Prevalence and Impact of Hyponatremia in Patients With Coronavirus Disease 2019 in New York City

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Objectives: Hyponatremia occurs in up to 30% of patients with pneumonia and is associated with increased morbidity and mortality. The prevalence of hyponatremia associated with coronavirus disease 2019 and the impact on outcome is unknown. We aimed to identify the prevalence, predictors, and impact on outcome of mild, moderate, and severe admission hyponatremia compared with normonatremia among coronavirus disease 2019 patients.

Design: Retrospective, multicenter, observational cohort study.

Setting: Four New York City hospitals that are part of the same health network.

Patients: Hospitalized, laboratory-confirmed adult coronavirus disease 2019 patients admitted between March 1, 2020, and May 13, 2020.

Interventions: None.

Measurements and Main Results: Hyponatremia was categorized as mild (sodium: 130–134 mmol/L), moderate (sodium: 121–129 mmol/L), or severe (sodium: ≤ 120 mmol/L) versus normonatremia (135–145 mmol/L). The primary outcome was the association of increasing severity of hyponatremia and in-hospital mortality assessed using multivariable logistic regression analysis. Secondary outcomes included encephalopathy, acute renal failure, mechanical ventilation, and discharge home compared across sodium levels using Kruskal-Wallis and chi-square tests. In exploratory analysis, the association of sodium levels and interleukin-6 levels (which has been linked to nonosmotic release of vasopressin) was assessed. Among 4,645 patient encounters, hyponatremia (sodium < 135 mmol/L) occurred in 1,373 (30%) and 374 of 1,373 (27%) required invasive mechanical ventilation. Mild, moderate, and severe hyponatremia occurred in 1,032 (22%), 305 (7%), and 36 (1%) patients, respectively. Each level of worsening hyponatremia conferred 43% increased odds of in-hospital death after adjusting for age, gender, race, body mass index, past medical history, admission laboratory abnormalities, admission Sequential Organ Failure Assessment score, renal failure, encephalopathy, and mechanical ventilation (adjusted odds ratio, 1.43; 95% CI, 1.08–1.88; $p = 0.012$). Increasing severity of hyponatremia was associated with encephalopathy, mechanical ventilation, and decreased probability of discharge home (all $p < 0.001$). Higher interleukin-6 levels correlated with lower sodium levels ($p = 0.017$).

Conclusions: Hyponatremia occurred in nearly a third of coronavirus disease 2019 patients, was an independent predictor of in-hospital mortality, and was associated with increased risk of encephalopathy and mechanical ventilation. (*Crit Care Med* 2020; XX:00–00)

Key Words: coronavirus disease 2019; hyponatremia; pneumonia; severe acute respiratory syndrome coronavirus 2

Hyponatremia (sodium < 135 mmol/L) occurs in 26–28% of patients (1, 2) with community-acquired pneumonia (CAP) and is associated with increased risk of ICU admission, prolonged length of stay, higher hospital cost, and increased mortality rates (2–8). Profound hyponatremia can be associated with life-threatening complications, including encephalopathy, cerebral edema, seizure, coma, and myelinolysis (with overly rapid sodium correction). The risk of hyponatremia among pneumonia patients appears to vary by pathogen, with up to 44–46% of *Legionella pneumophila* patients developing hyponatremia (sodium < 130 mmol/L) compared with 8–14% of patients with other CAP etiologies (9, 10). Moderate and severe hyponatremia have been described in case reports of severe acute respiratory syndrome

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coronavirus 2 (SARS-CoV-2) infection (11, 12). The authors of these studies have suggested that hyponatremia at admission may serve as an indicator of potential coronavirus disease 2019 (COVID-19) infection (12). However, data on the prevalence, severity, and impact of hyponatremia in the context of a large COVID-19 cohort is lacking.

