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Hypernatremia in Critically Ill COVID-19 Patients: Is it a manifestation of COVID-19 or acquired in the ICU?

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Abstract

Objective: It has been noted that COVID-19 patients experienced electrolyte problems more frequently, and these disturbances were linked to unfavorable results. The purpose of this study was to investigate the incidence and consequences of hypernatremia in severely ill COVID-19 patients receiving intensive care (ICU).

Methods: Retrospective data analysis was done on COVID-19 patients who were admitted to ICUs over a six-month period at two centers.

Results: Data from 270 patients were collected in total. 138 (51%) patients developed hypernatremia (Na >145 mmol/l) during ICU stay. Hypernatremia was observed to be more in older or ventilated patients, whereas less in patients with chronic kidney disease. However, in patients with and without hypernatremia, unfavorable outcomes like length of stay (LOS) or mortality were comparable. Frequency of hypertension, septic shock as well as SOFA score, and serum BUN levels were significantly higher in moderate to severe hypernatremic (Na ≥150 mmol/l) vs mild hypernatremic (Na=146-149 mmol/l) group. Moderate to severe hypernatremia had worse prognosis than the mild group: ICU LOS (12 vs 9-day, p=0.033), ICU mortality (86% vs 61%, p=0.001 and 28-day mortality (89% vs 68%, p=0.004). Elevated serum BUN levels and moderate to severe hypernatremia were independent predictors of both ICU and 28-day mortality.

Conclusion: Critically ill COVID-19 patients experienced hypernatremia more frequently than expected, suggesting that hypernatremia may be a manifestation of systemic involvement of COVID-19 rather than iatrogenic. Patients with and without hypernatremia were found to have similar outcomes.

Key words: COVID-19, hypernatremia, critically ill patient, mortality.

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INTRODUCTION

It has been well established that that Coronavirus disease (COVID-19) affects many organs, including the lungs, heart, blood vessels, brain, liver, kidney, skin, gastrointestinal system, and eyes. However, recently, electrolyte disturbance associated with the disease has also been described. Among these, sodium disorders are the most frequently reported. In noncritically ill hospitalized patients, hypernatremia is uncommon, with prevalence rates of 0–2% at the time of admission and 1% for patients who develop it while being treated there. Hypernatremia is, nevertheless, a disorder that affects critically sick patients in ICUs far more frequently. Up to 6% of patients admitted to the ICU had hypernatraemia already (1, 2). In the literature, the frequency of hypernatremia in ICUs varies between 6-26% (3), while this rate rises up to 50% for COVID 19 patients (2). One of the potential mechanisms put forth is that the renin-angiotensin-aldosterone system (RAAS), which is increased and activated by the Angiotensin II molecule and cannot be metabolized due to virus invasion of the angiotensin-converting enzyme 2 (ACE2) receptors, increases potassium excretion and sodium reabsorption (3).

In COVID 19 patients, hypernatremia has been linked to an increased need for a ventilator, a prolonged stay in the ICU, a decline in mental health, and an increased mortality rate (4). When the serum sodium concentration is above 150 mmol/L, mortality of up to 48% has been reported (3, 5). However, the literature about sodium disturbances and its relationship with COVID-19 is limited. The aim of the study was to determine the prevalence and clinical consequences of hypernatremia in critically ill COVID-19 patients. It also sought to investigate whether hypernatremia is associated with COVID-19 itself or is acquired in ICU.

METHODS

Patients and study design

Patients with COVID-19 pneumonia who were admitted to the medical ICUs of Ondokuz Mayıs University Hospital and Ondokuz Mayıs State Hospital between 01.10.2020 and 31.03.2021 were enrolled for the study. Clinical and laboratory data were taken out of each patient's electronic medical record. Patients who developed hypernatremia during the intensive care follow-up were analyzed retrospectively. Those who did not develop hypernatremia were considered as the control group. Control group included both patient with normonatremia or hyponatremia. A serum sodium level over 145 mmol/l was considered hypernatremia. Despite hypernatremia being classified as mild (146-149 mmol/l) moderate (150-159 mmol/l) and severe (above 159 mmol/l) (6), in this study patients with hypernatremia were split into two groups for this study: those with mild hypernatremia (146-

149 mmol/l) and those with moderate to severe hypernatremia (150 mmol/l) (7). The time point for the first peak of hypernatremia during ICU stay was determined. Accordingly, serum sodium peak level (Na-peak) and time from ICU admission to first Na-peak level were recorded.

