


Hyponatremia in COVID-19 patients: Experience from Bangladesh

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Abstract

Background: The purpose of the study was to measure the prevalence of hyponatremia and its association with clinical and laboratory characteristics of hospitalized coronavirus disease 2019 (COVID-19) patients at Dhaka Medical College and Hospital (DMCH).

Methods: This retrospective study was conducted in COVID-19 dedicated wards at DMCH from June to August 2020. Demographic, clinical, and laboratory data were collected from patient treatment sheets. Two groups of COVID-19 patients were retrospectively screened on the basis of plasma sodium level at admission: hyponatremic (sodium < 135 mM, $n = 84$) or normonatremic (sodium ≥ 135 mM, $n = 48$) patients. Severity was assessed using World Health Organization classification for COVID-19 disease severity. To compare the two groups, Pearson's χ^2 (qualitative variables) and Student's T tests (quantitative variables) were applied. The link between patients' clinical data and outcomes was investigated using logistic regression model.

Results: A total of 132 patients were included in the study, with a mean age of 51.41 (± 14.13) years. Hyponatremia was found in 84 patients (63.6%) and the remaining 48 patients (36.4%) had normal plasma Na^+ values. Among them, 74 (56.06%) presented with severe disease and 53 (40.15%) with moderate disease. At presentation, patients with moderate COVID-19 disease had 2.15 (1.04–4.5) times higher odds of suffering from hyponatremia. Besides, hyponatremia was independently associated with on admission SpO_2 ($p = 0.038$), hemoglobin ($p = 0.004$), and C-reactive protein ($p = 0.001$).

Conclusions: The authors suggest that patients' serum electrolytes be measured during initial hospital admission and then monitored throughout the hospital stay to predict the probability for referral for invasive ventilation and for better management.

KEYWORDS

Bangladesh, COVID-19, electrolyte imbalance, sodium

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1 | INTRODUCTION

The first cases of coronavirus disease 2019 (COVID-19) were diagnosed near a seafood market in Wuhan, China, toward the end of 2019.¹ Since then, the virus has spread to 215 countries and territories around the world, infecting more than 244 million people and leading to the death of nearly 5 million infected patients.² Bangladesh reported its first case of COVID-19 infection in the country on March 8, 2020, and the first death 10 days later on March 18.³ Since then, more than 1.5 million cases have been diagnosed. Another 27,814 people have lost their lives due to COVID-19-related complications.⁴

Clinical presentations of COVID-19 cases often vary, ranging from asymptomatic to critical, depending on patient age, comorbidities, immune status of that individual, affected organ, and several other factors. Common clinical symptoms of COVID-19 patients are fever, cough, respiratory distress, myalgia or fatigue, anosmia, diarrhea, and expectoration.⁵

Recently, some researchers have suggested that hyponatremia or decreased sodium levels in the blood may be associated with the development of severe disease in COVID-19 patients.^{6–9} There are several hypotheses regarding the pathophysiological mechanism of hyponatremia in COVID-19 patients. Among them, the most plausible explanation regarding hyponatremia in COVID-19 patients is closely linked to syndrome of inappropriate antidiuretic hormone secretion (SIADH), found in 40%–50% of hyponatremic patients due to acute respiratory distress syndrome. Disruption of the normal immune response and a massive release of proinflammatory cytokines can increase antidiuretic hormone secretions, leading to the development of SIADH.^{8,10,11}

In addition, renal cells express angiotensin-converting enzyme 2 receptors, a viral gateway for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), just like the lungs, hearts, and intestines. This direct attack by viral particles coupled with renal injury caused by ensuing cytokine storm results in electrolyte abnormalities.^{11,12} Besides, many patients develop diarrhea and vomiting, and loss of appetite during COVID infection. All these factors lower intravascular fluid volume and result in low extracellular fluid osmolality. Low sodium in COVID-19 patients appears to be associated with a more unfavorable outcome, as evidenced by previous researchers. It may be hypothesized that the decrease in sodium level indicates the presence of more advanced disease.¹³ As a low resource country, measurement of interleukin-6 (IL-6), the culprit mainly responsible for cytokine storm in COVID-19 patients, is problematic in Bangladesh. However, serum sodium level can be easily measured and this correction may positively influence patients' outcomes. Hence, in this study, we tried to observe the prevalence of hyponatremia among hospitalized COVID-19 patients and find a possible association between patients' clinical, laboratory and demographic characteristics, and hospital outcome.

