – 0.80) p = 0.05
SBP (mean SBP in mmHg (SD))	N = 2648 132 (± 22) p < 0.001	N = 4971 135 (±23)	N = 120 135 (± 25) p = 1.00
HR (mean HR in BPM (SD))	N = 2661 92 (±18) p = 0.003	N = 4965 91 (±20)	N = 123 95 (±25) p = 0.034
Capillary refill ≥3 s (N (%))	81 / 863 (9.4 %)	93 / 1369 (6.8 %)	6 / 33 (18.2 %) p = 0.008
Blood urea level (median level n mmol/L (IQR))	N = 2549 6.3 (4.5 – 9.3) p = 0.87	N = 4776 6.2 (4.5 – 9.2)	N = 115 12.6 (7.9 – 25.3) p < 0.000
eGFR rate using 2021 CKD-epi creatinine equation in (median clearance in ml/min/1.73 m^3 (IQR))	N = 2656 64 (45 – 90) p < 0.001	N = 4983 68 (46 – 94)	N = 125 41 (24 – 71) p < 0.001
CT-severity score (mean score (SD))	N = 909 12.4 (±5.5) p = 0.58	N = 1401 12.1 (±5.6)	N = 30 14.5 (±7.2) p = 0.06
Blood CRP level (median level in mg/L (IQR))	N = 2646 93.1 (49.0 – 154) p < 0.001	N = 4939 70.8 (28.0 – 131)	N = 123 75.0 (29.0 – 148) P = 1.00
Blood LDH level (median level in U/L (IQR))	N = 2238 349 (268 – 471) p < 0.001	N = 4226 323 (247 – 426)	N = 89 363 (255 – 447) p = 0.52

MEWS (median score (IQR))	N = 2337 3.0 (2.0 – 4.0) p < 0.001	N = 4055 3.0 (2.0 – 4.0)	N = 103 4.0 (2.0 – 5.0) p < 0.001
qSOFA (median score (IQR))	N = 2373 1.0 (0.0 – 1.0) p = 1.00	N = 4131 1.0 (0.0 – 1.0)	N = 104 1.0 (1.0 – 1.0) p < 0.001

SBP = systolic blood pressure; HR = heart rate; eGFR = estimated glomerular filtration rate; CKD-epi = chronic kidney disease Epidemiology Collaboration; CT = computed tomography; BPM = beats per minute; IQR = interquartile range; SD = standard deviation; CRP = c-reactive protein; LDH = lactate dehydrogenase; MEWS = modified early warning score; qSOFA = quick sequential organ failure assessment. % = percentage of patients in this group with indicated characteristic. Significance was assessed using a Kruskal-Wallis test with post-hoc correction (for numerical data) or Chi-square test (for categorical data). p – values for all groups indicate significance when compared to the normonatremia group. When no p – value was provided there was no significant difference to the normonatremia group. Subgroup analyses for hyponatremia is provided in the supplemental information.

Table 3 – Comparison of clinical outcomes between COVID-19 patients with hypo-, normo-, and hypernatremia

Outcome	**Hyponatremia** Na 134 mmol/L N = 2677	**Normonatremia** Na 136 – 145 mmo/L N = 5008	**Hypernatremia** Na 146 mmol/L N = 126
Duration of admission (median days (IQR))	N = 2372 7 (4 – 16) p < 0.001	N = 4116 7 (3 – 14)	N = 103 8 (4 – 15) P = 0.998
Death or palliative discharge (N (%))	405 / 2360 (17.2 %) [A]OR 1.04 (0.91 – 1.20) p = 0.56	729 / 4568 (16.0 %)	42 / 119 (35.3 %) [A]OR 2.25 (1.49 – 3.41) p < 0.001
ICU-admission (N (%)), 'do not intubate' excluded	439 / 1923 (22.8 %) [A]OR 1.27 (1.11 – 1.46) p < 0.001	710 / 3778 (18.8 %)	32 / 80 (40.0%) [A]OR 2.89 (1.83 – 4.58) p < 0.001
Duration of ICU-admission (days (IQR)) 'do not intubate' excluded	N = 299 8 (3 - 19) p = 0.356	N = 437 10 (4 – 19)	N = 25 11 (3.5 – 19) p = 0.356
Invasive ventilation (N (%)), 'do not intubate' excluded	352 / 1889 (18.6 %) [A]OR 1.12 (0.97 – 1.30) p = 0.121	623 / 3706 (16.8 %)	29 / 77 (37.7 %) [A]OR 2.95 (1.83 – 4.74) p < 0.001
Discharge alive within 42 days; N indicating the number of non-censored cases	N = 1527 [A]HR 0.96 (0.90 – 1.02) p = 0.15	N = 2747	N = 52 [A]HR 0.78 (0.59 – 1.03) p = 0.08
Use of tocilizumab, sarilumab, or anakinra (N (%))	134 / 688 (19.5%) [A]OR 1.256 (0.984 – 1.604) p = 0.068	199 / 1245 (16.0%)	3 / 34 (8.8%) [A]OR 0.550 (0.165 – 1.830) p = 0.330
Complications	Na 134 mmol/L N = 1821	Na 136 – 145 mmo/L N = 3206	Na 146 mmol/L N = 82
Bacterial pneumonia (N (%))	289 / 2212 (13.1 %) [A]OR 1.12 (0.96 – 1.31) p = 0.14	501 / 4307 (11.6 %)	18 / 109 (16.5 %) [A]OR 1.44 (0.85 – 2.40) p = 0.17

