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Research Article

The effect of dysnatremia on prognosis and mortality in critically ill patients with COVID-19

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Abstract

Objectives: Sodium disorders, the most common electrolyte disorders in hospitalized patients, are common in hospitalized patients with pneumonia. Numerous studies have shown that sodium abnormalities are independent risk factors for mortality, medical intensive care unit (ICU) admission, and prolonged hospital stay. The aim of the study was to investigate the prevalence of dysnatremia and the effect of dysnatremia on prognosis and mortality in critically ill COVID-19 patients.

Methods: This retrospective study was performed between June 1, 2021, and July 30, 2021, in COVID-19 ICUs. 149 critically ill, laboratory-confirmed COVID-19 patients admitted to the ICU were included in the study. The collected data included demographic data, comorbidities, severity of illness, and laboratory tests (serum C-reactive protein, lymphocyte, ferritin, sodium, chloride, and potassium levels). The prognosis was evaluated in terms of mortality, need for mechanical ventilation, and length of ICU stay.

Results: At ICU admission, hyponatremia was present in 33 (22.1%) patients, whereas hypernatremia was detected in 14 (9.5%) patients. 102 (68.4%) patients had normal sodium levels. The mortality rate for normonatremic, hyponatremic, and hypernatremic patients was 50.0%, 57.7%, and 78.6%, respectively. These results indicated a statistically significantly higher mortality rate in patients with baseline hypernatremia (p=0.05).

Conclusion: Among critically ill COVID-19 patients in the ICU, dysnatremia was common at admission and hyponatremia was more common than hypernatremia. Hypernatremia was related to mortality. Admission sodium levels can be a predictor of mortality in COVID-19 patients who are critically ill.

Keywords: Coronavirus disease 2019, dysnatremia, intensive care unit, hipernatremia, hyponatremia

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Sodium disorders are the most common electrolyte disorders in hospitalized patients. Dysnatremias: hyponatremia and hypernatremia (defined as the levels of serum sodium <135 mmol/L and above 145 mmol/L, respectively) are common in hospitalized patients with pneumonia. It has been shown in numerous studies that sodium abnormalities are independent risk factors for mortality, admission to medical intensive care units (ICU), and prolonged length of hospital stay [1]. The prevalence of hyponatremia in hospitalized patients is 30%. Many studies have demonstrated that in patients with bacterial pneumonia, hyponatremia is the most prevalent electrolyte abnormality. The syndrome of inappropriate antidiuretic hormone secretion and hypovolemia is the most common causes of hyponatremia [2–4]. Due to infection, proinflammatory cytokines (like interleukin-1β and interleukin-6) are secreted excessively, and as a result, non-osmotic release of arginine vasopressin, which causes hyponatremia due to SIAD, is induced [5, 6]. Therefore, hyponatremia is a good

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predictor of the severity of infections and the level of the inflammatory response [7]. The prevalence of hypernatremia is reported at 5.8% and is not common in patients with pneumonia [8]. The causes of hypernatremia can be either excessively high sodium intake or loss of free water or a combination of the two [9].

In March 2020, the World Health Organization announced the COVID-19 infection, caused by severe acute respiratory syndrome coronavirus 2, as a pandemic [10]. The disease mainly affects the respiratory system and causes acute respiratory distress syndrome and respiratory failure. The vast majority of COVID-19 patients are hospitalized with viral pneumonia [11]. It has been described that electrolyte abnormalities are common at admission in patients hospitalized with COVID-19 [12].

Some important publications have emerged regarding the prevalence and prognostic impact of dysnatremia in COVID-19 patients [13, 14].

The aim of this study was to investigate the prevalence of dysnatremia and the effect of dysnatremia on prognosis and mortality in critically ill COVID-19 patients.

Materials and Methods

Study design

This retrospective study was performed between June 1, 2021, and July 30, 2021, in Ersin Arslan Training and Research Hospital COVID-19 ICUs. The Ministry of Health of the Republic of Turkiye 2022-01-16T22_37_48 numbered and Gaziantep University Medical Ethics Committee 2022/75 numbered approvals have been received.

Patients

All patients who were admitted to Ersin Arslan Training and Research Hospital COVID-19 ICUs from June 1, 2021, to July 30, 2021, were included (n=199). The following were the criteria for exclusion: Negative reverse transcription-polymerase chain reaction (PCR) (n=39), chronic renal failure, a history of disease, and drug use that may affect electrolyte balance (n=11). At last, 149 patients were enrolled in the study.

