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Prevalence of hyponatremia in hospitalized patients with coronavirus disease 2019; a multicenter study

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ABSTRACT

Introduction: In patients with coronavirus disease 2019 (COVID-19), the prevalence of hyponatremia has been reported with varying outcomes.
Objectives: The aim of this study was to evaluate the prevalence of hyponatremia in hospitalized patients with COVID-19.
Patients and Methods: In this multicenter cross-sectional study, information about hospitalized patients with COVID-19 admitted between March 2020 and September 2020, including age, gender, and serum levels of sodium, creatinine, and potassium, as well as blood urea nitrogen (BUN), was analyzed, while *P* value level less than 0.05 was considered significant.
Results: A total of 667 hospitalized patients with COVID-19 were enrolled in the study, of which 54.4% were male. The median age of patients was 63 years old. About 39.4% of patients had hyponatremia on admission day. More than 80% of patients had mild hyponatremia. The median age of the hyponatremia group was significantly higher than that of eunatremia group.
Conclusion: Our data showed that hyponatremia is observed in hospitalized patients with COVID-19 and is often mild.

Original Article

Implication for health policy/practice/research/medical education:
In a study on 667 hospitalized patients with COVID-19, hyponatremia was detected in the patients, although it was often mild.
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Introduction

Coronavirus disease 2019 (COVID-19) is currently one of the most common diseases in the world (1). This disease causes mild to moderate symptoms in most people; however, it may cause severe symptoms and organ failure that require special care. At present, there is no definitive cure for this disease; however, various treatments have been suggested for this condition such as corticosteroids, monoclonal antibodies, plasmapheresis, intravenous immune globulin and hemoperfusion, which had not shown a significant therapeutic effect among COVID-19 patients with severe conditions (2). Although respiratory system involvement is a major feature of COVID-19 infection, renal involvement has also been reported in hospitalized patients (3). Since a significant percentage of hospitalized patients with community-acquired pneumonia had hyponatremia on admission day, estimating the prevalence of hyponatremia in hospitalized patients with COVID-19 may be important in managing the disease and preventing the complications of severe hyponatremia such as permanent neurological disorders and even death.

The risk of electrolyte disturbances such as hyponatremia among patients with pneumonia seems to vary according to each pathogen. For example, hyponatremia was developed in 44-46% of patients with Legionella pneumophila compared with 8-14% of patients with other community-acquired pneumonia etiologies (4).

Several studies have reported hyponatremia in patients with COVID-19; however, the prevalence of hyponatremia in these patients is varied (5). Determining the prevalence of hyponatremia in hospitalized patients with COVID-19 is important for health-related decision-making.

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Objectives

In this study, our primary aim was to determine the prevalence and severity of hyponatremia among hospitalized patients with COVID-19. Our secondary aim was to identify the other clinical and demographical related factors. In this cross-sectional study, we evaluated the prevalence of hyponatremia and its related factors in hospitalized patients with COVID-19 admitted to four hospitals in Qazvin province (Iran). This study presented valuable findings regarding the management of COVID-19 complications, especially hyponatremia, in hospitalized patients.

Patients and methods

Study design

In this cross-sectional study, we evaluated the prevalence of hyponatremia in patients with COVID-19 admitted to four hospitals, including Shafa, Bu'ali, Velayat, and Buin Zahra, located in Qazvin province (with a population of 1.2 million people) in Iran from March 2020 to September 2020.

Our target population was hospitalized patients with COVID-19. We selected four hospitals in Qazvin province as the sampled population and collected data from 1133 patients during the study period.

Patients' data including age, gender, serum level of sodium, creatinine, potassium, and blood urea nitrogen (BUN) (on the first day of hospitalization) were extracted from the health information system of the mentioned hospitals. The information in this database is collected from the recorded reports of hospital patients. The study period was from March 2020 to September 2020.

Inclusion criteria were COVID-19 diagnosis and hospitalization of patients. Exclusion criterion was unavailability of patient data.

Diagnosis of patients was based on a positive reverse transcription polymerase chain reaction (RT-PCR) test for COVID-19, positive imaging representing COVID-19, or having symptoms suggestive of COVID-19. The patients were hospitalized due to low-oxygen saturation, oral intolerance, impaired tests, and loss of consciousness.

After collecting data, patients were divided into three groups based on their serum sodium level. Patients with a serum sodium level of less than 135 mmol/L were assigned to the hyponatremia group, patients with a serum sodium level of 135 to 145 mmol/L were assigned to the eunatremia group, and patients with a serum sodium level of greater than 145 mmol/L were assigned to the hypernatremia group. Then, the incidence of hyponatremia in patients with COVID-19 was evaluated and its clinical and demographic characteristics were compared with the eunatremia group.

Data analysis

IBM SPSS statistics software version 22 was used for data analysis. In this study, *P* values less than 0.05 were considered significant. The chi-square and Mann-Whitney U tests were employed for the analysis.