2 | METHODOLOGY

2.1 | Study design and participant selection

This study was conducted in COVID-19 dedicated wards at Dhaka Medical College Hospital (DMCH), Bangladesh's largest government-run tertiary care hospital, from June to August 2020. The primary objective of this study was to measure the prevalence of hyponatremia in hospitalized COVID-19 patients and to find out its association with patient clinical characteristics.

This study contains retrospective data from a total of 132 SARS-CoV-2 reverse-transcriptase polymerase chain reaction-positive patients, aged 18 years and above, admitted at different COVID-19 wards in DMCH. Demographic, epidemiological, clinical, and on-admission laboratory data were collected from patient history sheets and anonymous data were sent to the core team for statistical analysis. Participating researchers independently checked all patient data and any missing data coupled with dubious self-reported data were omitted from the final analysis. No patient was interviewed during the study and only retrospective data were used for analysis. Hence, informed written consent was waived. Ethical permission was obtained from the ethical review board at DMCH (ERC-DMC/ECC/2020/91; date: May 18, 2020).

2.2 | Clinical classification of disease severity

For clinical classification of patients, the criteria put forth by World Health Organization (WHO) was used, and patients were classified into any of the following categories based on their clinical presentation—mild, moderate, severe, and critical (Table 1).¹⁴ The case definition used by WHO is provided below.

2.3 | Classification of hyponatremia

For this study, initially, the patients were categorized into four groups according to sodium level—mild hyponatremia (130–134 mmol/L), moderate hyponatremia (121–129 mmol/L), severe hyponatremia (<120 mmol/L), and normonatremia (135–145 mmol/L).¹⁵ In our study, no patient suffering from severe hyponatremia was found; hence, for analysis and considering the low sample size, we broadly categorized patients into two categories—normonatremia (135–145 mmol/L) and hyponatremia (<135 mmol/L).

2.4 | Statistical analysis

All statistical analysis was performed using R-programming language. The categorical variables were represented with the number of cases and their percentages. Median and interquartile ranges were calculated for continuous variables. The value of *p* was set <0.05 for all statistics tests. The χ^2 tests of independence were conducted to identify the significant

TABLE 1 WHO classification of COVID-19 disease severity

Disease severity	Definition
Mild	Symptomatic COVID-19 patients without viral pneumonia or hypoxia
Moderate	Patients with clinical signs of pneumonia but without signs of severe pneumonia, including SpO ₂ ≥ 90%
Severe	Patients with clinical signs of pneumonia plus one of the following features: <ul style="list-style-type: none"> • Respiratory rate > 30/min • SpO₂ < 90% on room air • Severe respiratory distress
Critical	COVID-19 patients with ARDS, sepsis, or septic shock

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; WHO, World Health Organization.

variables associated with hyponatremia. Associations between categorical variables were tested using Pearson's χ^2 test or Fisher's exact test, and for quantitative variable Student's *t* test was performed. Outcomes were measured with penalized logistic regression and Poisson regression model. For all statistical analyses, an α of 0.05 was considered as the threshold of significance.

3 | RESULTS

A total of 132 patients were included in the study with a mean age of 51.41 (± 14.13) years. Eighty-six (65.6%) were males and 45 (34.4%) were females (Table 2). Among the patients, 74 (56.06%) presented severe COVID-19 disease and 53 (40.15%) with moderate disease severity. Only one (0.7%) patient was identified to be suffering from critical disease. The most common comorbidity was hypertension (68, 64.8%), closely followed by diabetes mellitus (54, 53.5%), and then successively by ischemic heart disease, asthma, chronic obstructive pulmonary disease, chronic kidney disease, and malignancy (Table 2). The prevalence of hyponatremia in this study was found to be 63.6% ($n = 84$) and serum sodium level was found to be normal in the remaining 36.4% of patients ($n = 48$; Table 3).

Among the factors studied, significant association was observed between the sodium level and on admission SpO₂ ($p = 0.03$; odds ratio = 2.5; 95% CI: 1.1–5.7), hemoglobin level ($p = 0.004$), and CRP ($p = 0.001$). Moderate and severe disease states were more associated with hyponatremia ($p = 0.04$ and $p = 0.03$, respectively; Table 3). In our study, 75% less death occurred in normonatremic patient group compared with patients with hyponatremia. However, no statistical significance was found between sodium level and likelihood to require invasive ventilation and duration of hospital stay (Table 4).