In this study, our primary aim was to determine the prevalence of varying degrees of hyponatremia among patients with SARS-CoV-2 and to identify the association of hyponatremia with in-hospital mortality. Secondary aims included identifying demographic predictors of hyponatremia and evaluating the association of hyponatremia with length of stay, discharge home, and hospital complications, including encephalopathy, acute renal failure, and acute respiratory failure requiring mechanical ventilation. In an exploratory analysis, we evaluated the mechanisms of severe hyponatremia (Na ≤ 120 mmol/L) and evaluated the association of sodium levels and interleukin-6 (IL-6), which has been linked to nonosmotic release of vasopressin (antidiuretic hormone) (13, 14) and has been reported to be elevated in patients with COVID-19 (15, 16).

MATERIALS AND METHODS

Study Design and Participants

We conducted a retrospective, observational cohort study and screened hospitalized patients with laboratory-confirmed SARS-CoV-2 admitted to four New York City area hospitals (New York University [NYU] Langone Health network) between March 1, 2020, and May 13, 2020. Inclusion criteria were SARS-CoV-2 infection confirmed by RNA polymerase chain reaction (PCR) testing, age greater than or equal to 18 years, and available admission sodium (Na) values. Patients who were not hospitalized were excluded from analysis. Patients were divided into three levels of hyponatremia severity based at admission sodium values: mild (Na 130–134 mmol/L), moderate (Na 121–129 mmol/L), and severe (Na ≤ 120 mmol/L) and were compared with patients with normonatremia at admission (Na 135–145 mmol/L). Hyponatremia that developed during the hospital course was not evaluated since iatrogenic causes of hyponatremia would confound analysis of the effect of SARS-CoV-2 on sodium levels. In the primary analysis of in-hospital mortality, patients with hypernatremia (admission Na > 145 mmol/L) were excluded from analysis, as hypernatremia itself may be associated with increased mortality.

Data Collection

SARS-CoV-2 PCR positive patients were identified in the electronic medical record and demographics, medical comorbidities, admission laboratory values, and in-hospital outcomes (included in-hospital mortality, discharge disposition, and hospital length of stay) were extracted. The Sequential Organ Failure Assessment (SOFA) score at admission was used to assess initial severity of illness and has been shown to be predictive of organ failure and in-hospital mortality (17–19). In a subanalysis, patients with severe hyponatremia (Na ≤ 120 mmol/L) underwent additional chart review to identify the primary etiology of hyponatremia. The mechanism of hyponatremia was determined by a nephrologist (E.H.) after evaluation of each patient's volume status, urine and serum osmolality, urine chemistries, and response to treatment (20, 21). Patients with pseudohyponatremia due to elevated serum glucose, triglycerides, or osmotic agents were excluded from this subanalysis. This study was approved with a waiver of authorization and informed consent by the NYU Grossman School of Medicine institutional review board.

Study Outcomes

The primary outcome was in-hospital mortality. Secondary outcomes included: encephalopathy (diagnosed at admission by the treating clinician and annotated in a standardized admission checklist), acute renal failure, and acute respiratory failure requiring invasive mechanical ventilation, hospital length of stay, and discharge home (with or without home services). Other discharge dispositions (long-term acute care hospital, skilled nursing facility, acute inpatient rehabilitation center, inpatient or outpatient hospice, or continued hospitalization) were also recorded. In an exploratory analysis, we evaluated the frequency of syndrome of inappropriate antidiuretic hormone (SIADH) secretion among patients with severe hyponatremia and the relationship of sodium and IL-6 levels in the aggregate cohort.

Statistical Analyses

Demographic variables, medical comorbidities, admission laboratory values, medical complications, and in-hospital outcomes were compared across four admission sodium levels (normonatremia, mild, moderate, and severe hyponatremia) using the Kruskal-Wallis test for non-normally distributed continuous variables and chi-square test for categorical values. Unadjusted odds ratios (ORs) representing the relationship between each sodium level, and the outcomes of in-hospital mortality, acute respiratory failure requiring mechanical ventilation, and discharge home were calculated using binary logistic regression analyses. Similarly, univariate logistic regression models were used to assess the relationship between demographic, past medical history, admission laboratory values, and hospital complications with in-hospital mortality. Multivariable logistic regression models were constructed utilizing significant univariate variables to evaluate the relationship between progressive severity levels of hyponatremia and in-hospital death. The relationship between IL-6 and sodium levels in the entire cohort was assessed using Spearman rank correlation coefficient. All analyses were conducted using IBM SPSS Statistics for Windows Version 25 (IBM Corp., Armonk, NY). Using Bonferroni corrections for multiple comparisons, significance was set at p value of less than 0.002 for univariate analyses.

