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Research Paper

Dyschloremia During Severe COVID-19 Infection in Intensive Care Unit Patients

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ABSTRACT

Background: Dyschloremia is one of the most prevalent abnormalities that is highly associated with a high level of mortality in intensive care unit (ICU) patients. The current study evaluated serum chloride levels in COVID-19 patients hospitalized in the ICU.

Methods: This cross-sectional study was conducted on 245 patients with severe COVID-19 who were admitted to the intensive care unit (ICU). Electrolytes, albumin, liver function test, complete blood count, serum chloride, and VBG were among the laboratory markers compared. The Chi-square, t-test, and logistic regression models were used to examine the relationship between these markers and the key outcomes, which included severity, mortality, intubation, and hospitalization.

Findings: The Mean±SD age of patients was 58.16±17 years. The mean serum chloride level in the studied patients was 109.6±5.1 with a range of 100-134. According to the regression logistic model, variables like age, intubation status, pH, and chlorine levels significantly affected the outcome of COVID-19 disease. Patients with acidosis were 4.7 times more likely to die than those with alkalosis (P<0.001). The chance of dying in hyperchloremia is 2.38 times more compared to the normochloremia group (P<0.009).

Conclusion: Patients with severe COVID-19 may present with chlorine abnormalities, including hyperchloremia. Hyperchloremia is also associated with poor clinical outcomes and a higher mortality risk. This relationship was independent of acid-base disorder.

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1. Introduction

The outbreak of novel coronavirus pneumonia (COVID-19) began in Wuhan, a city in the People's Republic of China, and was quickly transmitted around the world [1]. Fever, cough, tiredness, and various organ failure are among the most common clinical manifestations in infected people [2]. Risk factors such as older age, diabetes, hypertension, cardiovascular disease, and electrolyte abnormalities are associated with severe to critical conditions of the infection [3-5]. One of the most prevalent abnormalities observed in critical care settings is acid-based and electrolyte imbalances, which must be accurately diagnosed to provide precise therapy to patients [6]. Experimental research on animal models of sepsis revealed that hyperchloremic acidosis was associated with serious manifestations such as increased amounts of inflammatory markers and decreased mean arterial pressure due to alternations in the levels of pH and chloride. Moreover, high chloride concentration in vivo models increased renal vasoconstriction and decreased renal blood flow and the glomerular filtration rate [7].

Multiple pathophysiologic pathways are involved in the regulation of serum chloride, which is important for maintaining the acid-base balance, osmotic pressure, body fluid electro-neutrality, and renal function management [8]. Hypochloremia and hyperchloremia are greatly linked with raised mortality in intensive care unit (ICU) patients. In 75% of patients, temporary hyperchloremia can occur during the first 24 hours of hospitalization in the ICU [9]. Despite neglecting the role of the chloride level in acid-base calculations, it is routinely measured in the laboratory findings of critically ill patients. Concerning the significant role of dyschloremia in acid-based disorders and its effects on organ function, the current study aimed to evaluate serum chloride levels in COVID-19 patients hospitalized in the ICU.

2. Materials and Methods

We carried out a single-center cross-sectional study on critically ill patients with COVID-19 admitted to the ICU at Velayat Hospital, Qazvin City, Iran. Patients with severe COVID-19, over 18 years old, who stayed longer than 24 hours in the ICU were considered eligible to be included in the study. Patients were excluded from the study if they had underlying diseases such as heart failure or kidney failure affecting the outcome of the study. A real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay on nasopharyngeal swab specimens validated the COVID-19 cases. According to the prevalence of chloride disorder in a study by Tani et al. (25.4%), the considering power=80% and α=5%, the sample size was selected 245 patients with COVID-19 [10].

The information on systolic blood pressure, arterial blood gases (pH, $PaCO_2$, PaO_2, and bicarbonate), the anion gap (AG), chloride, and glucose in patients admitted to the ICU from November 2020 to May 2021 was collected from patients' documents. Demographic data including age, body mass index (BMI), underlying disease, duration of hospitalization, and admission time were collected. The O_2 saturation with O_2 (disconnection of the O_2 supplement after 15 min), complete blood count (CBC) (Diff) and blood biochemistry parameters, including calcium, creatine (Cr), blood urea nitrogen (BUN), lymphocyte count, sodium, potassium phosphor, albumin, and magnesium were also evaluated in each patient. Hyperchloremia was characterized as a serum chloride level of more than 106 mmol/L [11].