The following were the exclusion criteria: Below the age of 18, readmission to ICU, negative polymerase chain reaction (PCR) for COVID-19, ICU stay shorter than 48 hours, the time interval between COVID-19 diagnosis and ICU admission longer than 14 days, presence of the moribund state. COVID-19 diagnosis time was considered as the date of COVID-19 PCR positivity.

The study been approved by the Turkish Republic Health Ministry General Directorate of Health Services, COVID-19 Scientific Research Evaluation Commission, and Ondokuz Mayıs University Ethics Committee (Approval number: 2021/213). Since the study was retrospective, informed consent was waived.

Data Collection

Demographic, clinical, and laboratory parameters at admission were recorded. These data were as follows: age, gender, place of admission (ward, emergency department); comorbidities including hypertension (HT), cardiovascular disease, obstructive pulmonary disease, chronic kidney disease (CKD), malignancy, cerebrovascular disease; severity of disease represented by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and the sequential organ failure assessment (SOFA) score; medications including corticosteroid therapy, thiazide, and loop diuretics; biochemical parameters including blood urea nitrogen (BUN), creatinine, C-reactive protein (CRP) and, serum glucose level; blood gas analysis variables including pH, partial pressure of arterial carbon dioxide (PaCO2) and standard base excess (SBE). Interventions at admission or during ICU stay such as invasive mechanical ventilation (IMV), administered intravenous fluid therapy, and renal replacement therapy (RRT), complications developed at admission, or during ICU stay such as septic shock or acute kidney injury (AKI) were also recorded. Outcomes were determined as hospital length of stay (HLOS), ICU- LOS as well as ICU and 28-day mortality.

Kidney Disease: Improving Global Outcome (KDIGO) guidelines were used to define AKI (8). The presence of fluid-refractory hypotension needing vasopressor therapy together with accompanying tissue hypoperfusion (lactate > 2 mmol/L) was described as septic shock (9).

We divided steroid therapy into two options high dose (≥ 40 mg of methylprednisolone or ≥ 6 mg of dexamethasone per day) and pulse dose (≥ 250 mg of methylprednisolone per day for at least 3 days) (10). Since liberal fluid delivery is

linked to poor clinical and organ-specific outcomes in critically ill patients, restrictive fluid strategy is used to prevent positive fluid balance in ARDS patients. Patients in our practice who cannot or should not receive enteral feeding only received intravenous dextrose 30% fluid as hypocaloric nutrition.

Statistical Analysis

The SPSS 21 program was used to analyze the data.Categorical data were presented as frequencies and percentages. For numerical data that was normally distributed, mean and standard deviation were used; for non-normally distributed data, median and interquartile ranges were used. Comparisons between categorical variables were made with Chi-square (x2) or Fisher's exact test. The Student's t-test for normally distributed independent variables and the Mann Whitney U test for non-normally distributed independent variables were both used to compare continuous variables. In order to determine the independent predictors of hypernatremia, binary logistic regression analysis was used to examine the significant factors with a p-value 0.25 in univariable analysis. Among the hypernatremic patients, subgroup analysis was performed between mild and moderate to severe hypernatremic patients to identify the risk factors for mortality and severity of hypernatremia using multivariable logistic regression analysis. Continuous variables which are independently related with ICU and 28-day mortality were assessed using receiver operating characteristics (ROC) and areas under curve (AUC). Cut-off values were calculated for sensitivity and specificity. The treshold for statistical significance was set at P 0.05.

RESULTS

270 patients in total were included at two centers during six months of hospitalization.138 (51%) of them developed hypernatremia during their ICU stay. Baseline characteristics of patients with and without hypernatremia are shown in table. In the group with hypernatremia, the median age was older (71 vs. 68 y, p=0.041). Among the comorbidities, CKD was more common in patients without hypernatremia (18 vs 9%, p=0.036) than in patients with hypernatremia. The rates of patients who underwent intubation and IMV were higher in hypernatremic patients than in those who did not (79 vs 67%, p=0.023). Other variables along with hospital and ICU outcomes including LOS and mortality were comparable between the two groups (Table-1). On multivariable logistic regression analysis, both advanced age [adjusted OR, 1.02; 95% CI, 1.01-1.05; p=0.030] and IMV [adjusted OR, 1.77; 95% CI, 1.02-3.08; p=0.044] were independent risk factors for hypernatremia whereas presence of CKD [adjusted OR,0.41; 95% CI, 0.20-0.87; p=0.019] was associated with a lower risk of hypernatremia compared with the absence of CKD. Subgroup analysis