Aspergillosis pneumonia (N (%))	67 / 1915 (3.5 %) [A]OR 1.44 (1.03 – 1.99) p = 0.031	83 / 3442 (2.4 %)	5 / 90 (5.6 %) [A]OR 2.26 (0.89 – 5.74) p = 0.084
ARDS (N (%))	224 / 2223 (10.1 %) [A]OR 1.08 (0.91 – 1.29) p = 0.377	404 / 4323 (9.3 %)	17 / 110 (15.5 %) [A]OR 1.78 (1.05– 3.04) p = 0.033
Treatment for septic shock (N (%)) *	94 / 2153 (4.4 %) [A]OR 1.33 (1.01 – 1.74) p = 0.04	135 / 4175 (3.2 %)	12 / 109 (11.0 %) [A]OR 3.37 (1.80 – 6.33) p < 0.001
Congestive heart failure (N (%))	64 / 2235 (2.9 %) [A]OR 0.95 (0.70 – 1.29) p = 0.73	125 / 4352 (2.9 %)	2 / 111 (1.8 %) [A]OR 0.48 (0.12 – 1.96) p = 0.31
Physical decline (N (%))	576 / 2116 (27.2 %) [A]OR 1.22 (1.08 – 1.38) p < 0.001	950 / 4126 (23.0 %)	30 / 106 (28.3 %) [A]OR 1.18 (0.77 – 1.82) p = 0.44
Delirium (N (%))	237 / 2136 (11.1 %) [A]OR 0.99 (0.83 - 1.17) p = 0.88	451 / 4146 (10.5 %)	27 / 107 (25.7 %) [A]OR 2.25 (1.42 – 3.56) p < 0.001

*ICU = Intensive care unit; ARDS = acute respiratory distress syndrome. [A]OR = adjusted odds ratio; odds ratio adjusted for sex assigned at birth, age, a history of chronic kidney disease, and a history of hypertension. [A]HR = adjusted hazard ratio; hazard ratio adjusted for sex assigned at birth, age, a history of chronic kidney disease, and a history of hypertension * Treatment for septic shock was defined as the need for vasopressors in order to maintain mean arterial blood pressure >65 mmHg and blood lactate level >2 mmol/L, in the absence of other causes including hypovolemia. Significance was assessed using a cox proportional-hazard model at the mean of the covariates (discharge alive) or logistic regression (all other values). p – values for all groups indicate significance when compared to the normonatremia group.*

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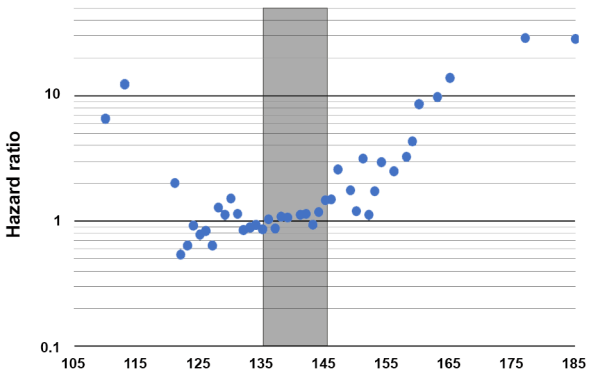
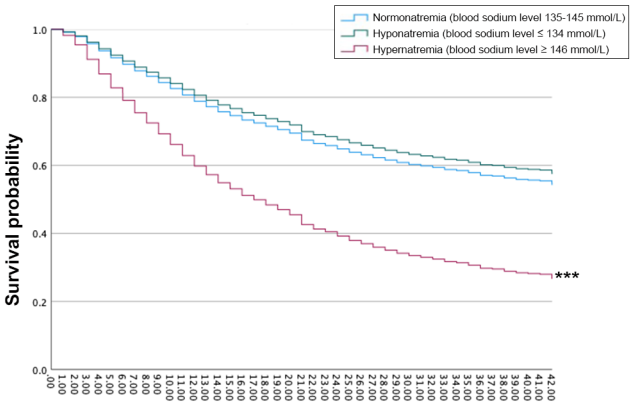
A. Hazard ratio of cox regression survival curve for each sodium value

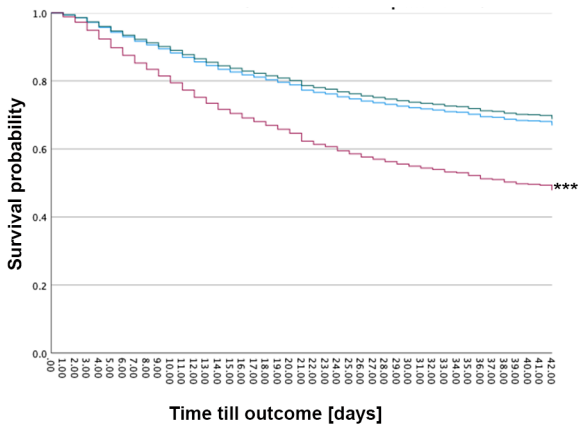


Covariate	Hazard ratio (95% CI)	*p* - value
Male sex assigned at birth	1.241 (1.094 - 1.407)	< 0.001
Age (years)	1.062 (1.056 - 1.068)	< 0.001
History of hypertension	1.116 (0.988 - 1.260)	0.077
History of chronic kidney disease	1.372 (1.182 - 1.592)	< 0.001
Sodium (mmol/L)	1.020 (1.008 - 1.032)	0.001

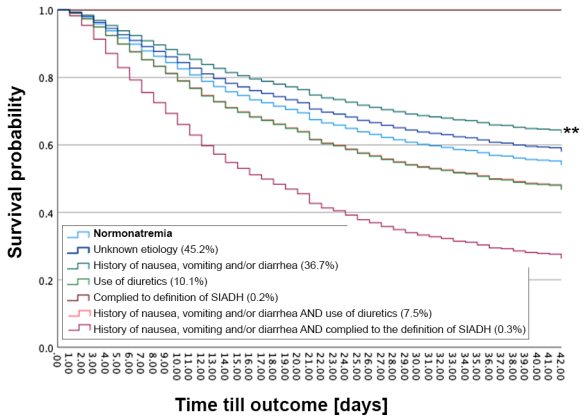
B. Cox regression survival curve at mean of covariates