RESULTS

Between March 1, 2020, and May 13, 2020, 4,947 SARS-CoV-2 positive adult patient encounters occurred. Of these, sodium

TABLE 1. Characteristics of Coronavirus Disease 2019 Patients With Hyponatremia and Normonatremia (*n* = 4,645)

Variable	Severe Hyponatremia (Na ≤ 120 mmol/L)	Moderate Hyponatremia (Na 121–129 mmol/L)	Mild Hyponatremia (Na 130–134 mmol/L)	Normonatremia (Na 135–145 mmol/L)	*p* (Across All Four Sodium Levels)
n (%)	36 (1)	305 (7)	1,032 (22)	3,079 (66)	
Demographic characteristics					
Age, yr, median (IQR)	71 (42–90)	66 (19–99)	64 (19–99)	65 (19–106)	0.009
Sex, male, *n* (%)	16 (44)	310 (68)	796 (63)	1,800 (59)	< 0.001
Race, *n* (%)					< 0.001
White	18 (50)	161 (35)	500 (39)	1,432 (47)	
Black	1 (3)	44 (9)	152 (12)	543 (18)	
Asian	11 (31)	45 (10)	98 (8)	167 (5)	
Native American	0	3 (1)	9 (1)	10 (< 1)	
Pacific Islander	0	9 (2)	21 (2)	18 (1)	
Unknown	6 (16)	196 (43)	491 (38)	909 (29)	
Body mass index, median (IQR)	26 (20–38)	27 (14–55)	28 (15–72)	28 (12–77)	0.003
Medical comorbidities					
Admission Sequential Organ Failure Assessment score, median (IQR)	0 (0–4)	0 (0–4)	0 (0–14)	0 (0–13)	0.005
Hypertension, *n* (%)	14 (39)	191 (42)	496 (39)	1,220 (40)	0.796
Diabetes, *n* (%)	7 (19)	163 (36)	410 (32)	766 (25)	< 0.001
Hyperlipidemia, *n* (%)	8 (22)	129 (28)	349 (28)	821 (27)	0.861
Chronic renal disease, *n* (%)	4 (11)	60 (13)	135 (11)	387 (13)	0.205
Congestive heart failure, *n* (%)	3 (8)	32 (7)	88 (7)	257 (8)	0.346
Hypothyroidism, *n* (%)	2 (6)	30 (7)	79 (6)	220 (7)	0.596
Dementia, *n* (%)	1 (3)	14 (3)	42 (3)	154 (5)	0.039
Admission laboratory findings, median (IQR)					
Admission Pao_2 (mm Hg)	107 (54–294)	83 (29–410)	76 (16–458)	77 (10–458)	0.215
Blood urea nitrogen (mg/dL)	12 (4–162)	17 (3–143)	16 (3–279)	17 (2–256)	0.002
Serum creatinine (mg/dL)	0.78 (0.44–20.0)	1.02 (0.50–19.70)	1.00 (0.34–22.60)	0.99 (0.3–23.5)	< 0.001
Serum potassium (mmol/L)	3.7 (1.8–6.2)	4.0 (2.7–8.3)	4.0 (2.5–8.7)	4.1 (2.3–8.8)	< 0.001
Serum chloride (mmol/L)	84 (64–92)	95 (82–108)	100 (86–113)	103 (86–121)	< 0.001
Serum triglycerides (mg/dL)	104 (54–472)	134 (27–1,052)	133 (27–2,527)	131 (23–6,619)	0.070
Serum glucose (mg/dL)	141 (82–275)	141 (42–801)	127 (25–637)	114 (24–754)	< 0.001
Serum uric acid (mg/dL)	5.1 (1.2–15.1)	4.0 (2.8–7.0)	5.8 (2.7–13.4)	5.8 (1.5–15.0)	0.318
Serum osmolality (mosmol/kg)	246 (228–309)	279 (258–1,006)	289 (262–396)	302 (257–440)	< 0.001
Admission interleukin-6 (pg/mL)[a]	23 (0–427)	19 (0–2,450)	15 (0–716)	14 (0–59,900)	0.047
Urine sodium (mmol/L)	30 (6–126)	25 (2–129)	31 (2–166)	36 (2–179)	< 0.001
Urine osmolality (mosmol/kg)	339 (104–660)	469 (108–1,023)	471 (83–1,023)	455 (130–1,046)	0.001

IQR = interquartile range.