Table 1. Baseline characteristics of the study patients and risk factors for development of hypernatremia

Variables[a]	All patients N=270	Patients without hypenatremia N=132	Patients with hypernatremia N=138	Univariate *p*-value	Multivariate *p*-value, OR (95 % CI)
Age	70 (63, 77)	68 (62, 75)	71 (64, 78)	**0.041**	**0.030**, 1.02 (1.01-1.05)
Male gender	161 (60 %)	84 (64 %)	77 (56 %)	0.189	
Place of admission				0.354	
Emergency Department	157 (58 %)	73 (55 %)	84 (61 %)		
Ward	113 (42 %)	59 (45 %)	54 (39 %)		
Preexisting Conditions					
Hypertension	150 (56 %)	73 (55 %)	77 (56 %)	0,935	
Diabetes Mellitus	106 (39 %)	54 (41 %)	52 (38 %)	0.587	
Obstructive lung disease	53 (20 %)	26 (20 %)	27 (20 %)	0.978	
Cardiovascular disease	68 (25 %)	40 (30 %)	28 (20 %)	0,058	
Chronic kidney disease	37 (14 %)	24 (18 %)	13 (9 %)	**0,036**	**0.019**, 0.41 (0.20-0.87
Malignancy	24 (9 %)	13 (10 %)	11 (8 %)	0.588	
Cerebrovascular disease	17 (6 %)	8 (6 %)	9 (7 %)	0.876	
Severity of Disease					
SOFA score	4 (3, 6)	4 (3, 6)	4 (3, 7)	0.187	
APACHE II score	20 (16, 27)	20 (16, 26)	21 (17, 27)	0.467	
Time interval, day					
COVID 19 diagnosis to ICU admission	5 (1, 9)	5 (1, 9)	6 (1, 8)	0.958	
Medications					
High dose steroid	153 (57 %)	71 (54 %)	82 (59 %)	0.351	
Standart dose steroid	102 (38 %)	51 (39 %)	51 (37 %)	0.776	
Furosemid	94 (34 %)	49 (37 %)	42 (30 %)	0.227	
Thiazide	28 (10 %)	16 (12 %)	12 (9 %)	0.356	
Laboratories at admission					
BUN, mg/dL	43 (27, 66)	40 (24, 66)	46 (28, 66)	0.276	
Glucose, mg/dL	179 (125, 277)	180 (117, 269)	176 (130, 289)	0.541	
Creatinin mg/dL,	1.1 (0.84, 1.73	1.1 (0.8, 1.9)	1.2 (0.8, 1.7)	0.562	
CRP, mg/dL	117 (57, 191)	108 (50, 162)	130 (64, 215)	0.062	
pH	7.41 (7.35, 7.46)	7.42 (7.35, 7.47)	7.40 (7.35, 7.46)	0.095	
$PaCO_2$, mmHg	37 (32, 44)	37 (32, 43)	37 (32, 44)	0.824	
SBE, mmol/L	-1 (-4.4, +2.4)	-0.35 (-3.6, +2.8)	-2 (-4.8, +1.7)	0.079	
Interventions					
IMV	197 (73 %)	88 (67%)	109 (79 %)	**0,023**	**0.044**, 1.77 (1.02-3.08)
RRT	47 (17 %)	29 (22 %)	18 (13 %)	0.053	
Complications					
Septic shock	179 (66 %)	84 (64 %)	95 (69%)	0.366	
AKI	133 (49 %)	59 (45 %)	74 (54%)	0.143	
Outcomes					
Hospital LOS day	16 (11, 25)	17 (10, 27)	15 (11-24)	0.387	
ICU LOS day	9 (6, 15)	9 (5, 14)	10 (7-15)	0.241	
ICU mortality	207 (77 %)	98 (74 %)	109 (79%)	0.357	
28 day mortality	218 (81 %)	103 (78%)	115 (83%)	0.269	