Statistical analysis

Statistical analysis was conducted using SPSS software, version 20, and $P<0.05$ was considered significant. Continuous data are described as Mean±SD, while categorical data were described as frequency and percentage. Dichotomous variables were compared between the groups using the Chi-square test, and continuous variables were analyzed using the independent t-test. Also, multiple logistic regression was used to predict the risk factors for death from COVID-19.

3. Results

The demographic information is reported in Table 1. Patients with increased serum chloride levels showed significantly higher serum sodium amounts. Also, the level of blood urea nitrogen (BUN) and albumin was higher in the hyperchloremia group compared to the normochloremia group ($P<0.001$) (Table 1). On average, patients were hospitalized for 7.32±2.72 days with a range of 2-16 days. The majority of patients were men (136 individuals, 54.4%) and 60 patients died (24%). Eighty-five patients (34%) underwent intubation during hospitalization, 58 (23.2%) patients had acidosis, and 187 (74.8%) had alkalosis. Based on the level of chloride on the first day of hospitalization, 189 patients (77.3%) had normochloremia, and 56 patients (22.7%) had hyperchloremia. The mean serum chloride level in the studied patients was 109±5.5 with a range of 58-134. There was no significant difference in inflammation, and blood indices were not significant among the two groups ($P>0.05$) (Table 1).

Table 1. Comparison of demographic information and blood and inflammatory indices among serum chloride levels

Variables	Mean±SD			P
	Normochloremia (n=189)	Hyperchloremia (n=56)	Total	
Age(y)	57.30±17.612	60.88±18.527	58.12±17.85	0.4
BMI(kg/m^2)	27.8937±4.6857	27.3725±4.27587	27.77±4.59	0.2
Duration of admission	7.12±2.659	7.84±2.814	7.28±2.70	0.06
Systolic blood pressure	123.67±18.894	119.79±25.955	122.78±20.73	0.45
Diastolic blood pressure	74.68±13654	70.66±16.479	73.76±14.41	0.17
Na	136.50±3.295	138.63±4.048	136.99±3.59	<0.001
K	4.098±0.4775	4.159±0.5957	4.12±0.51	0.6
Ca	8.44±0.609	8.22±0.736	8.39±0.65	0.1
P	4.21±1.743	4.03±1.270	4.16±1.62	0.7
Alb	3.50±0.543	3.26±0.48	3.44±0.54	0.01
Mg	2.14±0.389	2.17±0.426	2.15±0.4	0.3
BUN	21.47±16272	30.38±24.197	23.52±18.73	0.007
Cr	1.27±1.202	1.48±1.153	1.32±1.19	0.5
WBC	10.21±8.797	9.95±5.367	10.15±8.14	0.9
Lymphocyte	11.95±7.715	14.02±16.762	12.43±10.50	0.4
PMN	82.17±10.064	83.31±7.951	82.43±9.6	0.6
Hb	12.50±2.118	12.07±2.353	12.41±2.18	0.4
HCT	37.40±6.218	36.35±6.350	37.16±6.25	0.5

Abbreviations: Mg: Magnesium; Alb: Albium; Na: Sodium; Ca: Chloride; BMI: Body mass index; BUN: Blood urea nitrogen; Cr: Creatine; WBC: White blood cells; PMN: Polymorphonuclear neutrophils; Hb: Hemoglobin; HCT: Hematocrit

The amounts of sodium bicarbonate and anion gap were higher in the normochloremia group compared to the hyperchloremia group and were statistically significant (P<0.05) (Table 2). There was a significant relationship between chlorine levels and death rate (P=0.02) so 38 patients (63.3%) with normochloremia and 21 patients (35%) with hyperchloremia died (Table 3).

Findings showed that based on the fitted model, the following variables like age, intubation status (intubation as the reference), pH status (alkalosis as the reference), and chlorine levels (normochloremia as the reference) significantly affected the outcome of COVID-19 disease. The chance of death with increasing age in unadjusted and adjusted models was increased by 5% (OR adjusted= 1.05, P<0.001). These patients had a disrupted pH status, and according to the study, patients with acidosis were 4.7 times more likely to die than those with alkalosis. Intubation was also a risk factor for the death of patients and patients who were intubated had a 12.06-fold increased chance of death in a multiple regression model. Moreover, hyperchloremic patients were two times more likely to die than the normochloremic group, but this difference was not significant (P=0.1) (Table 4).

4. Discussion

This study demonstrated the association between serum chloride levels and mortality since it is a major outcome in patients with severe COVID-19 admitted to the ICU.