[a]Interleukin-6 data were available in 1,179 patients.

values were not available in 302 patients. Of the remaining 4,645 encounters, hyponatremia (Na < 135 mmol/L) occurred in 1,373 patients (30%). Mild (Na 131–135 mmol/L), moderate (Na 121–130 mmol/L), and severe hyponatremia (Na ≤ 120 mmol/L) occurred in 1,032 of 4,645 (22%), 305 of 4,645 (7%), and 36 of 4,645 (1%) patients, respectively (**Table 1**). Increasing severity of hyponatremia was significantly associated with male sex, Asian race, and history of diabetes (all $p < 0.002$). Older patients and those with lower body mass index (BMI) were also more likely to have hyponatremia, whereas black patients ($p < 0.001$) were less likely. Patients with a history of chronic renal disease, congestive heart failure, hypertension, hyperlipidemia, or hypothyroidism were not at increased risk of hyponatremia in the context of SARS-CoV-2 infection. Hyponatremia was associated with lower admission blood urea nitrogen (BUN), potassium, chloride, and serum osmolality, but higher creatinine and glucose. Admission Po_2 was not significantly associated with hyponatremia; however, data was only available in 1,266 of patients (28%).

The median time to resolution of hyponatremia (e.g., Na ≥ 135 mmol/L) was 1.05 days (range, 0–24 d) for the entire cohort. The time to sodium normalization was significantly longer as the severity of hyponatremia increased. The median time to sodium normalization was 0.7 days (range, 0.3–2.0 d) among those with mild hyponatremia, 2.1 days (range, 0–1.3 d) among those with moderate hyponatremia, and 3.9 days (range, 0.4–8.1 d) among patients with severe hyponatremia at admission ($p < 0.001$ across all three groups of hyponatremia). Hypertonic saline was administered to 13 of 1,373 of patients (1%), and it was more commonly used among those with severe hyponatremia ($n = 3$ with mild, $n = 2$ with moderate, and $n = 8$ with severe hyponatremia; $p < 0.001$).

Patients with moderate or severe hyponatremia were significantly more likely to require invasive mechanical ventilation (OR, 1.83; 95% CI, 1.50–2.25; $p < 0.001$) and were less likely to be discharged home (OR, 0.64; 95% CI, 0.53–0.77; $p < 0.001$; **Fig. 1**; **Table 2**). Additionally, patients with severe hyponatremia had eight-fold higher odds of being encephalopathic than patients with higher sodium levels (OR, 8.35; 95% CI, 4.29–16.27; $p < 0.001$).

After excluding 193 patients with admission hypernatremia (Na > 145 mmol/L), 4,452 patients were included in the analysis of in-hospital mortality. Univariate predictors of in-hospital mortality are shown in **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/F738) and include: increasing age, male sex, white race, higher BMI, worse admission SOFA score, history of hypertension, diabetes, chronic renal disease or congestive heart failure, admission hyponatremia, hypoxia, higher BUN, creatinine, potassium, or glucose, encephalopathy, acute renal failure, and acute respiratory failure requiring invasive mechanical ventilation.

In multivariable analysis, increasing severity of hyponatremia was independently associated with 38% increased odds of in-hospital mortality (adjusted OR, 1.43; 95% CI, 1.08–1.88; $p = 0.012$) after adjusting for other factors (**Table 3**).

IL-6 levels were available at admission on 1,179 patients (26%). The median IL-6 levels were progressively higher as the degree of hyponatremia worsened ($p = 0.047$; Table 1), and there was a small but significant correlation between hyponatremia and IL-6 levels (Spearman rho, –0.069; $p = 0.017$). Among patients with moderate-severe hyponatremia (Na ≤ 130 mmol/L), IL-6 levels were elevated (> 5 pg/mL) in 143 of 174 patients (82%) in whom it was measured. Higher IL-6 levels were not associated with mortality.