4 | DISCUSSION

In our study, gender and disease severity at presentation were statistically associated with hyponatremia, with the males being susceptible to severe disease compared to females. Previous research

TABLE 2 Baseline characteristics of the participants ($N = 132$)

	N	%
Age (years), mean (\pm SD)	51.41 (± 14.13)	
Sex		
Male	86	65.6%
Female	45	34.4%
Hypertension	68	64.8%
Diabetes mellitus	54	53.5%
Ischemic heart disease	37	38.5%
Asthma	27	31.4%
Chronic obstructive pulmonary disease	17	23.6%
Chronic kidney disease	10	13.9%
Malignancy	1	1.5%

comprising of case series showed that COVID-19 cases in men tended to be more severe than in women ($p = 0.035$).¹⁶ In the public data set available, the mortality rate in men was 2.4 times higher than that of women. Hawkins¹⁷ reported that increasing age is a decisive, independent risk factor for either hypo- or hypernatremia in the general population. However, gender was not a significant risk factor for disturbances in sodium concentration.¹⁷ In contrast, this study showed a preponderance of hyponatremia in the male population.

In this study, hyponatremia in COVID-19 patients was positively associated with moderate disease at presentation. It was found that patients with moderate disease were 2.15 (95% CI: 1.04–4.5) times more likely to present with hyponatremia. This finding is similar to findings or statements made by many other researchers, including Berni et al.,⁸ Luo et al.,⁶ and Post et al.⁷ Lippi et al.¹⁸ reported in a meta-analysis including a total pool of 1415 patients that sodium level was significantly lower in patients with severe COVID-19. Hence, findings from this study are congruent with existing literature.

Table 3 shows that among all the variables tested for association with sodium levels, SpO₂, hemoglobin level, and CRP showed significant association with hyponatremia on

TABLE 3 Characteristics and biological parameters of the two groups of patients

Characteristic	Hyponatremia (n = 84)	Normonatremia (n = 48)	p	Odds ratio (95% CI)
Fever	84 (100)	48 (100)	0.9 ^a	
Sex (female)	34 (40%)	11 (23%)	0.04	0.44 (0.19–0.97)
Cough	75 (89%)	46 (96%)	0.8 ^a	2.6 (0.6–19.3)
Breathlessness	77 (92%)	43 (90%)	0.4 ^a	0.8 (0.2–2.8)
Fatigue	60 (71%)	31 (65%)	0.4 ^a	0.7 (0.3–1.6)
Sore throat	41 (49%)	20 (42%)	0.4 ^a	0.8 (0.4–1.5)
Headache	25 (30%)	18 (38%)	0.2 ^a	1.4 (0.7–3.0)
Diarrhea	31 (37%)	13 (27%)	0.6 ^a	0.6 (0.3–1.4)
Nausea/vomiting	16 (19%)	11 (23%)	0.5 ^a	1.3 (0.5–3.0)
Anosmia	23 (27%)	16 (33%)	0.03 ^a	1.3 (0.6–2.9)
Admission SpO ₂ (≤93%)	68 (82%)	31 (65%)	0.03 ^a	2.5 (1.1–5.7)
WHO criteria				
Moderate	28 (33%)	25 (52%)	0.04 ^a	2.15 (1.04–4.5)
Severe	53 (63%)	21 (44%)	0.03 ^a	0.45 (0.2–0.94)
Critical	1 (1.2%)	0	0.9 ^b	4.98 (0.9–127.1)
Hospital stays (days), mean (±SD)	11.5 (±4.4)	12.0 (±5.2)	0.5 ^c	–
Hb% (g/dl), mean (±SD)	11.75 (±2.1)	12.0 (±5.2)	0.004 ^c	–
Neutrophil (%), mean (±SD)	78 (±11)	76 (±13)	0.3 ^c	–
Lymphocyte (%), mean (±SD)	17 (±10)	18 (±11)	0.6 ^c	–
CRP (mg/L), mean (±SD)	28 (±26)	17 (±13)	0.001 ^c	–
Ferritin (µg/L), mean (±SD)	732 (±869)	495 (±553)	0.06 ^c	–
D-dimer (g/L), mean (±SD)	1.34 (±1.28)	1.10 (±0.95)	0.2 ^c	–

Abbreviations: CI, confidence interval; CRP, C reactive protein; Hb, hemoglobin; n, number; SpO₂, percent saturation of oxygen in the blood; WHO, World Health Organization.

