Journal of Primary Care & Community Health
Volume 13: 1–7

DOI: 10.1177/21501319211067349
journals.sagepub.com/home/jpc
SAGE

Serum Sodium, Patient Symptoms, and Clinical Outcomes in Hospitalized Patients with COVID-19

Timothy E. Yen[1], Andy Kim[2], Maura E. Benson[2], Saee Ratnaparkhi[2], Ann E. Woolley[2*], and Finnian R. Mc Causland[1*]

Abstract

Introduction: Disorders of serum sodium (SNa) are common in hospitalized patients with COVID-19 and may reflect underlying disease severity. However, the association of SNa with patient-reported outcomes is not clear. **Methods:** The Brigham and Women's Hospital COVID-19 Registry is a prospective cohort study of consecutively admitted adult patients with confirmed SARS-CoV-2 infection (n = 809). We examined the associations of SNa (continuous and tertiles) on admission with: (1) patient symptoms obtained from detailed chart review; and (2) in-hospital mortality, length of stay, and intensive care unit (ICU) admission using unadjusted and adjusted logistic regression models. Covariates included demographic data and comorbidities. **Results:** Mean age was 60 years, 48% were male, and 35% had diabetes. The most frequent symptoms were cough (64%), fever (60%), and shortness of breath (56%). In adjusted models, higher SNa (per mmol/L) was associated with lower odds of GI symptoms (OR 0.96; 95% CI 0.92-0.99), higher odds of confusion (OR 1.08; 95% CI 1.04-1.13), in-hospital mortality (OR 1.06; 95% CI 1.02-1.11), and ICU admission (OR 1.09; 95% CI 1.05-1.13). The highest sodium tertile (compared with the middle tertile) showed similar associations, in addition to lower odds of either anosmia or ageusia (OR 0.30; 95% CI 0.12-0.74). **Conclusion:** In this prospective cohort study of hospitalized patients with COVID-19, hypernatremia was associated with higher odds of confusion and in-hospital mortality. These findings may aid providers in identifying high-risk patients who warrant closer attention, thereby furthering patient-centered approaches to care.

Keywords
community health, COVID, disease management, emergency visits, patient-centeredness

Dates received: 25 October 2021; revised: 29 November 2021; accepted: 30 November 2021.

Introduction

Since the emergence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the associated disease (Coronavirus Disease 2019 [COVID-19]) has claimed over 4 million lives.[1] Predominantly resulting in pulmonary symptoms, COVID-19 is often accompanied by significant extra-pulmonary manifestations[2] and laboratory abnormalities. In addition to the well-recognized derangements of inflammatory and coagulation pathway biomarkers, electrolyte disorders have also been frequently described.

Abnormal serum sodium (SNa) levels are particularly common in hospitalized patients with COVID-19, with observational studies reporting 20% to 30% prevalence of hyponatremia (<136 mmol/L)[3,4] and 4% to 7% hypernatremia (>145 mmol/L)[5] on admission. Hyponatremia and hypernatremia are important prognostic markers and have been associated with higher risk of sepsis, respiratory failure, length of hospital stay, and all-cause mortality in patients with COVID-19.[4-6]

While symptoms associated with COVID-19 may reflect involvement of the underlying organ system, they can also be non-specific.[2] Detailed evaluation of patient symptoms is challenging among hospitalized patients with COVID-19, given the need for isolation and infectious disease precautions. This

[1]Division of Renal Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[2]Division of Infectious Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

*These authors contributed equally to this work as senior authors.

Corresponding Author:
Finnian R. Mc Causland, Brigham and Women's Hospital, 75 Francis Street, Medical Research Building-4, Boston, MA 02215, USA.
Email: fmccausland@bwh.harvard.edu

may inadvertently limit provider ascertainment of the true symptom burden and highlights the need for simple risk stratification tools. Given the prognostic associations of dysnatremia with adverse clinical outcomes, we wished to investigate the association of admission serum sodium with patient symptoms within the context of COVID-19. We hypothesized that extremes of admission serum sodium concentration would be associated with higher symptom burden, as well as with length of stay, ICU admission, and in-hospital mortality.