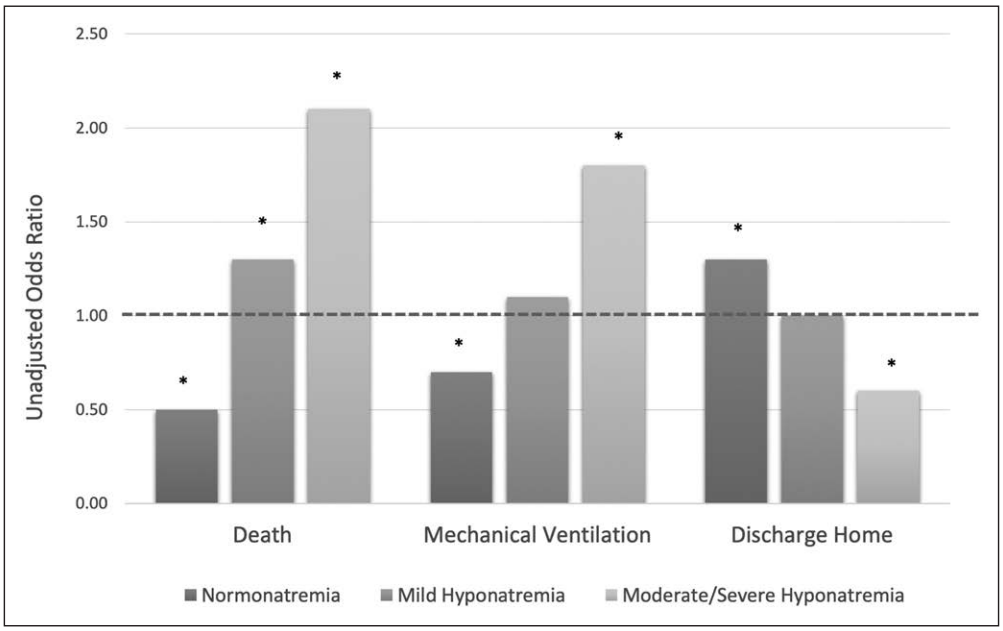

Figure 1. Unadjusted odds of in-hospital death, acute respiratory failure requiring mechanical ventilation, and discharge home among patients with moderate to severe hyponatremia (sodium ≤ 130 mmol/L), mild hyponatremia (sodium 131–134 mmol/L), and normonatremia (sodium 135–145 mmol/L). *$p < 0.005$.

Among patients with sodium less than or equal to 120 mmol/L, clinical or electrographic seizures occurred in two patients (6%), and cerebral edema was documented in one patient (3%). However, electroencephalogram data were only available in two patients, and head CT was only performed in 11 patients (31%). The most common mechanisms of hyponatremia among patients with Na less than or equal to 120 mmol/L were SIADH secretion (36%) and hypovolemia (36%; **Fig. 2**).

DISCUSSION

In this study, we found that hyponatremia was common among patients with COVID-19 and occurred in 30% of patients.

TABLE 2. Complications and Outcomes of Patients With Increasing Severity of Hyponatremia (*n* = 4,645)

Variable	Severe Hyponatremia (Na ≤ 120 mmol/L)	Moderate Hyponatremia (Na 121–130 mmol/L)	Mild Hyponatremia (Na 131–135 mmol/L)	Normonatremia (Na 136–145 mmol/L)	*p* (Across All Four Sodium Levels)
n (%)	36 (1)	305 (7)	1,032 (22)	3,079 (66)	
Hospital complications					
Encephalopathy, *n* (%)	16 (44)	40 (9)	82 (7)	237 (8)	< 0.001
Acute renal failure, *n* (%)	7 (19)	82 (18)	193 (15)	438 (14)	0.170
Acute respiratory failure requiring mechanical ventilation, *n* (%)	10 (28)	149 (33)	301 (24)	599 (20)	< 0.001
Hospital length of stay (d), median (interquartile range)	6.3 (1.8–52.5)	6.5 (0.2–51.4)	6.2 (0.2–60.4)	6.0 (0.1–60.5)	0.381
Discharge disposition, *n* (%)					
In-hospital death	6 (17)	124 (27)	236 (19)	408 (13)	< 0.001
Discharge home	23 (64)	228 (50)	780 (61)	1,927 (63)	< 0.001
Other discharge dispositions, *n* (%)					0.004
Hospitalized	0	3 (1)	17 (1)	45 (2)	
Long-term acute care hospital	1 (3)	9 (2)	13 (1)	22 (1)	
Nursing home	3 (8)	42 (9)	117 (9)	371 (12)	
Hospice	0	14 (3)	35 (3)	98 (3)	
Acute inpatient rehabilitation	2 (6)	12 (3)	23 (2)	90 (3)	