^aχ² test.

^bFisher's exact test.

^cStudent's t test.

TABLE 4 Association between hyponatremia and hospital outcome

Variable	p	Odds ratio (95% CI)
Hospital stay (days)	0.38 ^a	1.05 (0.95–1.16)
Invasive ventilation	0.11	0.42 (0.12–1.19)
Death	0.08	0.25 (0.3–1.14)

Note: Odds are calculated for normal serum level compared with hyponatremia.

Abbreviation: CI, confidence interval.

^aPoisson regression.

admission. A retrospective study enrolling 52 laboratory-confirmed patients showed that IL-6 was inversely correlated with sodium level, whereas sodium level was directly correlated with PaO₂/FiO₂ (P/F) ratio.⁸ Lower admission SpO₂ was

associated with hyponatremia, found in our study, which is somewhat similar to findings to that of Berni et al.⁸

We also found an association of hyponatremia with blood hemoglobin level. Lippi et al.¹⁸ found that the hemoglobin value was significantly lower in COVID-19 patients with severe disease than in those with milder forms, yielding a weighted mean difference of -7.1 g/L (95% CI: -8.3 to -5.9 g/L).¹⁹ This might be the reason why we observed an association between hyponatremia and hemoglobin level, as most of the patients were hyponatremic (63.6%) and suffering from the severe disease (74.2%) according to WHO classification.

CRP is an inflammatory marker. Elevated levels of CRP are the results of overproduction of various inflammatory markers, especially cytokines. Several studies have illustrated the relationship between CRP and poor prognosis in COVID-19 patients.²⁰ As most of the patients enrolled in the study suffered from severe disease, elevation in CRP level is justifiable and, hence, can be linked to hyponatremia as well.

Several studies have found an independent link between hyponatremia upon admission and transfer to ICU, use of mechanical ventilation, or death.^{13,15,21,22} In our study, we found conflicting result in case of mean duration of hospital stay, which was found to be more in normonatremic patient. This result may be due to small sample size of normonatremic patients, and requires further investigation with a large sample size for a definitive answer.

This study has several limitations. Due to time and budgetary constraints, only a small number of patients could be enrolled, unlike other studies with a large sample size.¹⁵ Besides, it could have been helpful and provided the researchers with a clearer picture of the association between disease progression and level of sodium if serum sodium level was measured on a regular interval, rather than one-time measurement after admission, during patients' hospital stay. Besides, we had to rely on patients' statements or statements from their attendants while documenting past histories and presenting complaints. There are possibilities of information bias in this regard as most of the patients admitted at DMCH are from low socioeconomic backgrounds with a low level of education. As we did work with retrospective data, there was little opportunity for us to control those biases.

5 | CONCLUSIONS

In this study, nearly two-thirds of patients were identified as hyponatremic. A strong association was observed between hyponatremia and disease severity. However, relationship between sodium level, and patient mortality and hospital outcome could not be established due to a relatively low sample size. Hence, the authors advocate future studies with a larger sample size to see whether increased or decreased sodium level is associated with adverse outcomes among COVID-19 patients.

ACKNOWLEDGMENTS

The authors would like to acknowledge the efforts put forth by frontline healthcare workers at DMCH to fight off this pandemic. This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Md. Khairul Islam. **Methodology:** Md. Khairul Islam and Md. Maruf A. Molla. **Data collection:** Md. Khairul Islam, Pratyay Hasan, Md. Mohiuddin Sharif, Tazdin D. Khan, Rifat H. Ratul, and Fahima S. Hossain. **Manuscript writing—first draft:** Md. Khairul Islam, Pratyay Hasan, and Md. Mohiuddin Sharif. **Statistical analysis:** Md. Khairul Islam, Md. Maruf A. Molla. **Review and editing:** Md. Maruf A. Molla. **Supervision:** Md. Khairul Islam and Md. Maruf A. Molla.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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How to cite this article: Islam MK, Hasan P, Sharif MM, et al. Hyponatremia in COVID-19 patients: Experience from Bangladesh. *Health Sci Rep* 2022;5:e565. doi:10.1002/hsr2.565