showed significant differences between mild hypernatremic patients vs moderate to severe hypernatremic patients in terms of median age (69 vs 72 years, p= 0.036), presence of hypertension (40% vs 62%, p=0.017), median SOFA score (3 vs 4 points, p=0.003), serum levels of BUN (35 vs 49 mg/dl, p=0.001), creatinine (0.9 vs 1.3 mg/dl, p= 0.001), CRP (93, 144 mg/dl, p=0.017), pH (7.43 vs 7.39, p=0.023) and SBE (-0.2, -2.2 mmol/l, p=0.012), AKI (40 % vs 75 %, p=0.040) as well as septic shock (53% vs 75%, p=0.011) (Table-1). However, multivariable analysis confirmed the presence of hypertension [adjusted OR, 2.52; 95% CI, 1.16-5.49; p=0.020], median SOFA score [adjusted OR, 1.27 ; 95% CI, 1.01-1.60; p=0.037], median serum BUN level [adjusted OR, 1.03; 95% CI, 1.01-1.05; p=0.043] and

presence of septic shock [adjusted OR, 2.46; 95% CI, 1.10-5.51; p=0.029] were significantly associated with moderate to severe hypernatremia.

Table 2 Baseline characteristics of the hypernatremic patients and predisposing factors for moderate to severe hypernatremia.

Variables[a]	**Mild hypernatremia** 146-149 mmol/L N=38(28 %)	**Moderate to severe hypernatremia** ≥150 mmol/L N=100 (72 %)	**Univariate *p***	**Multivariate *p*,** OR (CI, 95%)
Age, year	69 (62,75)	72 (65, 79)	**0.036**	NS
Male gender	23 (61 %)	54 (54 %)	0.49	
Place of admission			0.659	
Emergency Department	22 (58 %)	62 (62 %)		
Ward	16 (42 %)	38 (38 %)		
Preexisting Conditions				
Hypertension	15 (40 %)	62 (62 %)	**0.017**	**0.020, 2.52 (1.16-5.49)**
	12 (32 %)	40 (40%)	0.362	
Obstructive lung disease	7 (18 %)	20 (20 %)	0.835	
Cardiovascular disease	5 (13 %)	23 (23 %)	0.199	
Chronic kidney disease	2 (5 %)	11 (11 %)	0.515	
Malignancy	4 (11 %)	7 (7 %)	0.495	
Cerebrovascular disease	1 (3%)	8 (8 %)	0.444	
Severity of Disease				
SOFA score	3 (2, 6)	4 (3, 7)	**0.003**	**0.037, 1.27 (1.01-1.60)**
APACHE II score	18 (14, 26)	21 (18, 27)	0.137	
Time interval, day				
ICU admission to Na_{peak} level	5 (3, 8)	6 (4, 10)	0.088	
COVID 19 diagnosis to ICU admission	5 (2, 9)	6 (1, 8)	0.070	
Medications				
High dose steroid	18 (47%)	64 (64 %)	0.076	
Standart dose steroid	18 (47%)	33 (33 %)	0.118	
Furosemid	13 (34%)	29 (29 %)	0.552	
Thiazide	3 (8%)	9 (9 %)	0.569	
Peak Na level	147 (146, 148)	153 (151, 156)	**<001**	NA
Laboratories at admission				
Glucose, mg/dl	164 (132, 235)	184 (129, 302)	0.309	
BUN, mg/dl	35 (22, 49)	49 (33,74)	**0.001**	**0.043, 1.03(1.01-1.05)**
Creatinine, mg/dl	0.9 (0.8, 1.3)	1.3 (0.9, 1.8)	**0.001**	NS
CRP	93 (27, 182)	144 (83, 223)	**0.017**	NS
pH	7.43 (7.38, 7.47)	7.39 (7.31, 7.44)	**0.023**	NS
PCO2, mmHg	38 (34, 47))	37 (31, 44)	0.386	
SBE, mmol/l	-0.2 (-3.8, +4.1)	-2.2 (-5.7, +1.0)	**0.012**	NS
Interventions				
IMV	26 (68 %)	83 (83%)	0.060	
RRT	6 (16 %)	12 (12 %)	0.577	
Complications				
Septic shock	20 (53 %)	75 (75 %)	**0.011**	**0.029, 2.46 (1.10-5.51)**
AKI	15 (40 %)	59 (59 %)	**0.040**	NS
Outcome				
Hospital LOS, day	14 (10, 23)	15 (11, 25)	0.551	
ICU LOS day	9 (6, 12)	12 (7, 17)	**0.033**	NA
Mortality in ICU	23 (61 %)	86 (86 %)	**0.001**	NA
28 day mortality	26 (68 %)	89 (89 %)	**0.004**	NA

[a] Categorical variables are presented as frequency and percentage, continous variables are presented as median and inter-quartile ratio.