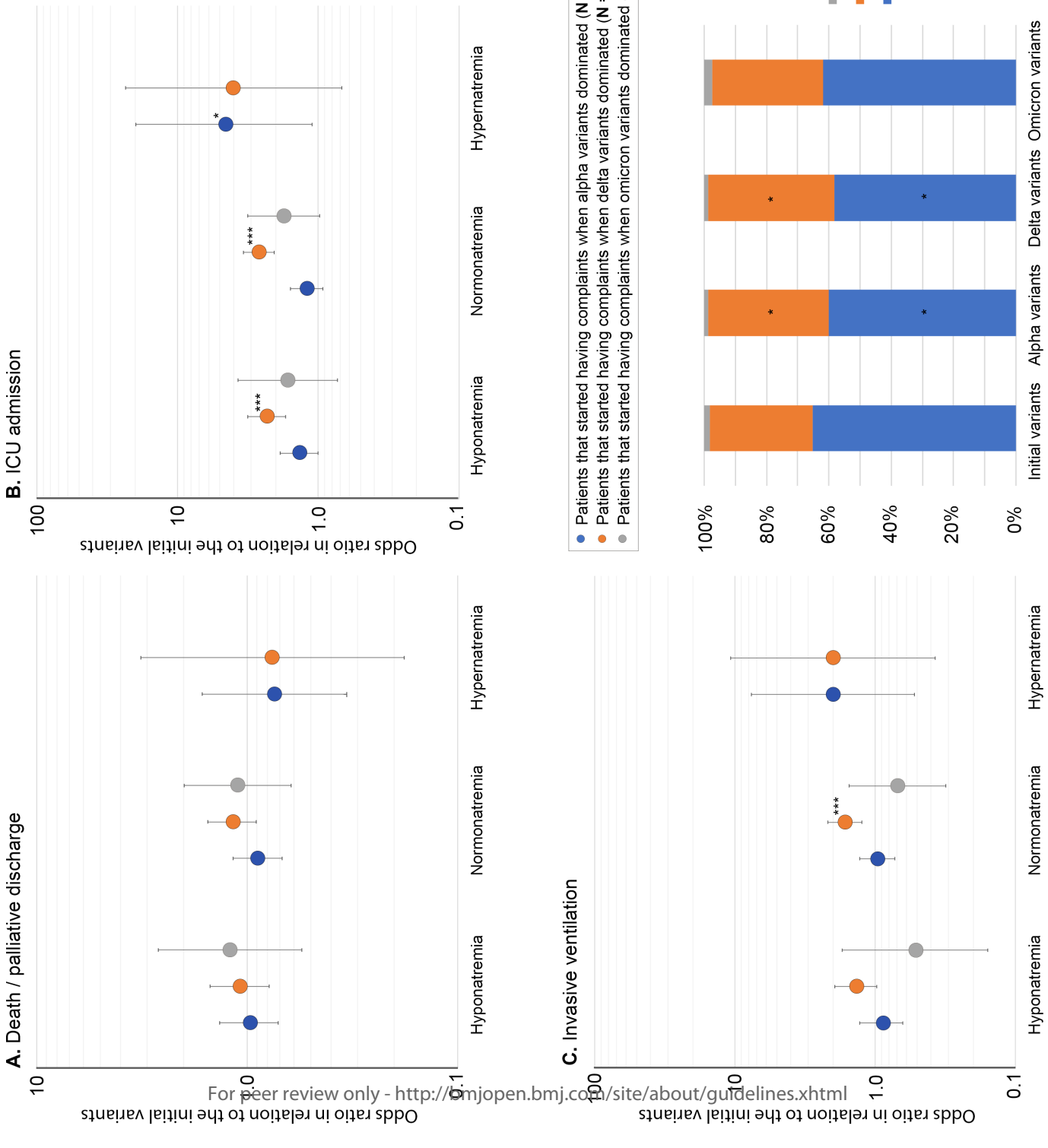


C. Cox regression survival curve at mean of covariates adjusted for age, sex assigned at birth, chronic kidney disease, and hypertension



D. Cox regression survival curve at mean of covariates seperated by etiology





What is the etiology of dysnatremia in COVID-19 and how is this related to outcomes in patients admitted during earlier and later COVID-19 waves? A multicentre, retrospective observational study in eleven Dutch hospitals

Supplemental information

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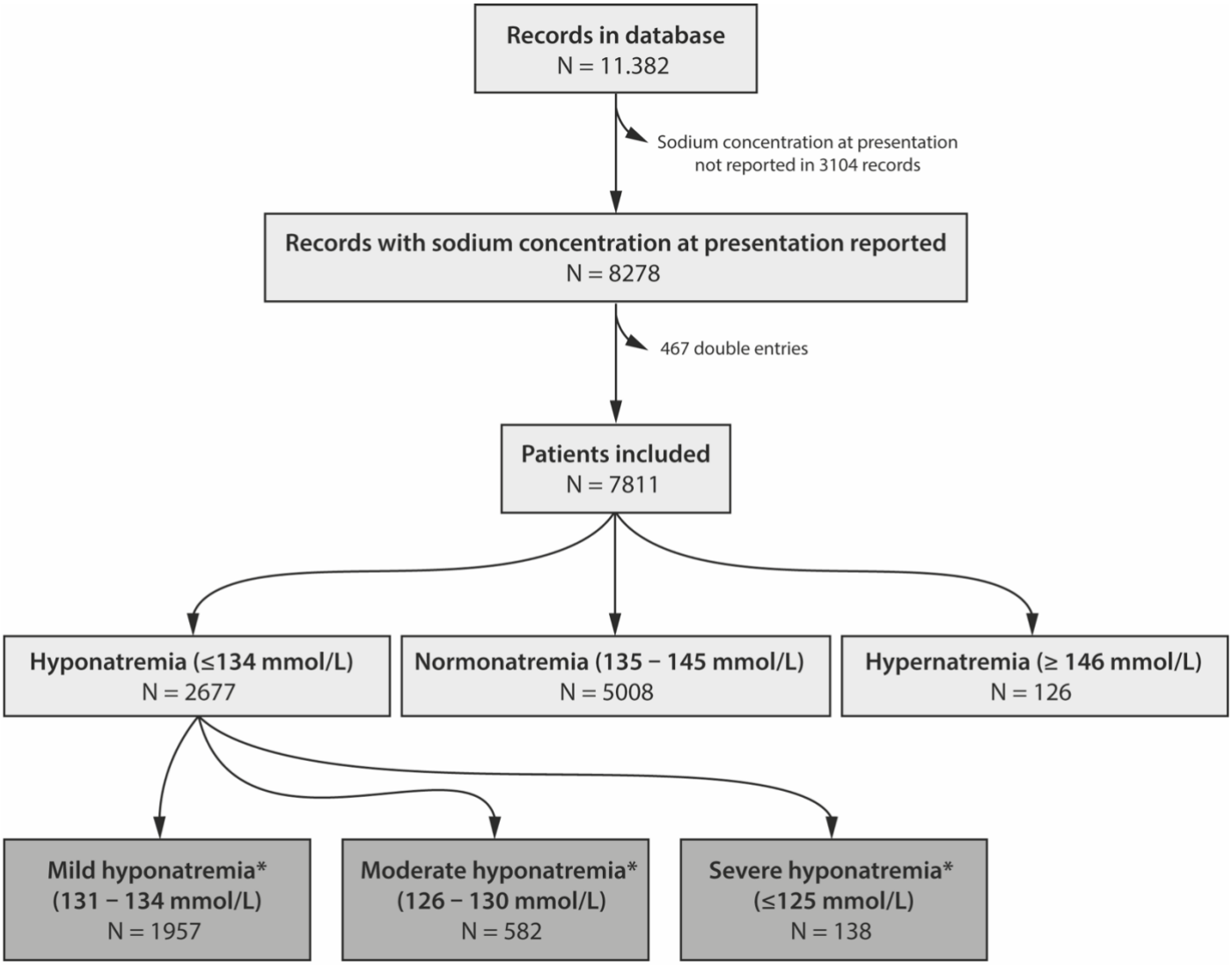


