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Serum sodium and serum potassium levels as a marker of severity in COVID-19 patients

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ABSTRACT

Objectives: This study aims to determine the predictive value of serum sodium and potassium levels at the time of admission in assessing the severity of COVID-19.

Material and Methods: This is a cross-sectional record-based descriptive study conducted at a tertiary care center in the State of Kerala, for six months. 227 COVID cases with electrolyte abnormalities were taken for the study. Serum sodium and serum potassium levels at the time of admission were noted. Details regarding the treatment received and the course of patients in the hospital were recorded. Any progress to severity, such as ICU admission, need for mechanical ventilation, and mortality was duly noted. Mean serum electrolyte levels were calculated. Patients were classified as hyponatremia, hypernatremia, hypokalemia, and hyperkalemia and evaluated for any association with markers of severity.

Results: The mean sodium level was 132.47 ± 6.1 mEq/L and the mean potassium level was 3.74 ± 0.73 mEq/L. Of the 227 cases, 179 had hyponatremia (78.9%) and three had hypernatremia (1.3%). Hypokalemia was present in 106 cases (46.7%), and hyperkalemia in 15 cases. Only sodium abnormality was present in 106 (46.7%) patients, only potassium abnormality in 45 (19.8%) patients, and both sodium and potassium were abnormal in 76 (33.5%) patients. Out of 227 hospitalized COVID-19 patients, 56 (24.7%) were transferred to the ICU and 39 (17.2%) needed ventilation. During the course of treatment, 24 (10.6%) out of 227 patients died. A significant association was found between hyponatremia and mortality ($p = 0.03$).

Conclusion: Hyponatremia is the primary electrolyte abnormality in COVID-19 patients and is significantly associated with mortality. Thus, hyponatremia can be used as a marker of severity in COVID-19 cases.

Keywords: COVID-19, electrolyte levels, serum sodium, serum potassium, mortality

INTRODUCTION

COVID-19 is an ongoing global pandemic caused by the severe acute respiratory syndrome virus (SARS-Cov-2). The World Health Organization (WHO) declared it a public emergency of international concern on January 30, 2020.[1]

Several studies have demonstrated evidence of electrolyte abnormalities in COVID-19 patients.[2–4] Among these, hypokalemia and hyponatremia are the most common.[5] Less often, hypochloremia and hypocalcemia are also observed.[2]

These electrolyte imbalances not only affect the treatment regimen but also provide insight into the severity of the disease. In a study conducted in Spain, prolonged hospital stay was noted

in patients with hypokalemia. Tezcan *et al.*[3] concluded that hyponatremia was the most frequent electrolyte abnormality, and those patients had a worse prognosis than COVID patients with typical electrolyte values.

This study aims to determine the predictive value of serum sodium and potassium levels at admission in assessing the severity of COVID-19. Suppose such an association is found in our population, in that case, the need for mechanical ventilation or Intensive Care Unit (ICU) admission can be foreseen, and a more cautious approach can be initiated in these patients.

Also, the study primarily focuses on the role of serum sodium and potassium levels at admission in predicting the severity of COVID-19.

MATERIAL AND METHODS

This was a Ccross-sectional record- based descriptive study conducted at a tertiary care center in the State of Kerala for six months. Ethical clearance was obtained from the Institutional Ethics Committee. The study population was all patients above 18 years of age, admitted with COVID-19 in COVID wards of the tertiary care center, satisfying inclusion and exclusion criteria.

Inclusion Criteria

All patients above 18 years of age who were admitted to COVID wards of a tertiary care center in the State of Kerala, with laboratory confirmation of COVID-19 by Real-Time Reverse Transcription-Polymerase Chain Reaction (RT-PCR) or antigen test with any electrolyte abnormality, were included in the study.

Exclusion Criteria

Patients with any comorbidity were excluded. Also, COVID patients directly admitted to ICU were excluded. Those patients who required oxygen support at the time of admission were not included.

Sample Size

The sample size was determined using a previous study conducted by Tezcan *et al*. titled "Baseline electrolyte irregularity would be related to poor prognosis in hospitalized coronavirus disease 2019 patients."[3]

The sample size was calculated to be n = 162. The present study comprised a sample size of n = 227 to improve the statistical accuracy. This higher sample size was possible due to the high patient volume catered by the tertiary healthcare center in which the study was conducted.