Our findings showed that a significant percentage of hospitalized patients with COVID-19 had hyponatremia and it should be considered an important complication of COVID-19 by physicians in order to prevent it from becoming severe and leading to death.

Results

During the study period, 1133 patients with COVID-19 were admitted to the four mentioned hospitals in Qazvin province, Iran. Of them, 466 patients were excluded from the study due to missed information. Finally, the data of 667 patients were evaluated. The median age of patients was 63 years (interquartile range [IQR]: 50-74) and 54.4% of the patients were male.

The demographic and clinical characteristics of the patients are presented in Table 1. In total, 39.4% of these patients had hyponatremia on the admission day.

The median age of patients with hyponatremia was significantly higher than that of patients with eunatremia ($P = 0.015$).

In addition, the median serum level of creatinine in the hyponatremia group was significantly higher than in the eunatremia group ($P = 0.007$).

The median serum level of potassium was significantly higher in patients with hypothermia than in the eunatremia group ($P = 0.001$).

Moreover, the median of the BUN, level in patients with hyponatremia was significantly higher than in patients with eunatremia ($P = 0.002$).

Moreover, for a more detailed analysis of hyponatremia groups, patients with hyponatremia were divided into three subgroups: mild, moderate, and severe. Table 2 shows the frequency of mild, moderate, and severe subgroups. Most (81%) of the patients in the hyponatremia group had mild hyponatremia.

We analyzed the mild and moderate subgroups due to their higher frequency. The demographic and clinical characteristics of the mild and moderate hyponatremia subgroups are listed in Table 3. The mean serum levels of potassium were significantly higher in the moderate subgroup than in the mild subgroup ($P = 0.028$). In addition, the median of the BUN level was significantly higher in the moderate subgroup than in the mild subgroup ($P = 0.002$).

Discussion

In this study, we evaluated the data of 667 hospitalized patients with COVID-19 who were admitted to four

Table 1. Demographic and clinical characteristics of patients with severe COVID-19

Characteristics	Hyponatremia	Eunatremia	P-value
Median age (IQR)	65 (55-75)	62 (48-74)	0.015*
Male gender (%)	56.3%	52.8%	0.414
Median serum creatinine (IQR)	1.10 (0.90-1.50)	1.03 (0.90-1.30)	0.007*
Median serum potassium (IQR)	4.00 (3.61-4.40)	3.90 (3.58-4.20)	0.001*
Median BUN (IQR)	20.00 (13.00-30.00)	17.00 (12.00-26.00)	0.002*

hospitals in Qazvin province during the study period. The prevalence of hyponatremia among these patients on admission day was about 40%. Moreover, median serum levels of potassium, creatinine, and BUN, as well as median age, were significantly higher in patients with hyponatremia than in patients with eunatremia.

Although the respiratory system is one of the most affected organs in COVID-19, kidney involvement is also commonly observed in hospitalized patients with COVID-19 with an unspecific mechanism (3). Since the angiotensin-converting enzyme 2 (ACE2) is expressed in the epithelial cells of various tissues, especially the kidney, this receptor plays an important role in association with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (6). Angiotensin-converting enzyme 2 expression is 100 times higher in kidney tissue than in the lung; therefore, if the virus becomes systemic after lung involvement, the kidney is believed to be one of the potential targets for the virus (7).

In the present study, 39.4% of the hospitalized patients with COVID-19 had hyponatremia. In infectious diseases such as COVID-19, hemodynamic disturbances or the resulting inadequate immune response may lead to kidney damage (8). In studies on this disease, the presence of virus particles in podocytes and primary renal tubules has been reported (8). In another study, by examining the autopsy of all patients with COVID-19, pathological findings such as microvascular occlusion, endothelial damage, and acute primary diffuse tubular damage were reported (9). These studies may indicate that the cause of kidney involvement in patients with COVID-19 is direct infection with the virus.

Another cause of hyponatremia in COVID-19 is renal impairment due to inflammatory cytokines. Since cytokine cascade is thought to cause several pathological changes in the kidney such as acute kidney injury (AKI), tubular necrosis, and dysfunction of the primary renal tubule, glomerulopathy, and electrolyte disturbances (8).

Interleukin 6, which is released by monocytes and macrophages, plays an important role in the development of hyponatremia in patients with COVID-19. This interleukin causes the non-osmotic release of vasopressin and secondary electrolyte disturbance (10). It is also involved in the pathogenesis of COVID-19. Moreover, it was observed that hyponatremia had a significant correlation with the serum level of interleukin 6 in patients with COVID-19 (11). This finding may indicate that hyponatremia in these patients is due to complications caused by cytokine storm (11).