Methods

Study Population

The Brigham and Women's Hospital (BWH) COVID-19 Registry is a prospective cohort study of consecutively admitted adult patients with confirmed SARS-CoV-2 infection. Patients were included if they: (1) tested positive for SARS-COV-2 on nasopharyngeal polymerase chain reaction testing; and (2) were admitted and received treatment inpatient for COVID-19 at BWH from March to November, 2020. Follow up data were accrued through March 31, 2021. The Massachusetts General Brigham (MGB) institutional review board approved this study and allowed a waiver of informed consent.

Data Collection

Data for this study were collected using the EPIC (Epic Systems, Verona, WI, USA) electronic medical health record by way of data retrieval from the MGB Research Patient Data Registry and confirmatory physician chart review. Information obtained included patient demographic and clinical features, laboratory values, and hospital outcomes (length of stay, ICU admission, in-hospital mortality).

Exposures and Outcomes

The primary exposure of interest was serum sodium concentration on admission, examined continuously (per mmol/L change) and in tertiles (with the middle tertile as the reference, in order to assess for non-linear associations). In sensitivity analyses, clinical categories were examined as the exposure of interest (hyponatremia if SNa $<$ 135 mmol/L; eunatremia if SNa 135-144 mmol/L; and hypernatremia if SNa $\geq$ 145). The primary outcomes of interest were the presence of individual patient symptoms, which included: cough, fever, shortness of breath, sore throat, rhinitis, myalgia/malaise, chest tightness, gastrointestinal symptoms, confusion, headache, anosmia/ageusia. In additional analyses, the associations of admission SNa with length of stay (until hospital discharge or death), ICU admission, and in-hospital mortality were examined.

Statistical Methods

Continuous variables were described as means $\pm$ standard deviation (SD) or median [25th-75th percentile]; categorical variables were described as proportions (percentages). Baseline characteristics, according to categories of admission SNa, were compared with tests for trend based on linear regression, χ^2 trend test, and the Cuzick nonparametric trend tests.

The association of admission SNa with (1) individual patient symptoms, (2) ICU admission, and (3) in-hospital mortality was assessed using unadjusted and adjusted logistic regression models. Multivariable models included adjustment for age, Hispanic ethnicity, body mass index, systolic blood pressure, hemoglobin, history of heart failure, diabetes mellitus, chronic kidney disease, and lung disease. The association of admission SNa with length of stay was examined with the use of negative binomial regression models. Evidence for effect modification of the association of admission SNa with outcomes of interest according to month of admission were assessed by the inclusion of cross-product terms.

In exploratory analyses, an assessment of the frequency of laboratory measurements used in determining the etiology of hyponatremia on admission was performed (serum osmolality [SOsm], urine osmolality [UOsm], and urine sodium [UNa]).

All analyses were conducted using the statistical software package Stata MP, version 16 (Stata Corp., College Station, Texas). A 2-sided $P < .05$ was considered statistically significant. No adjustment for multiple testing was made and only index admissions were considered.

Results

Patient Information

A total of 809 individuals with symptom data were available for analyses. Mean age was 60.3 $\pm$ 18.2 years, 26% were Hispanic, 29% were Black, and 47.5% were male. Those in higher tertiles of admission SNa were more likely have a history of lung disease, have higher SOsm, but less likely to be Hispanic, compared with those in lower tertiles (Table 1). Baseline characteristics according to clinical categories of admission SNa are presented in Supplemental Table 1.

Serum Sodium and Patient Symptoms

The mean admission SNa in the overall cohort was 138 $\pm$ 5.0 mmol/L. Patient symptoms are displayed by serum sodium tertile in Table 2, with confusion, GI symptoms, and ageusia/anosmia showing significant trends across tertiles.

Table 1. Characteristics of Patients With COVID-19 by Tertile of Admission Serum Sodium.