The samples of the patients were taken as venous blood from the antecubital region in the horizontal position, within 30 min at the most, after their admission to the ICU for treatment, ignoring hunger or satiety. Tubes with ethylenediaminetetraacetic acid (EDTA) were used for complete blood count and non-anticoagulant tubes were used to obtain serum determining other biochemical parameters. These samples were then sent to the laboratory for testing as soon as possible.

Clinical data collection

Data were collected over a 2-month period (June 2021–July 2021) using the ICU database; all patients who tested positively for COVID-19 were evaluated. The collected data included demographic data, comorbidities, severity of illness, the treatments given, and laboratory tests (serum C-reactive protein [CRP], lymphocytes, ferritin, sodium, chloride, and potassium levels). The prognosis was evaluated in terms of mortality, need for mechanical ventilation (MV), and length of ICU stay.

Laboratory measurements

Nasopharyngeal swab samples of the patients were tested in accordance with the protocol, real-time PCR test, DS Coronex COVID-19 Multiplex Real Time-qPCR Test Kit (DS Nano and Biotechnology Product Tracing and Tracking Co., Turkiye), and Roche Lightcycler 480 and Qiagen Rotor-Gene Q instruments, in line with the manufacturer's recommendations.

The blood samples taken from the patients in the EDTA tube and the lymphocyte cells obtained from the blood count parameters determined by the Cell Dyn 4000 device (Abbott Diagnostics, Santa Clara, California, USA) were evaluated.

Sodium, potassium, and chloride parameters were measured on a Beckman Coulter AU5800 auto-analyzer (Beckman Coulter Inc., California, USA). There are peak ether membrane electrodes for sodium and potassium and a chloride-specific PVC membrane on the ISE module in the device. An electric potential according to the Nernst Equation for the ions in question, when compared to an existing reference, the voltage created by this electric potential shows the ion concentration. Serum ferritin levels were measured by a spectrophotometric method in AU5800 (Beckman Coulter Inc., Brea, California, USA). CRP levels were also analyzed by the nephelometric method in BN II System (Siemens, Erlangen, Germany) device.

Statistical analysis

The results were presented as the mean plus standard deviation. The distribution of parameters within the group was homogeneous. Analysis was performed by determining dependent and/or independent variables from age, gender, comorbidity, need for MV, mortality, length of ICU stay, sodium, potassium, chloride, lymphocytes, ferritin, and CRP parameters. MV requirement, mortality, and length of ICU stay were determined as dependent variables; sodium, potassium, chloride, lymphocytes, ferritin, and CRP parameters were determined as independent variables. A p=0.05 with a 95% confidence interval was considered statistically significant. For analysis, a Chi-square test was performed.

Results

This study included 149 patients, 83 males (55.7%) and 66 females (44.3%), with a mean age of 64.0 years (Table 1). While 110 (73.8%) of the patients had comorbid diseases, 39 (26.2%) of them did not have any comorbid diseases. Comorbid diseases were as follows: Hypertension in 51

Table 1. The descriptive statistics, outcome measures, and laboratory parameters of the study population

Parameters	n	%	Mean	SD	%95 CI
Ages			64.0 (30–94)	13.57	±2.20
Gender					
Male	83	55.7		0.49	±0.08
Female	66	44.3			
Comorbidity					
Yes	110	73.8		0.44	±0.07
No	39	26.2			
APACHE II			24.2 (6–80)	9.83	±3.36
LOS in ICU (days)			9.51 (1–37)	7.28	±1.17
LOS in hospital (days)			14.89(1–58)		±7.52
Need for MV	95	63.7		0.48	±0.08
Mortality	81	54.3		0.49	±0.08
Treatment					
Steroid therapy	120	80.58		6.45	±2.98
Antibiotic therapy	132	88.59		7.32	±1.97
Antiviral therapy	83	55.70		5.30	±0.09
Vasopressor therapy	75	50.33		4.64	±0.75
Laboratory results					
Sodium (mEq/L)			138.5 (125–184)	6.40	±1.00
Potasium (mEq/L)			3.89 (2.8–7.2)	1.45	±2.36
Chloride (mEq/L)			103.1 (86–123)	5.60	±0.90
Lymphocyte (10^3/µl)			0.75 (0.08–8.86)	0.08	±1.34
Ferritin (ng/ml)			384 (41.7–1650)	32.8	±5.32
C-reactive protein (mg/L)			118.8 (3.4–322.4)	95.2	±1.54

SD: Standard deviation; CI: Confidence interval; APACHE II: Acute Physiology and Chronic Health Evaluation II; LOS: Length of stay; ICU: Intensive care unit; MV: Mechanically ventilation.