On the other hand, studies on rats that had a high-sodium diet showed that high sodium intake in these animals caused the downregulation of ACE2 expression in the kidneys (12). A previous study showed rats that received a high-sodium diet for more than three weeks had a 50% reduction in ACE2 expression in their kidneys. In addition, the expression of ACE2 was reported to be approximately 5-fold higher in hypertensive rats that had a low-sodium diet than in rats fed a high-sodium diet. Low-sodium levels were also linked to more severe disease in COVID-19 patients (13), while studies on these patients revealed that those with severe COVID-19 had significantly lower sodium levels (14). Additionally, a theory about the relationship between serum sodium levels and the severity of COVID-19 has been presented. It is stated that when serum sodium levels are low, the expression of ACE2 in the kidneys rises and this leads to a higher risk of renal involvement in patients with COVID-19 (15). This finding could indicate that

Table 2. Frequency of hyponatremia subgroups

Subgroups	Frequency	Percent
Mild	213	81.0
Moderate	43	16.3
Severe	7	2.7

Table 3. Demographic and clinical characteristics of patients with severe COVID-19

Characteristics	Mild	Moderate	P-value
Median age (IQR)	65.00 (54.00-75.00)	67.00 (59.00-74.00)	0.356
Male gender (%)	57.3%	48.8%	0.426
Median serum creatinine (IQR)	1.10 (0.90-1.40)	1.30 (0.90-2.30)	0.079
Median serum potassium (IQR)	4.00 (3.60-4.40)	4.20 (3.70-4.90)	0.028*
Median BUN (IQR)	19.00 (13.00-26.00)	28.00 (14.10-45.00)	0.002*

hyponatremia is not a complication of COVID-19, but rather a risk factor that exacerbates the disease in patients with COVID-19.

One of the most common causes of hyponatremia is the syndrome of inappropriate antidiuretic hormone secretion (SIADH). This syndrome is observed in 40-50% of individuals with electrolyte disorders (10). Its prevalence increases in conditions such as subarachnoid hemorrhage, brain trauma, and pneumonia. Inappropriate antidiuretic hormone secretion was detected during the development of various diseases, including acute respiratory distress syndrome (10,16). This syndrome has also been reported in patients with COVID-19 in numerous studies. Furthermore, SIADH was seen in patients with COVID-19 (17). Another study also reported a series of COVID-19 patients with SIADH, and all the patients with COVID-19 in this study had hyponatremia. After ruling out other etiologies, the authors concluded that this electrolyte disturbance was due to SIADH (18).

In our study, the median age of the hyponatremia group was significantly higher than that of the eunatremia group. Similar to SIADH, this condition is more common in those over 65 years old (19). Moreover, in this study, the median serum levels of creatinine in the hyponatremia group were significantly higher than in the eunatremia group. Hyponatremia in young patients with SIADH is associated with low-serum creatinine levels, whereas this association is not observed in elderly patients (20). Since the median age in our study population in the hyponatremia group was 65 years and according to the mentioned studies, we did not expect to detect low serum creatinine levels in this group.

In SIADH, the serum level of potassium is expected to be normal (21), which was in agreement with our findings. The median serum level of potassium in both eunatremia and hyponatremia groups was in the normal range. However, despite the normal range of serum potassium levels in both groups, we observed a significantly higher serum potassium level in the hyponatremia group. This phenomenon may be due to the fact that the patients in the hyponatremia group were older than the patients in the eunatremia group and it is believed that with the increase of age the risk of increased serum potassium levels is enhanced (22). This phenomenon can also explain the significantly higher median serum potassium levels in the moderate hyponatremia subgroup than the mild hyponatremia subgroup because the median age is higher in the moderate subgroup.

Conclusion

The present study was the first multicenter study in Qazvin province that was conducted to evaluate the prevalence of hyponatremia in hospitalized patients with COVID-19. A significant percentage of hospitalized patients with COVID-19 had hyponatremia and most of them in terms of severity were mild. This study emphasized the need for monitoring the COVID-19 patient's electrolyte status at the time of hospitalization.

Limitations of the study

One of the limitations of this study was that not all the patients were diagnosed by RT-PCR, which was due to the limitation of diagnostic tools and other factors. However, since there was a peak of the disease during the study period, patients with symptoms of COVID-19 were considered positive for the disease. This was the first multicenter study performed on hospitalized patients with COVID-19 to investigate the prevalence of hyponatremia in Qazvin province, Iran. The large sample size in this study allowed for a more accurate estimation of prevalence in this province.

Authors' contribution

SH, ASG and MK were the principal investigators of the study. SH and MK were included in preparing the concept and design. SH and MK revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the principles of the Declaration of Helsinki. The Ethics Committee of Qazvin university of medical sciences approved this study. The institutional ethics committee of Qazvin university of medical sciences approved all the study protocols (IR.QUMS.REC.1399.311). Informed consent was obtained at the time of hospital admission. Besides, ethical issues (including plagiarism, data fabrication and double publication) were completely avoided by the authors.

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