Increasing severity of hyponatremia was associated with a 43% increase in the odds of in-hospital mortality after adjusting for other confounders, including admission severity of illness as measured by SOFA scores. Similarly, moderate-severe hyponatremia (Na ≤ 130 mmol/L) conferred 83% increased odds of mechanical ventilation and a 57% decreased odds of discharge home. Patients with severe hyponatremia (Na ≤ 120 mmol/L) had an eight-fold higher risk of encephalopathy compared with patients with higher sodium levels. Despite these findings, the outcome of patients with severe hyponatremia was not universally poor and 64% were discharged home (Table 2).

Strengths of this study include the large number of COVID-19 patients, making this the biggest study, to our knowledge, examining hyponatremia in the context of SARS-CoV-2 infection. This study is also the first to describe predictors, complications, and outcomes of COVID-19-related hyponatremia. Additionally, we present one of the largest data series reporting on the inverse association of IL-6 levels and sodium, which implicates inflammation-associated nonosmotic antidiuretic hormone release (SIADH) as a major mechanism (13). Furthermore, we present a detailed examination of patients with pneumonia-associated severe hyponatremia (sodium ≤ 120 mmol/L), which is sparsely described in the literature (22).

Despite the common occurrence of hyponatremia in patients with CAP, the underlying mechanisms remain disputed (1). SIADH has been identified as a common etiology and may be induced by stimuli, including pain, nausea, hypovolemia, and certain medications (23). Other factors contributing to SIADH in pneumonia are hypoxic pulmonary vasoconstriction with subsequent reduced left atrial filling, leading to increased ADH secretion (24). Elevated IL-6 levels and inflammation have also been tied to nonosmotic ADH secretion (13). Since cytokine storming and elevated IL-6 levels in COVID-19 have been well described (15, 25–27), this mechanism is of particular interest. As has been noted in other reports (28), we found the most common causes of severe hyponatremia to be SIADH and hypovolemia. Hypovolemic hyponatremia may have been common in COVID-19 patients since nausea, vomiting, diarrhea, insensible losses, and anorexia frequently accompanied more typical pulmonary symptoms. We identified a small but significant relationship between IL-6 levels and hyponatremia, which supports the concept of IL-6 related nonosmotic release of ADH in some patients. The small magnitude of this relationship underscores the facts that the etiology of hyponatremia was heterogeneous in our cohort (with equal proportions due to SIADH and hypovolemia), the degree of IL-6 elevation reflects various factors related to disease severity and the pathophysiologic relationship of IL-6 and ADH secretion is complex and nonlinear. Understanding of the underlying mechanism of hyponatremia is critical since treatment varies based on etiology (e.g., isotonic volume resuscitation in hypovolemic

TABLE 3. Multivariable Predictors of In-Hospital Death Excluding Patients With Hypernatremia ($n = 4,452$)