(34.23%) patients, diabetes mellitus in 43 (28.86%) patients, cardiac diseases in 33 (22.15%) patients, malignancy in 11 (7.38%) patients, neurological disorders in 8 (5.37%) patients, respiratory system disease in 8 (5.37%) patients, and other diseases in 7 (4.70%) patients. 95 (63.7%) patients needed MV, the mean of the length of ICU stay was 9.5, and hospital stay was 14.89 days. Death occurred in 81 (54.3%) patients. At ICU admission, 102 (68.4%) patients had normal sodium levels, hyponatremia was present in 33 (22.1%) patients, whereas hypernatremia was detected in 14 (9.5%) patients. The descriptive statistics, treatment modalities, outcome measures, and biochemical indexes of the study population are stated in Table 1.

Table 2 illustrates the demographics, treatment modalities, outcome measures, and biochemical indices of the patients according to their serum sodium status. In terms of age, gender, comorbidities, treatment modalities, biochemical parameters, the requirement for MV, and length of ICU and hospital stay, there was no statistically important difference between the groups. Stratified by sodium status at admission, the mortality rate for normonatremic, hyponatremic, and hypernatremic patients was 50.0%, 57.7%, and 78.6%, respectively. These results indicated a statistically significantly higher mortality rate in patients with baseline hypernatremia (p=0.05).

Discussion

The COVID-19 pandemic has become a new and unexpected health problem all over the world. For this reason, the management of clinical and pharmacological treatments of patients was empirical in the beginning. The ongoing pandemic process has encouraged researchers to monitor clinical signs and laboratory parameters, explore optimal intervention strategies, and explore disease severity predictors that can identify possible early markers of patient outcomes. In our study investigating the prevalence of dysnatremia and the effect of dysnatremia on prognosis and mortality in critically ill COVID-19 patients, we showed that patients with hypernatremia at admission have a higher mortality rate.

Martino et al. and Ruiz-Sánchez et al., [13, 14] in their study of patients hospitalized with the diagnosis of COVID-19, showed that hyponatremia was common in patients at the time of admission. In their study of patients with COVID-19, using patients without COVID-19 but with similar symptoms as a control group, Atila et al. [15] showed that patients with COVID-19 experienced a significantly higher rate of hyponatremia compared to controls. Consistent with the literature, in our study at admission, hyponatremia was common among patients with COVID-19; it occurred in 22.14% of patients.

Table 2. The demographic characteristics, outcome measures, and laboratory parameters of the patients according to their serum sodium status

Parameters	Hyponatremia				Hypernatremia				Normonatremia			
	n	%	Mean±SD	p	n	%	Mean±SD	p	n	%	Mean±SD	p
	33	100			14	100			102	100		
Ages			64.4±4.41	0.69			71.5±9.48	0.94			64.2±2.21	**0.002**
Gender												
Male	15	18		0.98	9	11		0.39	59	71		**0.028**
Female	18	27		0.96	5	8		0.37	43	65		**0.019**
Comorbidity												
Yes	24	22		0.77	10	9		0.65	76	69		**0.009**
No	9	23		0.79	4	10		0.69	26	67		**0.048**
APACHE II			23.2±2.57	0.48			33.1±9.59	0.062			24.2±1.60	0.84
LOS in ICU (days)			10.2±3.43	0.76			6.06±1.78	0.88			9.57±1.18	0.27
LOS in hospital (days)			15.01±7.45	0.68			14.83±7.61	0.76			15.01±6.83	0.73
Need for MV	22	23		0.59	11	12		0.18	62	65		0.36
Mortality	19	23		0.48	11	14		**0.047**	51	63		**0.009**
Treatment												
Steroid therapy	30	25		0.73	12	10		0.65	78	65		0.63
Antibiotic therapy	31	24		0.68	11	8		0.46	90	68.18		0.35
Antiviral therapy	20	24		0.58	8	10		0.34	55	66.26		0.49
Vasopressor therapy	17	23		0.51	8	11		0.64	50	66.67		0.73
Laboratory results												
Potasium (mEq/L)			3.74±0.61	0.27			3.82±1.33	**0.0001**			3.89±2.38	**0.002**
Chloride (mEq/L)			98.8±1.74	**0.003**			110.1±4.1	**0.0001**			103.1±0.94	**0.038**
Lymphocyte (10^3/µl)			7.02±1.88	0.28			6.28±2.89	0.88			7.61±1.35	0.18
Ferritin (ml/ng)			378.7±114.3	0.34			307.4±209.2	0.76			386.6±53.8	0.27
C-reactive protein (mg/L)			124.1±30.5	0.24			161.2 ±5.47	0.29			114.1±15.5	0.09

SD: Standard deviation; APACHE II: Acute Physiology and Chronic Health Evaluation II; LOS: Length of stay; ICU: Intensive care unit; MV: Mechanically ventilation.