		Tertiles of Sodium			
	Total	Tertile 1	Tertile 2	Tertile 3	*P*-value
N	809	368	298	143	
Sodium range (mmol/L)		117-137	138-141	142-169	
Age (years)	60.3 ± 18.2	60.4 ± 8.4	58.6 ± 18.2	63.8 ± 17.3	.21
Male	384 (47.5%)	189 (51.4%)	128 (43.0%)	67 (46.9%)	.15
Black	230 (29.4%)	101 (28.3%)	89 (31.0%)	40 (29.2%)	.69
Hispanic	203 (26.2%)	105 (30.1%)	70 (24.2%)	28 (20.6%)	.02
Height (cm)	167.7 ± 10.7	168.1 ± 11.0	167.3 ± 11.1	167.5 ± 9.2	.42
Weight (kg)	83.5 ± 23.0	83.3 ± 22.6	83.8 ± 22.6	83.4 ± 24.9	.90
BMI	29.6 ± 7.3	29.4 ± 7.1	29.8 ± 7.0	29.6 ± 8.2	.58
BMI categories					.47
BMI 18.5 to <25	223 (27.7%)	100 (27.2%)	77 (26.0%)	46 (32.2%)	
BMI 25 to <30	256 (31.8%)	125 (34.1%)	91 (30.7%)	40 (28.0%)	
BMI ≥30	327 (40.6%)	142 (38.7%)	128 (43.2%)	57 (39.9%)	
SBP (mmHg)	130.1 ± 23.8	130.7 ± 22.9	130.9 ± 25.0	126.9 ± 23.9	.19
Hemoglobin (g/dL)	12.4 ± 2.1	12.5 ± 2.1	12.4 ± 2.1	12.1 ± 2.1	.13
Past medical history					
Hypertension	523 (65.0%)	242 (65.9%)	181 (61.1%)	100 (70.9%)	.62
Coronary artery disease	114 (14.2%)	49 (13.4%)	40 (13.5%)	25 (17.7%)	.27
Congestive heart failure	128 (15.9%)	51 (13.9%)	49 (16.6%)	28 (19.9%)	.09
Diabetes mellitus	282 (35.1%)	136 (37.1%)	91 (30.7%)	55 (39.0%)	.86
Atrial fibrillation	112 (13.9%)	54 (14.7%)	40 (13.5%)	18 (12.8%)	.54
Lung disease	253 (31.7%)	100 (27.6%)	99 (33.6%)	54 (38.3%)	.01
Chronic kidney disease	124 (15.4%)	51 (13.9%)	50 (16.9%)	23 (16.3%)	.37
Laboratory testing					
SNa (mmol/L)	138.0 [135.0-140.0]	135.0 [133.0-136.0]	139.0 [138.0-140.0]	143.0 [142.0-145.0]	<.001
SOsm (mOsm/L)	282.5 [265.0-304.0)	275.0 [258.0-293.0)	301.0 [299.0-342.0)	319.0 [317.0-362.0]	<.001
UOsm (mOsm/L)	428.5 [299.5-558.5]	375.5 [233.0-577.5]	414.0 [389.0-515.0]	459.0 [382.0-545.0]	.35
UNa (mmol/L)	45.0 [24.0, 74.0]	45.0 [26.0-83.0]	48.0 [24.0-72.0]	36.5 [20.0-90.5]	.54

Abbreviations: Body Mass Index, BMI; SNa, serum sodium; SOsm, serum osmolality; Una, urine sodium; UOsm, urine osmolality.
Continuous variables are presented as mean ± standard deviation or median [25%-75% percentiles]; categorical variables are presented as count (%).
P-values represent a test for trend.

In unadjusted analyses each mmol/L higher SNa was associated with an 8% higher odds of confusion (OR 1.08; 95% CI, 1.04-1.13) and lower odds of cough (OR 0.97; 95% CI 0.94-1.00) and GI symptoms (OR 0.96; 95% CI 0.93-0.99) (Table 3). In the adjusted model, the association of higher SNa with lower odds of GI symptoms (OR 0.96; 95% CI 0.92-0.99) and higher odds of confusion (OR 1.08; 95% CI 1.04-1.13) remained apparent.

In unadjusted categorical analyses, compared with the middle tertile, the highest tertile of admission SNa was associated with a 4-fold higher odds of confusion (OR 4.17; 95% CI 2.45-7.12) and a lower odds of GI symptoms (OR 0.53; 95% CI 0.34-0.83) and anosmia/ageusia (OR 0.27; 95% CI 0.11-0.64). These patterns of association persisted after multivariable adjustment, with a higher odds of confusion (OR 3.77; 95% CI 2.10-6.75), and lower odds of GI symptoms (OR 0.51; 95% CI 0.32-0.81) and anosmia/ageusia (OR 0.30; 95% CI 0.12-0.74).