Supplemental Figure 1. Flow chart of included patients. Sodium concentrations indicate corrected serum sodium concentrations at hospital presentation * indicates the subgroup analysis as provided in the supplemental information.

Supplemental Table 1 – Subgroup analysis of patient characteristics

	Na 135 – 145 mmol/L N = 5008	Na ≤134 mmol/L N = 2677	Na 131 – 134 mmol/L N = 1957	Na 126 – 130 mmol/L N = 582	Na ≤125 mmol/L N = 138
Sex assigned at birth (N (%))	♂ 2946 (58.8 %) ♀ 2060 (41.2 %)	♂ 1673 (62.5%) ** ♀ 1003 (37.5%)	♂ 1249 (63.9%) *** ♀ 707 (36.1%)	♂ 363 (62.4%) ♀ 219 (37.6%)	♂ 61 (44.2%) *** ♀ 77 (55.8%)
Age (median age in years (IQR))	N = 5008 66.1 (55.0-76.0)	N = 2675 67.0 (58.0-77.0) **	N = 1956 67.0 (57.0 – 76.0)	N = 581 68.1 (60.0 – 78.0) ***	N =138 70.6 (62.0 – 79.3) ***
BMI (median BMI in kg/m^2 (IQR))	N = 3374 27.7 (24.6 – 31.6)	N = 1740 27.2 (24.2 – 31.1) **	N = 1271 27.4 (24.4 – 31.5)	N = 379 26.3 (23.4 – 30.3) ***	N = 90 26.9 (23.7 – 30.9)
Order 'Do not intubate' (N (%))	796 / 2469 (32.2 %)	440 / 1442 (30.5 %)	304 / 1043 (29.1 %)	108 / 322 (33.5 %)	28 / 77 (36.4 %)
Sodium (mean corrected serum level in mmol/L (IQR))	138.02 (136.42 – 140.0)	132.59 (130.72 – 134.00) ***	133.3 (132.28 – 134.19) ***	129.42 (128.04 – 130.22) ***	123.94 (121.17 – 125.0) ***
Chronic cardiac disease (N (%))	1334 / 4982 (26.8 %)	760 / 2666 (28.5%)	541 / 1948 (27.8 %)	187 / 581 (32.2 %)	32 / 137 (23.4 %)
Hypertension (N (%))	1889 / 4586 (41.2 %)	1055 / 2374 (44.4 %) **	749 / 1735 (43.2 %)	240 / 520 (46.2 %)	66 / 119 (55.5 %) **
Chronic pulmonary disease (N (%))	844 / 4979 (17.0 %)	466 / 2662 (17.5 %)	328 /1945 (16.9 %)	111 / 580 (19.1 %)	27 / 137 (19.7 %)
Chronic kidney disease (N (%))	491 / 4587 (10.7 %)	329 / 2379 (13.8 %) ***	220 / 1738 (12.7 %)	92 / 522 (17.6 %) ***	17 / 119 (14.3 %)
Moderate to severe liver disease (N (%))	50 / 4972 (1.0 %)	30 / 2662 (1.1%)	25 / 1947 (1.3%)	3 / 579 (0.5 %)	2 / 136 (1.5%)
Diabetes (N (%))	1261 / 4972 (25.4 %)	664 / 2662 (24.9 %)	481 / 1946 (24.7 %)	148 / 579 (25.6 %)	35 / 137 (25.5 %)
Immunosuppressives (N (%))	295 / 4445 (6.6 %)	192 / 2283 (8.4 %) **	129 / 1669 (7.7 %)	56 / 497 (11.3 %) **	7 / 117 (6.0 %)
Thiazide diuretics (N (%))	394 / 4994 (7.9 %)	258 / 2671 (9.7 %) **	186 / 1953 (9.5 %)	55 / 580 (9.5 %)	17 / 138 (12.3 %)
Loop diuretics (N (%))	389 / 4994 (7.8 %)	187 / 2671 (7.0 %)	128 / 1953 (6.6 %)	50 / 580 (8.6 %)	9 / 138 (6.5 %)
SSRIs (N (%))	164 / 4994 (3.3 %)	78 / 2671 (2.9 %)	53 / 1953 (2.7%)	15 / 580 (2.6%)	10 / 138 (7.2 %)

*BMI = body mass index; IQR = interquartile range; % = percentage of patients in this group with indicated characteristic; SSRI = Selective Serotonin Reuptake inhibitor. SNRI = Selective Serotonin and Noradrenalin Reuptake inhibitor. Significance was assessed using a Kruskal-Wallis test with post-hoc correction (for numerical data; non-normally distributed) or Chi-square test (for categorical data). p – values for all groups indicate the adjusted significance after post-hoc correction when compared to the normonatremia group. * Indicates a p-value <0.05, ** indicates a p-value <0.01, *** indicates a p-value <0.001*