On the contrary, 9.59% of the patients had hypernatremia at admission. These data are in line with previous reports of dysnatremia and CAP, which found a higher prevalence of hyponatremia than hypernatremia [3, 16, 17].

In previous studies on the effects of low sodium levels on prognosis in COVID-19, it has been found that hyponatremia increases the need for advanced ventilator support and is associated with disease severity [18–20]. In their multicenter retrospective study, Hu et al. [21] showed that patients with hyponatremia requiring intensive oxygen support had a longer hospital stay compared to patients with both hypernatremia and normonatremia.

Unlike previous studies, no significant correlation was found between hyponatremia or the severity of the disease and the need for advanced ventilator support. We think that this may be due to the fact that our study population consists of critically ill patients, the severity of the disease has increased in this patient group, and most of the patients need oxygen therapy and mechanical ventilator support. Again, according to our study, there was no relationship between the length of stay in the ICU and hyponatremia.

There have been many studies showing the relationship between CRP levels and mortality in COVID-19 [22–24]. Martino et al. [13] showed in their study that sodium levels at the time of admission were inversely proportional to biochemical parameters such as basal CRP. In our study, there was no correlation between admission sodium levels and other laboratory parameters. This may be because our study, unlike other studies, was conducted on critically ill patients.

Frontera et al., [19] in their study examining the prevalence and impact of hyponatremia in COVID-19 patients, showed that hyponatremia is an independent predictor of in-hospital mortality in COVID-19. Tezcan et al. [20] examined the prognosis of baseline electrolyte anomalies in patients with COVID-19 and showed that baseline electrolyte imbalances, especially hyponatremia, are associated with poor prognosis in COVID-19. In our study, similar to the results of Tzoulis et al.'s [18] study, no association was found between hyponatremia and mortality in patients with COVID-19. Tzoulis et al. [18] in their study examining the relationship between dysnatremia and mortality and morbidity in COVID-19 patients admitted to the hospital, also showed that hypernatremia was not associated with the

need for advanced respiratory support and was associated with death without an increase in the need for respiratory support.

Yen et al. [25] showed that in their cohort of hospitalized patients with COVID-19, hypernatremia was independently associated with in-hospital mortality. In their study examining the prevalence and outcome of dysnatremia in patients with COVID-19 and comparing them with controls, Atila et al. [15] showed that hypernatremia at presentation was associated with 30-day mortality in both patients with and without COVID-19.

Hirsch et al. [17] investigated the prevalence and outcomes of hyponatremia and hypernatremia in patients hospitalized with COVID-19 and showed in their study that both hyponatremia and hypernatremia are associated with longer hospital stays and that patients with moderate to severe hypernatremia have the highest risk of in-hospital death.

In our study, no relationship was found between hypernatremia and the length of the ICU stay or the need for advanced respiratory support. However, hypernatremia was significantly associated with mortality.

This study has some limitations. First, the lack of information about volume status and insufficient laboratory data did not allow us to accurately determine the etiology of dysnatremia. Second, as the study was retrospective and observational, we only evaluated baseline electrolyte levels. The data did not show the effect of electrolyte abnormalities developed during hospitalization on outcomes.

The main strength of our study is that, while most of the recent studies on this subject included all hospitalized patients, we only conducted research on critically ill patients.

Conclusion

In conclusion, we found that, among the critically ill patients with COVID-19 at the ICU, dysnatremia was commonly present at admission, with hyponatremia being more prevalent than hypernatremia. Hypernatremia was related to mortality in critically ill patients with COVID-19. In critically ill COVID-19 patients, admission sodium levels can be a predictor of mortality. Further studies are needed in a larger patient population.

Conflict of Interest: The authors declare that there is no conflict of interest.

Ethics Committee Approval: The study was approved by The Gaziantep University Clinical Research Ethics Committee (No: 2022/75, Date: 09/03/2022).

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