In sensitivity analyses, the relationship between clinical classifications of SNa and patient symptoms was examined. In this cohort, 20.4% of patients had hyponatremia (<135 mmol/L), 74.2% had eunatremia (135-144 mmol/L), and 5.4% had hypernatremia (≥145). Overall, broadly similar patterns of associations were noted (Supplemental Table 3).

Serum Sodium, ICU Admission, and In-Hospital Mortality

Higher SNa was strongly associated with admission to ICU and in-hospital mortality in unadjusted and adjusted analyses (Table 3). Each mmol/L increase of SNa was associated with a 9% higher adjusted odds of ICU admission (OR 1.09; 95% CI 1.05-1.13) and a 6% higher adjusted odds of in-hospital death (OR 1.06; 95% CI 1.02-1.11). Similarly, patients in the highest tertile of sodium had higher odds of

Table 2. Patient Symptoms by Tertiles of Sodium on Admission.

	Overall	Tertile 1	Tertile 2	Tertile 3	*P*-value
N	809	368	298	143	
Cough	519 (64.2%)	240 (65.4%)	193 (64.8%)	86 (60.1%)	.32
Fever	483 (59.8%)	228 (62.1%)	178 (59.7%)	77 (53.8%)	.10
SOB	456 (56.4)	203 (55.2)	170 (57.0)	83 (58.0)	.52
Sore Throat	107 (13.3%)	49 (13.4%)	42 (14.1%)	16 (11.2%)	.62
Rhinitis	90 (11.1%)	35 (9.5%)	40 (13.4%)	15 (10.5%)	.46
Malaise or Myalgia	446 (55.1%)	207 (56.3%)	164 (55.0%)	75 (52.4%)	.45
Chest Tightness	130 (16.1%)	52 (14.2%)	57 (19.2%)	21 (14.7%)	.52
GI Symptoms	301 (37.2%)	146 (39.7%)	118 (39.6%)	37 (25.9%)	.013
Confusion	104 (12.9%)	35 (9.5%)	27 (9.1%)	42 (29.4%)	<.001
Headache	103 (12.9%)	44 (12.1%)	46 (15.6%)	13 (9.2%)	.76
Anosmia or Ageusia	93 (11.5%)	45 (12.2%)	42 (14.1%)	6 (4.2%)	.05
In-hospital mortality	144 (17.8%)	53 (14.4%)	46 (15.4%)	45 (31.5%)	<.001
Length of stay(days)	7 (4-14)	7 (4-13)	6 (4-14)	8 (4-19)	.37
ICU admission	210 (26.0%)	82 (22.3%)	60 (20.1%)	68 (47.6%)	<.001

Abbreviations: GI, gastrointestinal; ICU, intensive care unit; SOB, shortness of breath.
Continuous variables are presented as mean ± standard deviation or median (25%-75% percentiles); categorical variables are presented as count (%).
P-values represent a test for trend.

ICU admission (OR 2.26; 95% CI 1.32-3.89) and in-hospital mortality (OR 3.86; 95% CI 2.39-6.24). There was no association of admission SNa, modeled continuously or in tertiles, with length of stay.

In sensitivity analyses examining clinical categories of SNa, there was no association between hyponatremia and risk of ICU admission, length of stay, or in-hospital mortality. In adjusted analyses, hypernatremia was associated with a 10-fold higher odds of ICU admission (OR 10.5; 95% CI 4.7-23.4) and greater than fourfold higher odds of in-hospital mortality (OR 4.6; 95% CI 2.2-9.8). In our adjusted negative binomial regression model, hypernatremia was associated with longer length of stay (IRR 1.35; 95% CI 1.01-1.80) when compared to eunatremia (Supplemental Table 3).

Admission Hyponatremia Workup

Among 809 patients, 165 (20%) had hyponatremia with SNa < 135 mmol/L on the day of admission. Among these patients SOsm, UOsm, and UNa were ordered on the same day in 9%, 5.4% and 8.4% of cases, respectively (Table 4).