OR, odds ratio; *SOFA*, sequential organ failure assessment; *APACHE II*, Acute Physiology and Chronic Health Evaluation II; *COVID 19*, Coronavirus disease 2019; *ICU*, intensive care unit; *BUN*, blood urea nitrogen; *CRP*, C-reactive protein; *$PaCO_2$*, partial pressure of arterial carbon dioxide; *SBE*, standard base excess; *IMV*, invasive mechanical ventilation ; *RRT*, renal replacement therapy; *AKI*, acute kidney injury; *LOS*, length of stay; *NA*, not applicable; *NS*, nonsignificant.

Table 3 Demographic and clinical variables in survivors and nonsurvivors among hypernatremic patients

Variables[a]	ICU outcome				Hospital outcome			
	Survivors N=29 %)	Nonsurvivors N=109	Univariate p value	Multivariate p- value OR (CI 95	Survivors N=23 %)	Nonsurvivors N=115	Univariate p value	Multivariate p- value OR (CI 95
Male gender	12 (41%)	65 (60%)	0.079	NS	8 (34 %)	69 (60 %)	0.026	**0.023** 3.7 (1.24, 11.2)
Hypernatremia			0.001	**0.045**			0.004	**0.047**
Mild	15 (52 %)	23 (21 %)		2.58 (1.03-	12 (52 %)	26 (23 %)		2.9 (1.1,
Moderate to severe	14 (48 %)	86 (79 %)		6.49)	11 (48 %)	89 (77 %)		8.5)
Place of admission			0.004	NS			0.019	NS
Emergency ward	11 (38 %)	73 (67 %)			9 (39 %)	75 (65 %)		
Ward	18 (62 %)	36 (23 %)			14 (61 %)	40 (35 %)		
Laboratory at admission								
BUN, mg/dL	24 (19, 44)	49 (34, 70)	<0.001	**0.012** 1.03 (1.01- 1.06)	23 (19, 31)	49 (34, 68)	<0.001	**0.014** 1.04 (1.02- 1.08)
SBE, mmol/l	1.5 (-4.8, 5.5)	-2.2 (-4.9, 0.8)	0.015	NS	1.6 (-4.1, 6.4)	-2.2 (-5.1, 0.8)	0.015	NS
SOFA	3.0 (2.0, 5.5)	5.0 (5.0, 5.0)	0.001	NS	3.0 (2.0, 4.0)	5.0 (5.0, 5.0)	0.001	NS
APACHE II	18 (14, 24)	21 (21, 21)	0.049	NS	17 (14, 22)	21 (21, 22)	0.049	NS
Pulse steroid	9 (31 %)	73 (67 %)	0.001	NS	9 (39 %)	73 (64 %)	0.030	NS
Standart steroid	19 (66 %)	32 (29 %)	0.001	NS	13 (57 %)	38 (33 %)	0.033	NS
IMV	18 (62 %)	91 (84 %)	0.012	NS	14 (61 %)	95 (83 %)	0.019	NS
Septic shock	15 (52 %)	80 (73 %)	0.028	NS	11 (48 %)	84 (73 %)	0.017	NS

[a] Categorical variables are presented as frequency and percentage, continous variables are presented as median and inter-quartile ratio.

OR, odds ratio; *SOFA*, sequential organ failure assessment; *APACHE II*, Acute Physiology and Chronic Health Evaluation II; *ICU*, intensive care unit; *BUN*, blood urea nitrogen; *SBE*, standard base excess; *IMV*, invasive mechanical ventilation; *NS*, nonsignificant

Outcomes including ICU LOS (12 vs 9, p=0.033), ICU mortality (86% vs 61%, p=0.001 and 28-day mortality (89% vs 68%, p=0.004) were significantly worse in moderate to severe hypernatremic patients compared to the mild hypernatremic group while hospital LOS (15 vs 14 days, p=0.551) was similar in both groups (Table-2).