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Table 2. Acid-base variables between hyperchloremic and normochloremic patients

Variables	Mean±SD		P
	Normochloremia (n=189)	Hyperchloremia (n=56)	
O_2sat with O_2	90.03±7.154	91.39±6.041	0.1
pH	7.3±0.08	7.3±0.07	0.2
Bicarbonate	22.86±4.4	21.46±3.8	0.003
pCO_2	36.66±9.04	36.32±7.76	0.1
Anion gap	6.630±4.54	5.304±4.0	<0.001

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Patients with hyperchloremia exhibited a higher mortality rate compared with those with a normal chloride level, even after adjusting for related variables. Hence, hyperchloremia was independently associated with the risk of hospital mortality.

The iatrogenic mechanism, which occurs due to the excessive use of chloride-rich solutions during resuscitation, may lead to the development of hyperchloremia. Furthermore, excessive dehydration and increased reabsorption of chloride in the kidneys are other causes associated with hyperchloremia [9].

One of the most important findings of the present study was the link between serum chloride levels and acid-base hemostasis. In Berend et al.'s study (2012), it was emphasized that one of the most frequent electrolytes in serum acid-base was chloride levels, especially in diagnostic tests in clinical situations [8].

In the current study, there was no significant relationship between the chloride level and pH. None of the hyperchloremic patients had metabolic acidemia, and the nature of their acid-base disorders was not different from those of non-hyperchloremic patients. These results suggest that hyperchloremia might be associated with a poorer outcome independent of metabolic acidosis. The same association was also observed between hypochloremia and alkalosis. Hence, our observation provides new insight into the correlation between hyperchloremia and COVID-19. Dyschloremia, which is a common complication, can be observed in critically ill patients with varied etiologies. In the Pourfridoni et al.'s study (2021), one of the most common disorders among COVID-19 patients was hypochloremia, which may increase mortality [12]. Their results are in contrast to our study possibly because of the categorization of patients in our study that does not have hypochloremia patients.

The serum chloride level is mainly regulated by the intestinal tract and the kidney [13]. In critically ill patients, hyperchloremia is caused mostly by bicarbonate loss through the gastrointestinal (GI) or renal tract volume loading with low bicarbonate fluid content and excessive

Table 3. Frequency of outcomes in studied patients

Variables		No. (%)		P
		Normochloremia (n=189)	Hyperchloremia (n=56)	
Outcome	Death	38(63.3)	21(35)	0.02
	Live	151(79.5)	35(18.4)	
PH,	Acidosis	36(62.1)	21(36.2)	0.07
	Normal	6(85.7)	1(14.3)	
	Alkalosis	147(79.5)	34(18.4)	

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Table 4. Multiple logistic regression model for the final outcome of patients with COVID-19

Variables		Unadjusted			Adjusted		
		B	OR	P	B	OR	P
Age (y)		0.047	1.05	<0.001	0.044	1.04	<0.001
Intubation		2.4	11.05	<0.001	2.5	12.06	<0.001
CL[#]		0.86	2.38	0.009	0.7	2.02	0.1
PH[##]	Normal	1.36	3.9	0.08	1.96	7.1	0.06
	Acidosis	1.55	4.7	0.001	1.58	4.89	<0.001

[#]Reference: Normocoloremi, [##]Reference: Alkalosis, CL: Chloride.

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infusion of chloride-rich fluids (the iatrogenic mechanism), e.g. 0.9% sodium chloride (NaCl) infusion with 154 mmol/L chloride (Cl) [1-3]. Excessive water loss and dehydration, net water loss, or excessive chloride loss due to increased renal chloride reabsorption are other causative mechanisms [11]. The crucial issue is that physicians working in the ICU should note that replacement fluids based on albumin may have high levels of chloride [14]. Additionally, further occurrences of hyperchloremia in the ICU may be caused by hydrochloric acid (HCl), acetazolamide, and or triamterene infusions, or by particular cortisone derivatives causing NaCl retention [15, 16].

In patients admitted to the ICU, diarrhea and GI loss may be the most common reason for bicarbonate loss and hyperchloremia. In the current study as well as prior studies in this field, the cause of hyperchloremia was not ascertained. Data also demonstrate that a total volume infusion of 2000 mL of chloride-rich fluids can cause hyperchloremic metabolic acidosis in healthy individuals [17]. It is worth mentioning that in most studies, normal saline was administered as a resuscitative fluid, whereas we administered ringer lactate solution mainly as volume therapy and a limited amount of 0.9% NaCl (1000 mL) to all patients. In addition, patients undergoing diuretic therapy were excluded from the study. Since the beginning of the COVID-19 outbreak up until now, a limited number of studies have demonstrated dyschloremia as one of the clinical findings in COVID-19 patients [12, 18-21].