Discussion

In this cohort of 809 hospitalized patients with COVID-19, we found that higher serum sodium on admission (whether analyzed by mmol/L change, tertile or clinical category) was associated with specific patient symptoms, particularly a higher odds of confusion, in addition to a higher risk of ICU admission and death.

Patient symptoms and abnormal serum sodium can be consequences of one another. This interplay becomes especially important in the context of COVID-19, as SARS-CoV-2 infection can cause gastrointestinal (nausea, vomiting, diarrhea) symptoms, increased insensible losses due to fevers, and anorexia, which can lead to hypernatremia from dehydration or, in certain conditions, to hypovolemic hyponatremia.[7,8] Further, non-osmotic release of ADH can be triggered by nausea,[9] stress, and pain, which are common features of COVID-19 and may lead to a syndrome of inappropriate antidiuretic hormone secretion (SIADH), with resultant hyponatremia,[10] Conversely, there are also multiple symptoms that arise as a result of dysnatremia. For example, hyponatremia itself is associated with nausea, vomiting, headache, and confusion, while hypernatremia can cause somnolence and confusion.[11,12]

In our study, admission serum sodium was inversely associated with risk of GI symptoms. These findings are consistent with the report from Ruiz-Sánchez et al,[4] where hypernatremia was associated with a lower risk of diarrhea in COVID-19 patients. One potential reason for this relationship may relate to hypovolemia from gastrointestinal losses with subsequent hypovolemic hyponatremia in the setting of a relative excess in free water replacement.

Our study found significant associations between higher SNa and increased risk of confusion. Confusion is both an etiology and side effect of hypernatremia, as impaired mentation may cause a patient to restrict free water intake. Consideration of mental status with the interpretation of serum sodium is especially important in the COVID-19 context, as up to 9% of these patient suffer from impaired

Table 3. Univariate and Multivariate Analysis of Patient Symptoms and Serum Sodium.