Study Variables

The variables considered in the study are:

1. Demographic variables.
2. Serum sodium levels – standard value: 135–145 mEq/L.
3. Serum potassium levels – standard value: 3.5–5 mEq/L.
4. Hyponatremia is defined as serum sodium levels less than 135 mEq/L, and hypernatremia is defined as serum sodium levels greater than 145 mEq/L.
5. Hypokalemia is defined as serum potassium levels below 3.5 mEq/L, and hyperkalemia is defined as serum potassium levels above 5 mEq/L.
6. The severity of the disease is assessed by the following factors: requirement for ICU care, need for mechanical ventilation, and mortality.

Data collection Technique

Case records of patients satisfying inclusion and exclusion criteria were selected and analyzed from January 2021 till the sample size was obtained in June 2021. Information was also taken regarding socio-demographic variables, history of other morbidities, serum electrolyte levels at admission, and treatment details.

Statistical Analysis

Statistical analyses were conducted using the SPSS (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp) software. The data were consolidated, and continuous variables (age, duration of hospital stay, sodium, and potassium levels) were presented as mean or median, and categorical variables (gender, electrolyte imbalances, management using oxygen, antivirals, steroids, ventilator, ICU, and death status) as frequency (%) appropriately after assessing the normality with Kolmogorov–Smirnov test. The severity of the COVID-19 disease was decided based on ICU, ventilator, or death status. Chi-square tests were used to analyze the association between the electrolyte abnormality and the severity of the disease, with each parameter tested separately. Electrolyte abnormalities were individually analyzed (hyponatremia, hypernatremia, hyperkalemia, and hypokalemia) and grouped as – sodium abnormalities, potassium abnormalities, and sodium and potassium abnormalities. The significance was considered when the p-value was less than 0.05.

RESULTS

A total of 227 patients with a mean age of 50.33 ± 15.25 years (SD = 15.25) were included in this study. There were 116 (51.1%) males and 111 (48.9%) females. Of the 227

Table 1: Demographic and disease-related features of the COVID-19 patients.

Demographic Variables	
Age (years), Mean (SD)	50.33 (15.25)
Gender	
Male, n (%)	116 (51.1)
Female, n (%)	111 (48.9)

SD: Standard deviation

hospitalized COVID-19 patients, 56 (24.7%) were transferred to the ICU, and 39 (17.2%) needed ventilation. Furthermore, 24 (10.6%) of the 227 patients died, during the course of treatment [Table 1].

The Course of Stay at the Hospital

Of the 227 patients with electrolyte imbalances, 119 required oxygen support, 101 were treated with antivirals, and 102 received steroids. Fifty-six patients required ICU admission, 39 of them required mechanical ventilation, and 24 patients died during their stay in the hospital.

Electrolyte Abnormality

Most patients had hyponatremia (78.9%), followed by hypokalemia (46.7%). Only sodium abnormality was present in 106 (46.7%) patients, only potassium abnormality in 45 (19.8%) patients, and both sodium and potassium were abnormal in 76 (33.5%) patients [Tables 1 and 2].

While studying the association of different variables like hyponatremia, hypernatremia, hypokalemia, and hyperkalemia with the severity of disease (ICU admission, requirement of mechanical ventilation, and mortality), we could only find a significant association between hyponatremia and mortality ($p = 0.03$) [Tables 3 and Table 4].

DISCUSSION

In this cross-sectional study, we have analyzed 1100 case sheets of COVID-positive patients admitted to the COVID ward from January 1, 2021 to May 24, 2021. Any patients with comorbidities were excluded. From these, 227 patients who had electrolyte abnormalities – either sodium or potassium or both were included in the study. Of this, 116 were males, and 111 were females. We studied the association of these electrolyte imbalances with the severity of the disease.

Table 2: Course of stay and treatment details at the hospital.