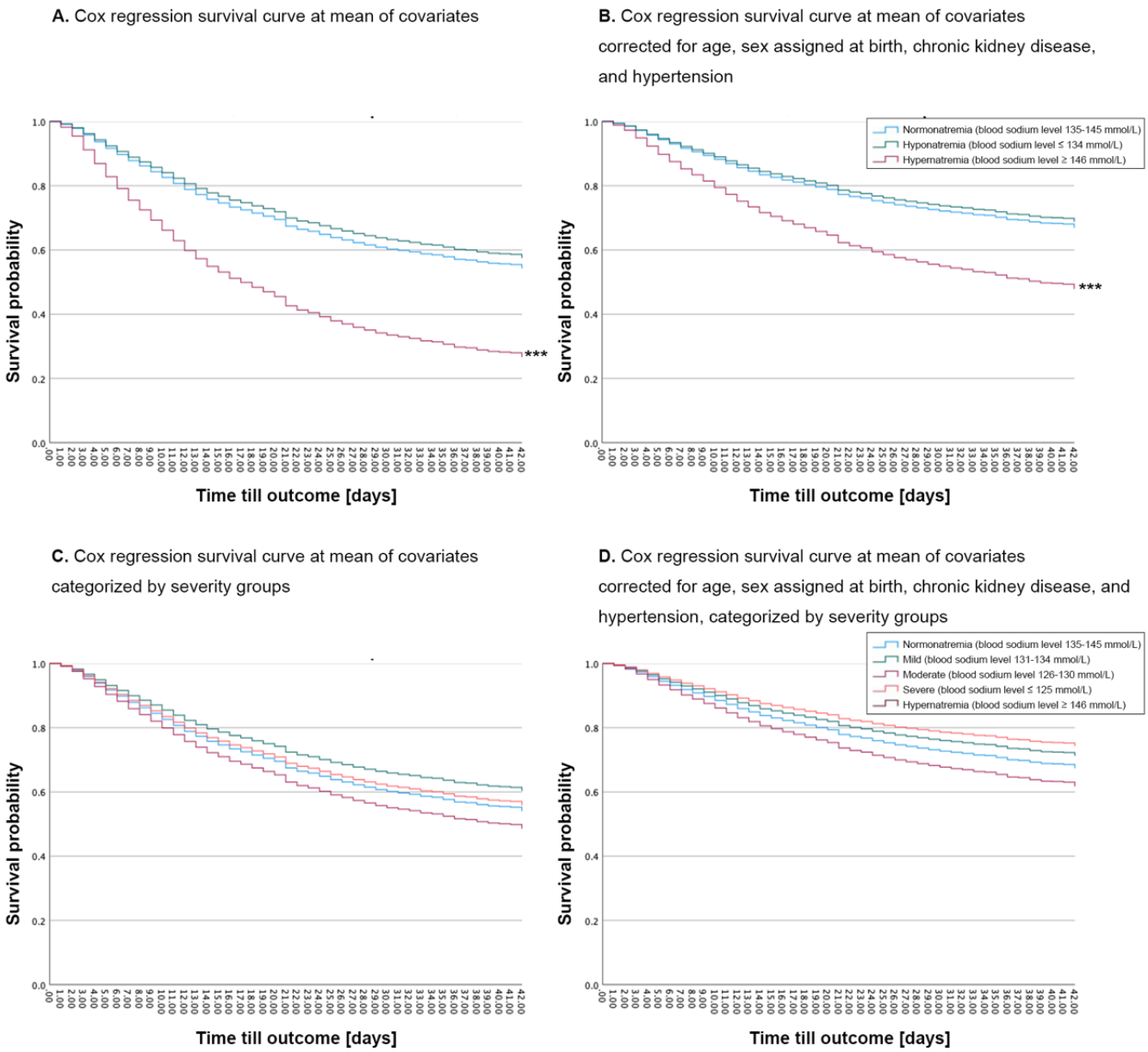
Supplemental Table 2 – Definitions for comorbidities

Comorbidity	**Included diseases**
Chronic pulmonary disease	Alpha-1 trypsin deficiency; asbestosis; cryptogenic organizing pneumonia; lymphangioeiomyomatosus; lung disease immuno-deficiency and chromosome breakage syndrome; bronchopulmonary dysplasia; primary ciliary dyskinesia; bronchiectasis; cystic fibrosis; chronic bronchitis or emphysema; lung fibrosis; sarcoidosis; obstructive sleep apnea; pulmonary hypertension
Chronic cardiac disease	**Chronical heart disease:** Myocardial infarction; Cardiac arrhythmias (AVNRT, atrial fibrillation, (supra)ventricular tachycardia, ventricular tachycardia, brugada syndrome, sick sinus syndrome, wolf parkinson white syndrome; decompensated heart failure, cardiomyopathy; valve disease (aortic valve stenosis, aortic valve insufficiency **Congential heart disease:** aortic valve insufficiency or aortic valve stenosis; Atrial septal defect or ventricular septal defect; hypoplastic left heart syndrome; Ebstein's anomaly; patent ductus arteriosis; tetralogy of Fallot; transposition of the great vessels
Chronic kidney disease	Acute tubulointerstitial nephritis; hemolytic uremic syndrome (HUS); amyloidosis; Anti-glomerular basement membrane disease; bartter syndrome; kidney damage due to medication, chronic bladder infections / kidney infections / diabetes, high blood pressure, arteriosclerosis; cryoglobulinemia, renal cystic disease; cystinosis; dense deposit disease (DDD); Focal segmental glomerulosclerosis (FSGS); Gitelman syndrome; glomerulonephritis; HNF1beta associated kidney disease; renal fusion (horseshoe kidney); IgA nephropathy; medullary sponge kidney; membranous nephropathy; minimal change disease; solitary kidney; Nail-patella syndrome (NPS); nephrogenic diabetes insipidus; nephroptosis; nephrotic syndrome; renal angiolipoma; renal cell carcinoma; primary hyperoxaluria; reflux nephropathy; atrophic kidney; scleroderma; lupus nephritis; Alport's syndrome; systemic vasculitis
Moderate to severe liver disease	Liver disease that caused cirrhosis (e.g. Budd Chiari, hemochromatosis, hepatitis, Wilson's disease)