Variable		sNa (mmol/L)		sNa Tertiles				
				Tertile 1		Tertile 2	Tertile 3	
Symptoms		(N = 809)	*P*-value	(N = 368)	*P*-value	(N = 298)	(N = 143)	*P*-value
Cough	Unadjusted	0.97 (0.94-1.00)	.03	1.03 (0.75-1.42)	.87	REF	0.82 (0.54-1.24)	.35
	Adjusted	0.98 (0.95-1.01)	.11	0.95 (0.68-1.33)	.78	REF	0.90 (0.58-1.40	.65
Fever	Unadjusted	0.98 (0.96-1.01)	.22	1.11 (0.81-1.51)	.53	REF	0.79 (0.53-1.18)	.24
	Adjusted	0.99 (0.96-1.02)	.34	1.06 (0.75-1.49)	.73	REF	0.84 (0.54-1.29)	.42
SOB	Unadjusted	1.0 (0.98 -1.03)	.8	0.93 (0.68-1.26)	.63	REF	1.04 (0.70-1.56)	.84
	Adjusted	1.01 (0.98-1.04)	.63	0.88 (0.63-1.21)	.42	REF	1.06 (0.69-1.62)	.80
Sore throat	Unadjusted	1.0 (0.96-1.04)	.87	0.95 (0.61-1.47)	.80	REF	0.77 (0.42-1.42)	.40
	Adjusted	1.0 (0.95-1.05)	.94	0.99 (0.62-1.58)	.97	REF	0.88 (0.46-1.66)	.69
Rhinitis	Unadjusted	1.01 (0.97-1.06)	.49	0.68 (0.42-1.10)	.12	REF	0.76 (0.40-1.42)	.38
	Adjusted	1.01 (0.96-1.06)	.78	0.79 (0.48-1.3)	.37	REF	0.85 (0.44-1.65)	.62
Malaise or myalgia	Unadjusted	0.99 (0.96-1.02)	.43	1.05 (0.77-1.43)	.75	REF	0.90 (0.60-1.34)	.61
	Adjusted	0.99 (0.96-1.02)	.61	1.02 (0.74-1.41)	.90	REF	0.93 (0.61-1.42)	.73
Chest tightness	Unadjusted	1.0 (0.97-1.05)	.7	0.70 (0.46-1.05)	.09	REF	0.72 (0.42-1.25)	.25
	Adjusted	1.02 (0.97-1.06)	.45	0.64 (0.41-1.47)	.05	REF	0.82 (0.46-1.47)	.51
GI symptoms	Unadjusted	0.96 (0.93-0.99)	.01	1.00 (0.73-1.37)	.98	REF	0.53 (0.34-0.83)	.01
	Adjusted	0.96 (0.92-0.99)	.01	0.95 (0.68-1.32)	.76	REF	0.51 (0.32-0.81)	<.001
Confusion	Unadjusted	1.08 (1.04 -1.13)	<.001	1.05 (0.62-1.79)	.84	REF	4.17 (2.45-7.12)	<.001
	Adjusted	1.08 (1.04-1.13)	<.001	0.91 (0.51-1.63)	.76	REF	3.77 (2.10-6.75)	<.001
Headache	Unadjusted	0.98 (0.94-1.02)	.26	0.74 (0.47-1.15)	.18	REF	0.55 (0.29-1.05)	.07
	Adjusted	0.97 (0.92-1.02)	.2	0.74 (0.46-1.20)	.23	REF	0.57 (0.29-1.14)	.11
Anosmia or ageusia	Unadjusted	0.97 (0.93-1.01)	.14	0.85 (0.54-1.33)	.48	REF	0.27 (0.11-0.64)	<.001
	Adjusted	0.95 (0.90-1.00)	.06	0.91 (0.54-1.46)	.69	REF	0.30 (0.12-0.74)	.01
In-hospital mortality	Unadjusted	1.06 (1.02-1.10)	.00	0.92 (0.60-1.41)	.71	REF	2.52 (1.57-4.04)	<.001
	Adjusted	1.06 (1.02-1.11)	.00	0.82 (0.50-1.34)	.43	REF	2.26 (1.32-3.89)	.00
Length of stay (days)*	Unadjusted	1.00 (0.99-1.02)	.45	1.04 (0.90-1.19)	.61	REF	1.12 (0.94-1.35)	.21
	Adjusted	1.01 (1.00-1.02)	11	0.96 (0.83-1.11)	.58	REF	1.09 (0.91-1.31)	.35
ICU admission	Unadjusted	1.08 (1.05-1.12)	.00	1.14 (0.78-1.65)	.50	REF	3.60 (2.33-5.55)	<.001
	Adjusted	1.09 (1.05-1.13)	.00	1.05 (0.69-1.58)	.83	REF	3.86 (2.39-6.24)	<.001

Abbreviations: GI, gastrointestinal; ICU, intensive care unit; SOB, shortness of breath.
Tertiles-1 and Tertile-3 were analyzed using Tertile-2 as the reference.
*Reported as incident rate ratio.

consciousness.[2] Our study suggests that the presence of hypernatremia may identify a subset of particularly high-risk patients in this regard. These non-respiratory symptoms of COVID-19 are generally not incorporated into the moderate or severe categories of current disease severity scales, but may have important prognostic associations that warrant further evaluation for future risk stratification.

Although we did not find an association between hyponatremia and patient symptoms in our analysis, future studies that stratify hyponatremia by etiology may be useful.[6] We did not know the precise etiology of each patient's dysnatremia in our cohort, which in turn restricted our ability to speculate on the underlying pathophysiology that might connect a symptom with an abnormal admission SNa. A large part of this constraint can be attributed to the low frequency of simultaneous measurements of SOsm, UNa, and UOsm, which are crucial tests for determining the etiology of a hyponatremia. This issue was present in several other studies examining dysnatremia in COVID-19. Frontera et al[3] reported serum osmolality measured for <15% of their cohort while Hirsch et al[5] had serum osmolality and urine chemistry data for only approximately 10% of their cohort.

Several large studies in COVID-19 patients have reported a U-shaped association of extremes of serum sodium with both mortality and intensive care admission.[4,6,13] In our study, we found similar risk associations with hypernatremia, but not with hyponatremia. This may be due to fewer cases of severe hyponatremia in our cohort as compared to other study groups. Only 4.2% of our patients having an SNa < 130 mmol/L on admission compared to 8% (<131 mmol/L) and 9.1% (<130 mmol/L) in

Table 4. Admission Hyponatremia Work-Up Tests.