On multivariable logistic regression analysis, the patients with moderate to severe hypernatremia and high serum BUN levels were significantly associated with either ICU [adjusted OR, 2.58; 95% CI, 1.03-6.49; p=0.045 and adjusted OR, 1.03; 95% CI, 1.01-1.06; p=0.012 respectively] and 28-day mortality [adjusted OR, 2.93; 95% CI, 1.10-8.52; p=0.047, and adjusted OR, 1.03; 95% CI, 1.02-1.08; p=0.014, respectively] whereas male gender [adjusted OR, 3.70; 95% CI, 1.24-11.21; p=0.023] had significant impact just on 28-day mortality (Table-3).

Diagnostic accuracy of BUN levels above 31 mg/dL for predicting ICU and 28-day mortality were 83% sensitivity, 69% specificity, AUC 0.78 (95 % CI, 0.67-0.89) p<0.001 (Figure-1) and 82% sensitivity, 79% specificity, AUC 0.81(95%CI, 0.69-0.93) p<0.001 (Figure-2), respectively.

DISCUSSION

The present study demonstrated that nearly half of the critically ill COVID-19 patients developed hypernatremia during ICU stay. No difference was observed in ICU and hospital outcomes between hypernatremic versus non-hypernatremic groups. However, patients with moderate to severe hypernatremia had a worse prognosis than the mild group. In critically ill COVID-19 patients, hypernatremia could be a manifestation of the disease.

Age is a well-known independent risk factor for hypernatremia (11). Underlying mechanisms are age-related physiological changes such as impaired thirst drive, decreased renal concentrating ability, and compromised adaptability to fluid losses. Decreased water intake may exacerbate the condition. As mentioned in our results advanced age predicts hypernatremia strongly. In ventilated patients, hypernatremia may develop due to failure to provide adequate free water as well as increased insensible loss of fluid (12). We figured out that patients on IMV had 1.7 fold increased odds of hypernatremia compared to non-intubated patients.

Since the renal ability to concentrate and dilute urine is impaired in CKD, the susceptibility to dysnatremia increases. In the early stages of CKD, the kidneys are capable of excreting a normal ingested load of sodium and other solutes but it achieves this by excreting large volumes of water due to its reduced concentration capacity (13, 14). However, as the glomerular filtration rate decreases over time, the renal water excretion ability decreases, thus it becomes less possible to develop hypernatremia (13). Nevertheless, in advanced stages of CKD predisposition to both hypernatremia and hyponatremia may be possible. The prevalence of hypernatremia in studies of patients with CKD shows great variability as 3.5 to 24.7%, depending on the methodological differences (15, 16). According to our data proportion of patients with CKD in the hypernatremic group was 9% which was only half of the nonhypernatremic group.

Dysnatremia, either hyponatremia or hypernatremia is demonstrated to be associated with poor outcomes including increased mortality and length of hospital stay both in COVID-19 era according to the the current literatüre (3, 17, 18). Unlike the previous studies, we were unable to show a relationship between elevated serum sodium levels and prognosis in patients admitted to the ICU with a diagnosis of COVID-19. We could not explain this result however it may be attributed to the small size of the study sample. Also, the severity of illness regarding APACHE score, SOFA score, and the frequency of adverse events such as septic shock or AKI were similar in both groups which may contribute to a similar prognosis between groups. However, the subgroup analysis revealed that patients with moderate to severe hypernatremia had a

higher death rate and longer stay in the ICU than those with mild hypernatremia. This result implies that the noticeable effect of hypernatremia occurs after 150 mmol/l. In patients with moderate to severe hypernatremia, both ICU and 28-day mortality were increased up to 2.58 and 2.93 times of mild group respectively. ICU length of stay is also prolonged much more in moderate to severe hypernatremic patients than in mild hypernatremic ones.