Duration of hospital stay (days), Median (IQR)	**10 (7–12) days**
Treatment	
Oxygen, n (%)	119 (52.4)
Antivirals, n (%)	101 (44.5)
Steroids, n (%)	102 (45)
ICU admission, n (%)	56 (24.7)
Ventilator use, n (%)	39 (17.2)
Death, n (%)	24 (10.6)

IQR: Interquartile range, ICU: Intensive care unit

Table 3: Serum electrolyte levels.

Electrolyte levels (mEq/L)	
Sodium, Median (IQR)	133 (130–134)
Potassium, Median (IQR)	3.6 (3.3–4)
Electrolyte abnormality	
Hyponatremia, n (%)	179 (78.9)
Hypernatremia, n (%)	3 (1.3)
Hypokalemia, n (%)	106 (46.7)
Hyperkalemia, n (%)	15 (6.6)
Both electrolytes abnormal, n (%)	76 (33.48)

IQR: Interquartile range

The most common electrolyte imbalance observed was hyponatremia, followed by hypokalemia. Hypernatremia and hyperkalemia were seen only in a few cases.

The exact cause of hypokalemia is not known. However, some studies by Moreno *et al*.[6] showed a link between hypokalemia and decreased Angiotensin Converting Enzyme–2 (ACE 2) receptor activity in COVID-19 patients. Typically, the renin-angiotensin-aldosterone (RAAS) pathway causes activation of angiotensinogen 1, and this is converted to angiotensin II by angiotensin-converting enzyme (ACE). This angiotensin 2 is degraded by the ACE 2 enzyme acting as a counterbalance to ACE.[7] The coronavirus enters the body by binding to ACE 2 and causes ACE 2 depletion, and as a result, there is an imbalance in the RAAS pathway.[8] Elevated angiotensin levels cause hypokalemia by stimulating the action of aldosterone.

Hypokalemia is severely dangerous to patients as it may contribute to myocardial dysfunction and ventricular arrhythmia. It also causes muscle weakness that leads to respiratory paralysis [6]. In many studies conducted worldwide, it was observed that severe hypokalemia, as well as hyperkalemia,[9] is associated with more extended hospital stays and ICU admissions in COVID patients.

However, in this study, though patients with hypokalemia required mechanical ventilation and ICU admission, we could not prove a significant association between potassium imbalance and the severity of the disease. The hypokalemia observed in the study was not severe which may be because the mean potassium ion level was 3.6). A similar study could not establish a significant association between potassium levels and COVID-19.[10] Thus, the role of potassium disturbances in COVID-19 and its complications are still being determined,

Table 4: The association between various variables and the severity of disease (ICU admission, need for mechanical ventilation, and death).

Variables	Frequency (%)	Chi-square	p-value
Association with ICU admission			
Hyponatremia (n = 179)	44 (24.58)	2.81	0.26
Hypernatremia (n = 3)	2 (66.67)		
No Sodium abnormality (n = 45)	10 (22.22)		
Hypokalemia (n = 106)	22 (20.75)	1.74	0.44
Hyperkalemia (n = 15)	4 (26.67)		
No Potassium abnormality (n = 106)	30 (28.3)		
Only Sodium abnormality (n = 106)	30 (28.3)	1.43	0.50
Only Potassium abnormality (n = 45)	10 (22.22)		
Both Sodium and Potassium abnormality (n = 76)	16 (21.05)		
Association with a need for mechanical ventilation			
Hyponatremia (n = 179)	32 (17.88)	1.51	0.47
Hypernatremia (n = 3)	1 (33.33)		
No Sodium abnormality (n = 45)	6 (13.33)		
Hypokalemia (n = 106)	15 (14.15)	2.97	0.24
Hyperkalemia (n = 15)	1 (6.67)		
No Potassium abnormality (n = 106)	23 (21.7)		
Only Sodium abnormality (n = 106)	23 (21.7)	2.85	0.24
Only Potassium abnormality (n = 45)	6 (13.33)		
Both Sodium and Potassium abnormality (n = 76)	10 (13.16)		
Association with death			
Hyponatremia (n = 179)	19 (10.61)	6.90	0.03
Hypernatremia (n = 3)	2 (66.67)		
No Sodium abnormality (n = 45)	3 (6.67)		
Hypokalemia (n = 106)	12 (11.32)	1.43	0.51
Hyperkalemia (n = 15)	0 (0)		
No Potassium abnormality (n = 106)	12 (11.32)		
Only Sodium abnormality (n = 106)	12 (11.32)	0.92	0.63
Only Potassium abnormality (n = 45)	3 (6.67)		
Both Sodium and Potassium abnormality (n = 76)	8 (10.53)		

ICU: Intensive care unit

so further studies are needed. In our study, the mean serum sodium level at admission was 132.47 ± 6.1 mEq /L.