	Hyponatremia (<135 mmol/L)
N	165
SNa	133 [131-134]
SOsm (mOsm/kg)	274 [258-280]
SOsm measurements available	29 (18%)
UOsm (mOsm/kg)	420 [187-588]
UOsm measurements available	19 (12%)
UNa (mEql/L)	33 [22-66]
UNa measurements available	21 (13%)

Abbreviations: SNa, serum sodium; SOsm, serum osmolality; UNa, urine sodium; UOsm, urine osmolality.
Continuous variables are presented as median [25%-75% percentiles]; categorical variables are presented as count (%).

published studies from Frontera et al[3] and Hirsch et al[5] Further, the etiology of hyponatremia appears to be an important consideration in interpreting risk. A longitudinal cohort study of 488 patients with COVID-19 failed to find an association between undifferentiated hyponatremia and in-hospital mortality, however the subgroup of hypovolemic hyponatremia was associated with greater risk.[6] Similarly, in our study, only hypernatremia (opposed to hyponatremia) was associated with longer length of stay, further highlighting the prognostic significance of this phenomenon in our study. Although dysnatremia has been shown to be a risk factor for increased length of stay in multiple settings, these findings have not been entirely consistent across studies in the setting of COVID-19.[5,6,14,15]

Our study offers a unique examination into association between serum sodium levels and multiple clinical symptom manifestations in the COVID population. Other strengths of our study include the prospective cohort design, detailed data collection, and diverse patient population. However, there are several limitations to our study. The observational nature of this study prevents us from establishing a causal link between admission sodium and symptoms. Despite adjustment for several potential confounders, the possibility of residual confounding remains. In addition, the results from this single-center teaching hospital may not be broadly generalizable.

Although COVID-19 severity is frequently categorized according to degree of respiratory dysfunction, non-respiratory patient symptoms occur throughout the spectrum of the disease and deserve careful consideration.[16] Patient satisfaction is a vital part of delivering quality holistic care but is frequently diminished in the COVID-19 setting due to the special challenges the pandemic places on healthcare systems and providers.[17] When hospitalized, patients with COVID-19 are typically kept in isolated rooms and are at risk of receiving less individual attention from their medical teams.[18-22] We hope that highlighting potential risk factors for adverse symptoms may allow healthcare teams to address these issues and improve the patient experience.

Conclusion

In this cohort of hospitalized patients with COVID-19, hypernatremia was independently associated with higher odds of confusion and in-hospital mortality. Recognition of this relationship may help to identify high-risk individuals, prompt providers to elicit and address adverse symptoms, and thereby promote a more patient-centered approach to care.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: AEW received personal fees from COVAXX outside the submitted work; FRM received research funding from Advanced Instruments and Fifth Eye paid directly to Brigham and Women's hospital.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Research reported in this publication was supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under Award Number T32DK007527.

ORCID iD

Timothy E. Yen https://orcid.org/0000-0001-6385-1521

Supplemental Material

Supplemental material for this article is available online.

References

1. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard with vaccination data. Accessed August 19, 2021. https://covid19.who.int/
2. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. *Nat Med*. 2020;26:1017-1032. doi:10.1038/s41591-020-0968-3
3. Frontera JA, Valdes E, Huang J, et al. Prevalence and impact of hyponatremia in patients with Coronavirus disease 2019 in New York City. *Crit Care Med*. 2020;48(12):e1211-e1217. doi:10.1097/CCM.0000000000004605
4. Ruiz-Sánchez JG, Núñez-Gil IJ, Cuesta M, et al. Prognostic impact of hyponatremia and hypernatremia in COVID-19 pneumonia. A HOPE-COVID-19 (Health Outcome Predictive Evaluation for COVID-19) registry analysis. *Front Endocrinol*. 2020;11:599255. doi:10.3389/fendo.2020.599255
5. Hirsch JS, Uppal NN, Sharma P, et al. Prevalence and outcomes of hyponatremia and hypernatremia in patients hospitalized with COVID-19. *Nephrol Dial Transplant*. 2021;36(6):1135-1138. doi:10.1093/ndt/gfab067