Variable	Adjusted OR (95% CI)	p
Significant variables		
Sodium level graded as normal, mild, moderate, and severe hyponatremia	1.43 (1.08–1.88)	0.012
Age	1.05 (1.03–1.07)	< 0.001
Body mass index	1.05 (1.02–1.08)	0.001
Admission blood urea nitrogen	1.02 (1.00–1.03)	0.013
Acute respiratory failure requiring mechanical ventilation	7.16 (4.48–11.44)	< 0.001
Admission Pao_2	0.99 (0.99–0.99)	0.006
Nonsignificant variables		
Admission Sequential Organ Failure Assessment score	0.99 (0.81–1.21)	0.921
Race (white vs other)	0.77 (0.51–1.16)	0.206
Sex (male)	0.79 (0.53–1.18)	0.255
History of congestive heart failure	1.30 (0.69–2.47)	0.416
History of chronic kidney disease	0.82 (0.44–1.53)	0.536
History of hypertension	0.70 (0.47–1.04)	0.078
History of diabetes	0.84 (0.53–1.35)	0.474
Acute renal failure	1.32 (0.88–1.96)	0.177
Encephalopathy	1.09 (0.61–1.93)	0.782
Admission creatinine	0.88 (0.74–1.04)	0.130
Admission potassium	1.04 (0.78–1.40)	0.775
Admission glucose	1.00 (1.00–1.00)	0.656
Hypertonic saline	0.41 (0.05–3.14)	0.387

OR = odds ratio.

hyponatremia vs volume restriction or judicious hypertonic saline administration in SIADH) (16, 21).

Certain limitations of this study should be mentioned. First, although there appeared to be a dose response effect for worsening hyponatremia on mortality (Fig. 1), sodium levels may be a marker for systemic illness, rather than directly responsible for mortality. However, multivariable adjustment for admission SOFA scores makes the likelihood of a direct causal relationship more plausible. Since hyponatremia can cause encephalopathy, seizures, cerebral edema, or cerebral pontine myelinolysis (if corrected too quickly), it is conceivable that hyponatremia or its treatment may directly impact survival. Second, we could only determine the etiology of hyponatremia in the severe hyponatremia subset of the cohort since serum

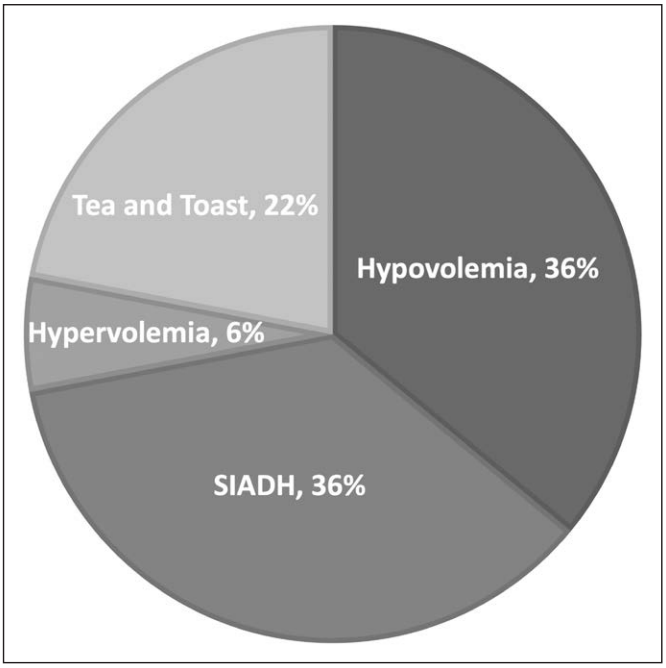

Figure 2. Primary etiology of hyponatremia among patients with admission sodium less than or equal to 120 mmol/L ($n = 36$ patients). SIADH = syndrome of inappropriate antidiuretic hormone.

osmolality and urine studies were available in less than 15% of the cohort. Additionally, assessing volume status is required to determine the mechanism of hyponatremia, and this is not easily evaluated retrospectively. Third, brain imaging and electroencephalogram data were limited in this cohort, and the rates of neurologic complications related to hyponatremia may be underestimated, particularly since many patients were sedated and/or paralyzed to facilitate ventilation, limiting neurologic assessments.

CONCLUSIONS

Hyponatremia occurred in nearly a third of COVID-19 patients, and was associated with increased risk of encephalopathy, acute respiratory failure requiring mechanical ventilation, and was an independent predictor of in-hospital mortality. Elevated IL-6 levels were associated with hyponatremia and may implicate inflammation-related SIADH in some patients. Further prospective studies of SARS-CoV-2 related hyponatremia may identify if sodium correction impacts outcome.

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