The leading cause of hyponatremia in COVID patients is thought to be Syndrome of inappropriate antidiuretic hormone secretion (SIADH), and it may be due to inflammatory cytokine release,[11] stress, positive pressure ventilation, etc. in COVID patients.[12] Many studies have shown a rise in inflammatory markers such as Interleukin 6 (IL-6) in COVID patients with hyponatremia.[4,13] IL-6 can act as a stimulus for the secretion of antidiuretic hormone (ADH) from magnocellular neurons of the hypothalamus.[14] The other reasons for hyponatremia include loss of sodium via the gastrointestinal tract in patients with diarrhea, cerebral edema, use of diuretics, etc.[12,15] We have excluded patients with comorbidities,[16] so that the use of diuretics can be excluded.

In this study, it has been noticed that there is a significant association between sodium imbalance at the time of admission and mortality among COVID-19 patients. A meta-analysis by Giovanni Corona, Corinna Giuliani, and others[17] showed that even moderate hyponatremia is associated with increased mortality. In a retrospective study conducted among the cohort of the preliminary international Health Outcome Predictive Evaluation for COVID-19 (HOPE-COVID-19) registry of 4664 patients, 20% had hyponatremia, which is independently associated with mortality.[16] Serum sodium and C-reactive protein have been recognized as significant markers for progressing to severe cases of COVID-19.[18]

Contrary to the majority of studies [19,20] confirming this finding, another study showed that all patients with hyponatremia are not a risk factor for in-hospital mortality, except for the subgroup of patients with hypovolemic hyponatremia.[21]

Some other studies conducted in China [22] also showed that patients with sodium imbalances required intense oxygen support and high doses of antibiotics and steroids. However, we could not establish a significant association between sodium levels and other markers of severity, like oxygen requirement and mechanical ventilation.

The exact cause of the increased mortality rate found in hyponatremia patients is unknown. In a study conducted in New York, it was observed that patients with severe hyponatremia (Na ≤ 120 mmol/L) had an eight-fold increased risk of encephalopathy when compared with patients with higher sodium levels.[12] Another reason for increased mortality might be due to the reason that acute severe hyponatremia can cause cerebral edema and can be lethal if not recognized and appropriately treated.[17] The correction of hyponatremia itself may cause potentially fatal complications, i.e., the osmotic demyelination syndrome.[17] However, another research concluded that the absence of correction of hyponatremia 72–96 h after hospital admission was associated with higher mortality in patients with COVID-19.[23]

CONCLUSION

In conclusion, our study showed that hyponatremia is the primary electrolyte abnormality in COVID-19 patients and is significantly associated with mortality. Thus, in COVID-19 patients with electrolyte abnormalities at the time of admission, serum sodium values can be used for risk stratification.

The main limitation of our study is that there was no control group consisting of non-COVID patients presenting with pneumonia or other infections, not allowing us to compare the effect of hyponatremia between the two groups. Future studies can be conducted by incorporating data from COVID patients without electrolyte imbalances at admission as the control group for doing risk stratification of patients with electrolyte abnormalities.

More studies are warranted to explore how hyponatremia leads to increased mortality in COVID-19 patients. A future intervention study with serial monitoring of serum electrolytes at a 24 hour interval, from time of admission till time of discharge/death, could much clarify the role of serum electrolyte levels on prognosis of COVID-19. Also, more studies are necessary with brain imaging and electroencephalogram to study the neurological effects of hyponatremia and its contribution to mortality.

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Ethical approval

The research/study was approved by the Institutional Ethics Committee at Govt. Medical College Kollam, Parippally, number IEC.No.1/EC-5/2021/GMCKLM, dated 08-07-2021..

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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