6. Tzoulis P, Waung JA, Bagkeris E, et al. Dysnatremia is a predictor for morbidity and mortality in hospitalized patients with COVID-19. *J Clin Endocrinol Metab*. 2021;106(6):1637-1648. doi:10.1210/clinem/dgab107
7. Kopel J, Perisetti A, Gajendran M, Boregowda U, Goyal H. Clinical insights into the gastrointestinal manifestations of COVID-19. *Dig Dis Sci*. 2020;65(7):1932-1939. doi:10.1007/s10620-020-06362-8
8. Gheorghe G, Ilie M, Bungau S, Stoian AMP, Bacalbasa N, Diaconu CC. Is there a relationship between covid-19 and hyponatremia? *Medicina*. 2021;57(1):55. doi:10.3390/medicina57010055
9. Rowe JW, Shelton RL, Helderman JH, Vestal RE, Robertson GL. Influence of the emetic reflex on vasopressin release in man. *Kidney Int*. 1979;16(6):729-735. doi:10.1038/ki.1979.189
10. Fieldman NR, Forsling ML, Le Quesne LP. The effect of vasopressin on solute and water excretion during and after surgical operations. *Ann Surg*. 1985;201(3):383-390. doi:10.1097/00000658-198503000-00022
11. Weismann D, Schneider A, Höybye C. Clinical aspects of symptomatic hyponatremia. *Endocr Connect*. 2016;5(5):R35-R43. doi:10.1530/EC-16-0046
12. Arampatzis S, Frauchiger B, Fiedler G-M, et al. Characteristics, symptoms, and outcome of severe dysnatremias present on hospital admission. *Am J Med*. 2012;125(11):1125.e1-1125.e7. doi:10.1016/j.amjmed.2012.04.041
13. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020;323:2052-2059. doi:10.1001/jama.2020.6775
14. Mc Causland FR, Wright J, Waikar SS. Association of serum sodium with morbidity and mortality in hospitalized patients undergoing major orthopedic surgery. *J Hosp Med*. 2014;9(5):297-302. doi:10.1002/JHM.2168
15. Berardi R, Caramanti M, Castagnani M, et al. Hyponatremia is a predictor of hospital length and cost of stay and outcome in cancer patients. *Support Care Cancer*. 2015;23(10):3095-3101. doi:10.1007/s00520-015-2683-z
16. COVID-19 treatment guidelines 2. Accessed September 26, 2021. https://www.covid19treatmentguidelines.nih.gov/
17. Lopez-Picazo JJ, Vidal-Abarca I, Beteta D, López-Ibáñez M, García-Vázquez E. Impact of the COVID-19 pandemic on the hospital: inpatient's perceived quality in Spain. *J Patient Exp*. 2021;8:2374373521998625. doi:10.1177/2374373521998625
18. Fang J, Liu YT, Lee EY, Yadav K. Telehealth solutions for in-hospital communication with patients under isolation during COVID-19. *West J Emerg Med*. 2020;21(4):801-806. doi:10.5811/westjem.2020.5.48165
19. Lasater KB, Aiken LH, Sloane DM, et al. Chronic hospital nurse understaffing meets COVID-19: an observational study. *BMJ Qual Saf*. 2021;30(8):639-647. doi:10.1136/bmjqs-2020-011512
20. Belasen AT, Oppenlander J, Belasen AR, Hertelendy AJ. Provider–patient communication and hospital ratings: perceived gaps and forward thinking about the effects of COVID-19. *Int J Qual Health Care*. 2021;33(1):mzaa140. doi:10.1093/INTQHC/MZAA140
21. Drożdżal S, Rosik J, Lechowicz K, et al. COVID-19: pain management in patients with SARS-CoV-2 infection-molecular mechanisms, challenges, and perspectives. *Brain Sci*. 2020;10(7):1-10. doi:10.3390/brainsci10070465
22. Zeh RD, Santry HP, Monsour C, et al. Impact of visitor restriction rules on the postoperative experience of COVID-19 negative patients undergoing surgery. *Surgery*. 2020;168(5):770-776. doi:10.1016/j.surg.2020.08.010