Supplemental Table 3 – Subgroup analysis of signs and symptoms

Signs and symptoms	Na 135 – 145 mmol/L N = 3206	Na ≤134 mmol/L N = 1821	Na 131 – 134 mmol/L N = 1346	Na 126 – 130 mmol/L N = 383	Na ≤125 mmol/L N = 92
Nausea / vomiting (N (%))	1150 / 4129 (27.9 %)	679 / 2273 (29.9 %)	490 / 1663 (29.5 %)	151 / 499 (30.3 %)	38 / 111 (34.2%)
Diarrhea (N (%))	1146 / 4157 (27.6 %)	804 / 2298 (35.0%) ***	574 / 1686 (34.0 %) ***	180 / 501 (35.9%) ***	50 / 111 (45.0 %) ***
Anosmia (N (%))	352 / 3330 (10.6 %)	244 / 1904 (12.8 %)**	174 / 1395 (12.5 %)	62 / 420 (14.8 %)	8 / 89 (9.0 %)
Confusion (N (%))	651 / 4381 (14.9 %)	311 / 2319 (13.4%)	207 / 1688 (12.3 %)	78 / 511 (15.3 %)	26 / 120 (21.7 %)
Seizures (N (%))	31 / 3452 (0.9 %)	10 / 1977 (0.5%)	6 / 1448 (0.4 %)	2 / 434 (0.5 %)	2 / 95 (2.1 %)
FiO2 (median fraction (IQR))	N = 2084 0.36 (0.28 – 0.50)	N = 1159 0.36 (0.28 – 0.50)	N = 848 0.36 (0.28 – 0.48)	N = 258 0.36 (0.32 – 0.60)	N = 53 0.36 (0.31 – 0.75)
SBP (mean SBP in mmHg (SD))	N = 2648 132 (± 22)	N = 4971 135 (±23)***	N = 1934 132 (±22) ***	N = 578 132 (±22)**	N = 136 138 (±27)
HR (mean HR in BPM (SD))	N = 4965 91 (±20)	N = 2661 92 (±18) **	N = 1946 92 (±18) *	N = 580 92 (±18)	N = 135 90 (±19)
Disturbed capillary refill (N (%))	93 / 1369 (6.8 %)	81 / 863 (9.4 %)	51 / 614 (8.3 %)	27 / 206 (13.1 %)	3 / 43 (7.0 %)
Blood urea level (median level n mmol/L (IQR))	N = 4776 6.2 (4.5 – 9.2)	N = 2549 6.3 (4.5 – 9.3)	N = 1892 6.3 (4.6 – 9.1)	N = 559 6.2 (4.5 – 10.2)	N = 128 5.5 (4.2 – 9.8)
eGFR rate using 2021 CKD-epi creatinine equation in (median clearance in ml/min/1.73 m^3 (IQR))	N = 4983 68 (46 – 94)	N = 2656 64 (45 – 90) ***	N = 1944 64 (46 – 89) ***	N = 575 63 (41 – 90) ***	N = 137 79 (46 – 92)
CT-severity score (mean score (SD))	N = 1401 12.1 (±5.6)	N = 909 12.4 (±5.5)	N = 684 12.3 (±5.4)	N = 190 12.6 (±5.4)	N = 35 12.5 (±6.7)
Blood CRP level (median level in mg/L (IQR))	N = 4939 70.8 (28.0 – 131)	N = 2646 93.1 (49.0 – 154) ***	N = 1933 93.0 (48.2 – 151) ***	N = 577 103 (54.6 – 166) ***	N = 136 82.5 (36.0 – 145)
Blood LDH level (median level in U/L (IQR))	N = 4226 323 (247 – 426)	N = 2238 349 (268 – 471) ***	N = 1651 346 (269 – 467) ***	N = 479 361 (269 – 482) ***	N = 108 331 (240 – 543)
Modified early warning score (MEWS) (median score (IQR))	N = 4055 3.0 (2.0 – 4.0)	N = 2337 3.0 (2.0 – 4.0) ***	N = 1709 3.0 (2.0 – 4.0) ***	N = 509 3.0 (2.0 – 4.0)	N = 119 3.0 (2.0 – 4.0)
Quick sequential organ failure assessment (median score (IQR))	N = 4131 1.0 (0.0 – 1.0)	N = 2373 (0.0 – 1.0)	N = 1735 1.0 (0.0 – 1.0)	N = 517 1.0 (0.0 – 1.0)	N = 121 1.0 (0.0 – 1.0)

*SBP = systolic blood pressure; HR = heart rate; CKD-epi = chronic kidney disease Epidemiology Collaboration BPM = beats per minute; IQR = interquartile range; SD = standard deviation; CRP = c-reactive protein; LDH = lactate dehydrogenase; % = percentage of patients in this group with indicated characteristic. Significance was assessed using a Kruskal wallis test with post-hoc correction (for numerical data) or Chi-square test (for categorical data). * Indicates a p-value <0.05, ** indicates a p-value <0.01, *** indicates a p-value <0.001*



Supplemental Figure 2. Cox proportional survival curves at the mean of covariates for (A) unadjusted 6-week mortality categorized by normo-, hypo-, and hypernatremia, (B) 6-week mortality adjusted for age, sex assigned at birth, a history of chronic kidney disease, and a history of hypertension stratified in normo-, hypo-, and hypernatremia, (C) unadjusted 6-week mortality stratified in normo- and hypernatremia and mild, moderate, and severe hyponatremia, and (D)) 6-week mortality adjusted for age, sex assigned at birth, a history of chronic kidney disease, and a history of hypertension stratified in normo- and hypernatremia and mild, moderate, and severe hyponatremia. * Indicates a p-value <0.05, *** indicates a p-value <0.001