Hyperchloremia impacts the clinical outcomes of critically ill patients with different mechanisms, such as hyperchloremic metabolic acidosis. Tani et al. (2012) discovered that individuals with metabolic acidosis had a higher mortality rate across all subgroups (hyperchloremia, normochloremia, and hypochloremia) [10]. As mentioned above, in our study, hyperchloremic patients did not have metabolic acidemia, and therefore, metabolic acidosis could not be the cause of the poorer outcomes in the hyperchloremic group. Increased serum chloride levels, independent of other risk factors, were associated with a higher risk of acute kidney injury (AKI) in critical illness in several studies [21-24]. Zhang et al. discovered a link between maximal chloride levels and AKI incidence. However, the chloride level at ICU admission was not related to the development of AKI [25]. Shao et al. discovered that the findings were consistent with previously published investigations [26]. A study conducted on patients with myocardial infarction undergoing percutaneous interventions did not show an analogous association between hyperchloremia and AKI [27]. Our results were in line with those of previous studies; none of the patients in the hyperchloremic group had kidney injury, and there was no significant relationship between the chloride level and Cr.

Many studies have found that the concentration of inflammatory indicators, such as cytokines, is higher in COVID-19 patients' serum. Pro-inflammatory cytokines, such as interleukins (interleukin-1 and interleukin-6), have an effective role in the acute response to critical illness [28, 29]. Moreover, a few studies suggest that hyperchloremia may have an effect on plasmatic coagulation cascades and or platelet function [14, 30]. Given that many studies have demonstrated the relationship between COVID-19 and hypercoagulable states [31, 32] and relying on the results of other studies in this context, the association between hyperchloremia and a higher mortality rate in our study can be justified by the serum chloride level and the interaction of the immune and coagulation systems. Lippi et al. found no statistical differences in serum chloride levels between patients with severe and non-severe COVID-19 (WMD: 0.30 mmol/L [95% CI, 0.41 to 1.01 mmol/L]) [5].

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Moreover, Sjöström et al. found no association between death and admission levels of chloride in their study. In addition, there was no relationship between mechanical ventilation and the chloride level at admission time [20]. In another study conducted in Turkey, 408 hospitalized patients with COVID-19 were examined. It was observed that patients with hyponatremia, hypochloremia, and hypocalcemia had worse outcomes than other patients [33]. Accordingly, the results of these studies contradicted our research.

5. Conclusion

Comparing patients with COVID-19 in terms of different variables, chloride levels, and clinical outcomes demonstrated that age, sex, BMI, and comorbidity were not confounding variables. So far, no study has been performed to show the prevalence of hyperchloremia in COVID-19 patients, and our study is one of the first reports in this field.

According to the results, hyperchloremia might be a useful indicator of prognosis and management for severe COVID-19 ICU patients.

This study had some limitations that need to be discussed. The first limitation is not analyzing COVID-19 treatments (i.e. antivirals, antibiotics, and corticosteroids). Therefore, their roles might have been underestimated in our study, and their effects on the disease prognosis may have been ignored. The second limitation is related to performing sequential measurements of the chloride level, but in our study, we only considered the chloride level in the first 24 h of admission. More detailed findings may have been obtained through sequential testing and average chloride levels and also reduced laboratory errors. The last limitation was the generalizability of our results possibly limited by the single nature of the patients and situations. Due to the limitations of our study and given that chloride homeostasis in COVID-19 has been briefly discussed in previous studies, a further prospective clinical trial using a standard fluid protocol is required to obtain definitive findings.

Ethical Considerations

Compliance with ethical guidelines

This work was approved by the ethical board of Qazvin University of Medical Sciences (Code: IR.QMSU.REC.1399.468). This study was done according to Helsinki guidelines, and all information was stored confidentially.

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Authors' contributions

Study design: Maryam Gheraati and Negar Sheikhdavoodi; Data analysis: Monirsadat Mirzadeh and Atefeh Khoshkchali; Writing the manuscript: Negar Sheikhdavoodi and Monirsadat Mirzadeh; Preliminary preparation of the final content: Negar Sheikhdavoodi; Reading and approval of the final manuscript: All authors.

Conflict of interest

The authors declared no conflicts of interest concerning the research, authorship, or publication of this article.

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