The presence of hypertension, high SOFA score, increased serum BUN levels at admission and septic shock in the follow-up were predisposing factors for the development of moderate to severe hypernatremia. Of these the most surprising data is the link between hypertension and moderate to severe hypernatremia. Several possible mechanisms may explain this relationship. Nearly half of the patients with essential hypertension are sensitive to salt. This sensitivity gets stronger with aging. As a result, the relationship between arterial blood pressure and sodium excretion is altered, thus higher blood pressure is needed to ensure salt excretion (19). In critically ill patients with a history of hypertension, due to factors related to the environment, such as sedation, diuretics, increased insensible fluid loss, sepsis, etc., blood pressure may not increase in response to increased salt load. This suggests that inadequate reduction of sodium excretion in these patients leads to hypernatremia. Furthermore, hypertension is the most common comorbidity recorded in patients with COVID-19 patients (20, 21). The significance of hypernatremia as a risk factor for severe COVID-19 outcomes has been reported from multiple observational and retrospective studies (20,22). If hypernatremia is a manifestation of COVID-19 as we suppose, the presence of hypertension might also increase the severity of hypernatremia. Association between hypernatremia and sepsis is not fully elucidated. However, the positive correlation between hypernatremia and septic shock has been shown in some studies (23, 24). As sepsis may contribute to hypernatremia, it may also be a manifestation of sepsis, especially in elderly patients (23). We report more than twofold risk of moderate to severe hypernatremia in patients with septic shock than patients without septic shock. Osmotic diuresis may directly lead to or contribute to the development of hypernatremia by causing severe fluid loss. Osmotic diuresis due to urea is a well-known cause of hypernatraemia in intensive care unit (25). Our findings suggest that high BUN levels may play an important role in predicting the severity of hypernatremia and mortality among the critically ill COVID-19 patients with hypernatremia. Several studies concluded that the male gender is strongly associated with a higher risk of death in hospitalized COVID-19 patients (25,26). On contrary, we could not demonstrate the same

association in this cohort. However, among hypernatremic patients with COVID-19, the male gender had a higher odds ratio (3.7 fold) of 28-day mortality in comparison with females. This finding may imply that hypernatremia increases the male gender's contribution to COVID-19 mortality. Surprisingly, the use of corticosteroids had no impact on the development of hypernatremia in the study population. Corticosteroids may facilitate hypernatremia by mineralocorticoid effect and sodium retention as a consequence. It can induce hypernatremia not only in this way but also by causing electrolyte-free fluid loss (27). The underlying mechanism is known as excess corticosteroids cause urinary concentration defect and polyuria by down-regulating urea transporters without affecting the aquaporin channels (28). Furthermore, corticosteroids lead to osmotic urea diuresis by elevating BUN levels via catabolism. The relation between steroid therapy and hypernatremia is not proven fully in clinical studies. Despite some studies revealing that corticosteroids are associated with a higher risk of hypernatremia (5, 27, 28), a recent study showed a significant association between ICU acquired hypernatremia and high dose steroid therapy, but no association between pulse steroid therapy and hypernatremia (29). In this cohort, 95 % of the patients with COVID-19 had received either a high dose or pulse steroid for COVID-19 pneumonia. The proportion of patients who received steroid treatment was similar in both the hypernatremic and non-hypernatremic groups. The lack of expected effect of corticosteroids on water sodium balance may be explained by the critical illness-related corticosteroid insufficiency (CIRCI) state. In CIRCI, target tissue resistance to corticosteroids may occur despite high levels of serum cortisol. Evidence from studies of severe acute respiratory syndrome (SARS) suggests that COVID-19 which is an infection with SARS-CoV-2 is associated with CIRCI (30). This study is mainly limited by its retrospective design. Despite being conducted at two centers our results cannot be generalized due to the small size of the study population. Since we had missing data on sodium input, we could not establish whether there was a relationship between sodium input and hypernatremia. Nevertheless, our data is valuable regarding its contribution to the limited data on the impact of COVID-19 on sodium water balance and thereby the association with adverse outcomes. Also, detailed subgroup analysis of hypernatremic patients with COVID-19 provided valuable information on the comparison of the risk factors and outcomes between mild and moderate to severe hypernatremia.

CONCLUSION

Hypernatremia was recorded at a higher frequency than expected in patients with COVID-19 pneumonia admitted to the

intensive care unit. This unusual finding may be a primary manifestation of the SARS-CoV-2 virus, which involves multiple systems. Elevated BUN levels and moderate to severe hypernatremia may predict mortality in critically ill COVID-19 patients who developed hypernatremia. However, further investigations are needed by large scale studies.

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