Supplemental Table 4 – Subgroup analysis of outcome and complications

Outcome	Na 135 – 145 mmol/L N = 3206	Na ≤134 mmol/L N = 1821	Na 131 – 134 mmol/L N = 1346	Na 126 – 130 mmol/L N = 383	Na ≤125 mmol/L N = 92
Duration of admission (median days (IQR))	N = 4116 7 (3 – 14)	N = 2372 7 (4 – 16) ***	N = 1735 7 (4 –15) **	N = 514 8 (4 – 18)*	N123 8 (3 – 18)
Death or palliative discharge (N (%))	729 / 4568 (16.0 %)	405 / 2360 (17.2 %) [A]OR 1.042 (0.906 – 1.200)	269 / 1723 (15.6 %)	115 / 518 (22.2 %)	21 / 119 (17.6 %)
ICU-admission (N (%), 'do not intubate' excluded	710 / 3778 (18.8 %)	439 / 1923 (22.8 %) [A]OR 1.274 (1.112 – 1.458)***	314 / 1422 (22.1 %) [A]OR 1.205 (1.036 – 1.401)*	104 / 410 (25.4 %) [A]OR 1.487 (1.170 – 1.889)***	21 / 91 (23.1 %) [A]OR 1.431 (0.868 – 2.360)
Duration of ICU-admission (days (IQR)) 'do not intubate' excluded	N = 437 10 (4 – 19)	N = 299 8 (3 - 19) p = 0.356	N = 215 8 (3 – 20)	N = 68 8 (4 – 18)	N = 16 9 (4 – 21)
Invasive ventilation (N (%)), 'do not intubate' excluded	623 / 3706 (16.8 %)	352 / 1889 (18.6 %) [A]OR 1.122 (0.970 – 1.298)	250 / 1396 (17.9 %)	85 / 402 (21.1 %)	17 / 91 (18.7 %)
Discharge alive within 42 days; N indicating the number of non-censored cases	N = 2747	N = 1527 [A]HR 0.955 (0.897 – 1.017) p = 0.154	N = 1153	N = 302	N = 72
Use of tocilizumab, sarilumab, or anakinra (N (%))	199 / 1245 (16.0%)	134 / 688 (19.5%) [A]OR 1.256 (0.984 – 1.604) p = 0.068	91 / 480 (19.0 %)	36 / 169 (21.3 %)	7 / 39 (17.9%)
Complications	**Na 135 – 145 mmol/L N = 3206**	**Na ≤134 mmol/L N = 1821**	**Na 131 – 134 mmol/L N = 1346**	**Na 126 – 130 mmol/L N = 383**	**Na ≤125 mmol/L N = 92**
Bacterial pneumonia (N (%))	501 / 4307 (11.6 %)	289 / 2212 (13.1 %) [A]OR 1.123 (0.962 – 1.312)	207 / 1619 (12.8 %)	72 / 483 (14.9 %)	10 / 110 (9.1 %)
Aspergillosis pneumonia (N (%))	83 / 3456 (2.4 %)	67 / 1915 (3.5 %) [A]OR 1.436 (1.034 – 1.993)	49 / 1402 (3.5 %) [A]OR 1.426 (0.995 – 2.044)	14 / 417 (3.4 %) [A]OR 1.352 (0.759 – 2.410)	4 / 96 (4.2 %) [A]OR 1.839 (0.657 – 5.148)
ARDS (N (%))	404 / 4323 (9.3 %)	224 / 2223 (10.1 %) [A]OR 1.081 (0.909 – 1.286)	161 /1627 (9.9 %)	52 / 486 (10.7 %)	11 / 110 (10.0 %)
Treatment for septic shock (N (%)) [&]	135 / 4175 (3.2 %)	94 / 2153 (4.4 %) [A]OR 1.326 (1.013 – 1.737)*	66 / 1570 (4.2 %) [A]OR 1.274 (0.943 – 1.721)	25 / 478 (5.2 %) [A]OR 1.570 (1.012 – 2.438)*	3 / 105 (2.9%) [A]OR 0.920 (0.287 – 2.946
Congestive heart failure (N (%))	125 / 4352 (2.9 %)	64 / 2235 (2.9 %) [A]OR 0.946 (0.696 – 1.287)	34 / 1637 (2.1%)	23 / 488 (4.7 %)	7 / 110 (6.4 %)
Physical decline (N (%))	950 / 4126 (23.0 %)	576 / 2116 (27.2 %) [A]OR 1.221 (1.082 – 1.377)**	414 / 1544 (26.8 %) [A]OR 1.206 (1.054 – 1.380)**	136 / 468 (29.1 %) [A]OR 1.303 (1.053 – 1.614)*	26 / 104 (25.0 %) [A]OR 1.059 (0.674 – 1.666)

Delirium (N (%))	451 / 4146 (10.5 %)	237 / 2136 (11.1 %) [A]OR 0.987 (0.833 - 1.170)	157 / 1557 (10.1 %)	62 / 474 (13.1 %)	18 / 105 (17.1 %)

*ICU = Intensive care unit; ARDS = acute respiratory distress syndrome; OR = odds ratio; [A]OR = adjusted odds ratio; odds ratio corrected for sex assigned at birth and age; IQR = interquartile range. [#]Uncorrected for sex assigned at birth and age [&] Treatment for septic shock was defined as the need for vasopressors in order to maintain mean arterial blood pressure >65 mmHg and blood lactate level >2 mmol/L, in the absence of other causes including hypovolemia. Significance was assessed using a Kruskal wallis test with post-hoc correction (time to discharge alive) or logistic regression (all other values). * Indicates a p-value <0.05, ** indicates a p-value <0.01, *** indicates a p-value <0.001*

Supplemental Table 5 – Characteristics of patients with the order 'do not intubate'

	Order 'do not intubate'	**No order 'do not intubate'**	**p-value**
Sex assigned at birth (N (%))	♀ 531/ 1576 (33.7 %) ♂ 743 / 2388 (31.1 %)	♀ 1045 / 1576 (66.3 %) ♂ 1645 / 2388 (68.9 %)	p = 0.095
Age (median age in years (IQR))	79 (73 – 84)	62 (53 -71)	p < 0.001
BMI (median BMI in kg/m^2 (IQR))	26.2 (23.1 – 30.1)	27.9 (25.0 – 31.9)	p < 0.001
Corrected sodium level at presentation in mmol/L (IQR))	135.9 (± 4.5)	136.6 (±5.1)	p < 0.001
ICU admission (N (%))	83 / 1275 (6.5 %)	781 / 2690 (29 %)	p < 0.001
Chronic pulmonary disease (N (%))	361 / 1270 (28.4 %)	359 / 2680 (13.4%)	p < 0.001
Asthma (N (%))	95 / 1269 (7.5 %)	256 / 2678 (9.6%)	p = 0.036
Chronic obstructive pulmonary disease (N (%))	125 / 267 (46.8 %)	80 / 293 (27.3 %)	p < 0.001
Chronic kidney disease (N (%))	259 / 1270 (20.4 %)	250 / 2681 (9.3%)	p < 0.001
Chronic cardiac disease (N (%))	637 / 1266 (50.3 %)	564 / 2683 (21.0%)	p < 0.001
Hypertension (N (%))	755 / 1270 (59.4 %)	1051 / 2685 (39.1 %)	p < 0.001
Moderate to severe liver disease (N (%))	21 / 1267 (1.7 %)	28 / 2680 (1.0 %)	p = 0.123
Diabetes (N (%))	457 / 1270 (36.0 %)	679 / 2680 (25.3 %)	p < 0.001
Neoplasm (N (%))	156 / 1273 (12.3 %)	130 / 2682 (4.8 %)	p < 0.001

BMI = Body Mass Index; IQR = interquartile range. Significance was assessed using a Student's t-test (for normally distributed numerical data), Mann-Whitney test (for non-normally distributed numerical data) or Chi-square test (for categorical data). p – values for all groups indicate the 2-tailed significance between the two groups.

Supplemental Table 6 – Patient characteristics, signs and symptoms, outcome measures, and complications of patients with hyponatremia (Na ≤ 134 mmol/L) that did not use diuretics stratified based on their urinary sodium excretion.

Patient characteristics	**Urinary sodium excretion < 30 mmol/L** % or IQR N = 72	**Urinary sodium excretion ≥ 30 mmol/L** % or IQR N = 73	**p - value**
Age (median age in years (IQR))	N = 72 67 (56 – 74)	N = 73 69 (59 – 76)	p = 0.47
Sex assigned at birth (N (%))	♂ 38 (53%) ♀ 34 (47%)	♂ 43 (59%) ♀ 30 (41%)	p = 0.51
Vomiting/nausea (N (%))	32 / 71 (45.1 %)	19 / 67 (28.4 %)	p = 0.05
Diarrhea (N (%))	26 / 67 (38.8 %)	28 / 68 (41.2 %)	p = 0.86
Heart rate (mean HR in BPM (SD))	N = 71 89.7 (± 16.3)	N = 72 93.1 (±18.9)	p = 0.25
Systolic blood pressure (mean SBP in mmHg (SD))	N = 70 135 (± 24.8)	N = 71 137 (±24.1)	p = 0.68
Disturbed capillary refill (N (%))	3 / 27 (11.1 %)	4 /31 (12.9 %)	p = 1.00
eGFR rate using 2021 CKD-epi creatinine equation in (median clearance in ml/min/1.73 m^3 (IQR))	N = 71 67 (49 – 90)	N = 73 71 (32 – 92)	p = 0.49
CRP (median level in mmol/L (IQR))	N = 70 111 (52.5 – 163)	N = 71 70 (35.0 – 154)	**p = 0.028**
LDH (median level in U/L (IQR))	N = 57 351 (270 – 491)	N = 61 273 (227 – 434)	**p = 0.021**
CT-severity score (median score (IQR))	N = 33 11.0 (7.0 – 15.0)	N = 40 12.0 (6.0 – 16.8)	p = 0.86
Outcome			
Death or palliative discharge (N (%))	14 / 72 (19.4%)	18 / 73 (24.7 %)	p = 0.55
ICU-admission (N (%), 'do not intubate' excluded	24 / 65 (36.9 %)	25 / 61 (41.0 %)	p = 0.72
Invasive ventilation (N (%)), 'do not intubate' excluded	18 / 64 (28.1 %)	23 / 60 (38.3 %)	p = 0.26

CRP = C-reactive protein; LDH = lactate dehydrogenase; CT = computed tomography; ICU = intensive care unit; eGFR = estimated glomerular filtration rate; CKD-epi = chronic kidney disease Epidemiology Collaboration; IQR = interquartile range; SD = standard deviation. Significance was assessed using a Student's t-test (for normally distributed numerical data), Mann-Whitney test (for non-normally distributed numerical data) or Chi-square test (for categorical data). p – values for all groups indicate the 2-tailed significance between the two groups.

Supplemental Table 7 – Patient characteristics, signs and symptoms, outcome measures, and complications for each SARS-CoV-2 variant

	Initial	**Alpha**	**Delta**	**Omicron**	**p-value**
Sex assigned at birth (N (%))	♀ 2431 (39.3 %) ♂ 3754 (60.7 %)	♀ 322 (40.3 %) ♂ 477 (59.7 %)	♀ 300 (42.9 %) ♂ 399 (57.1 %)	♀ 52 (42.6 %) ♂ 70 (57.4 %)	p = 0.266
Age (median age in years (IQR))	67 (57 – 77)	63 (53 – 73)	65 (52 – 77)	71 (59 – 76)	p <0.001 for alpha vs. initial / omicron p = 0.012 for alpha vs. delta p = 0.006 for delta vs. initial
BMI (median BMI in kg/m^2 (IQR))	27.4 (24.3 – 31.2)	27.9 (24.9 – 32.9)	27.7 (24.4 – 32.2)	26.8 (23.8 – 30.4)	p = 0.012 for alpha vs. initial
Corrected sodium level at presentation in mmol/L (IQR))	136.5 (134.0 – 139.0)	136.0 (133.3 – 138.4)	136.1 (133.0 – 138.6)	136.1 (133.8 – 138.9)	p <0.001 for alpha / delta vs. initial
Patients with hyponatremia that presented with diarrhea or vomiting (N (%))	1524 / 3327 (45.8 %)	191 / 398 (48.0 %)	130 / 389 (33.4 %)	27 / 73 (37.0 %)	p < 0.001 for delta vs. alpha / initial
Patients with hyponatremia that used diuretics at presentation (N (%))	348 / 2042 (17.0 %)	46 / 305 (15.1 %)	60 / 283 (21.2 %)	18 / 40 (45.0 %)	p < 0.001 for omicron vs. initial / alpha / delta
Patients with hyponatremia that complied to the definition of SIADH (N (%))	12 / 94 (12.8 %)	0 / 2 (0 %)	0 / 4 (0 %)	0 / 0 (0 %)	p = 0.647
Patients with hyponatremia of unknown etiology (N (%))	939 / 2045 (45.9 %)	142 / 308 (46.1 %)	121 / 283 (42.8 %)	8 / 40 (20 %)	p = 0.009 for omicron vs. initial / alpha / delta

BMI = body mass index; SIADH = syndrome of inappropriate antidiuretic hormone secretion; IQR = interquartile range. Significance was assessed using a Kruskal wallis test with post-hoc correction (for numerical data) or logistic regression (for categorical data). p – values for all groups indicate the 2-tailed significance between the two groups.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6 and 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6 and 7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6 and 7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	FIG 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1, p 24
		(b) Indicate number of participants with missing data for each variable of interest	Table 1-4, p 24 to 29
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	FIG 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3, p 27-29
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8, 9, 11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.