https://journalrip.com doi: 10.34172/jrip.2025.38689

Journal of Renal Injury Prevention

The prognostic value of hyponatremia severity in predicting clinical outcomes of COVID-19 patients; a retrospective cohort study

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ARTICLE INFO

Article Type:
Original

Article History:
Received: 24 Aug. 2025
Revised: 1 Oct. 2025
Accepted: 6 Oct. 2025
Published online: 12 Oct. 2025

Keywords:
COVID-19
Electrolyte imbalance
Sodium imbalance
Hyponatremia
Prognostic marker
Clinical outcomes
Intensive care unit admission
Mechanical ventilation
Mortality

ABSTRACT

Introduction: Hyponatremia, a common electrolyte disturbance, has been increasingly recognized as a potential prognostic marker in patients with COVID-19.
Objectives: This retrospective cohort study aimed to evaluate the predictive value of hyponatremia severity in predicting clinical outcomes among patients with COVID-19.
Patients and Methods: This retrospective cohort study included 315 adult COVID-19 patients with hyponatremia admitted to Khorshid hospital in Isfahan, Iran, from May to December 2020. Data were extracted from electronic health records using a standardized form, including demographics, clinical data, and laboratory results within 24 hours of admission. Patients were categorized by hyponatremia severity, and clinical outcomes such as intensive care unit (ICU) admission, need for mechanical ventilation, and mortality were recorded. The primary outcome of this study was to assess the relationship between the severity of hyponatremia and adverse clinical outcomes in COVID-19 patients.
Results: Severe or moderate hyponatremia was correlated with increased odds of ICU admission compared to mild hyponatremia, with an unadjusted odds ratio (OR) of 2.69 and an adjusted OR of 2.05. The association was even stronger for mechanical ventilation, where severe or moderate hyponatremia increased the odds substantially, with an unadjusted OR of 10.12 and an adjusted OR of 9.40. Regarding mortality, severe or moderate hyponatremia was associated with the highest increase in risk, demonstrating an unadjusted OR of 12.56 and an adjusted OR of 13.30.
Conclusion: The results indicated that severe or moderate hyponatremia in COVID-19 patients is strongly associated with worse clinical outcomes. These findings highlight hyponatremia severity as a robust predictor of disease severity and poor prognosis in COVID-19, emphasizing the importance of monitoring and managing sodium levels in affected patients to improve outcomes.

Original

Implication for health policy/practice/research/medical education:
In this retrospective cohort study, we found that severe or moderate hyponatremia was associated with significantly higher odds of intensive care unit (ICU) admission compared to mild hyponatremia, with an unadjusted odds ratio (OR) of 2.69 and an adjusted OR of 2.05 after accounting for confounders. This relationship was even more pronounced for mechanical ventilation, where severe or moderate hyponatremia increased the odds markedly, with unadjusted and adjusted ORs of 10.12 and 9.40, respectively. Regarding mortality, severe or moderate hyponatremia conferred the greatest risk, with unadjusted and adjusted ORs of 12.56 and 13.30, respectively. These findings highlight a robust and independent association between hyponatremia severity and worse clinical outcomes in COVID-19 patients.

Please cite this paper as: Ashrafi L, Sajad RS. The prognostic value of hyponatremia severity in predicting clinical outcomes of COVID-19 patients; a retrospective cohort study. J Renal Inj Prev. 2025; x(x): e38689. doi: 10.34172/jrip.2025.38689.

Introduction

COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a global health crisis characterized by a wide clinical spectrum from asymptomatic infection to severe respiratory failure and death (1-3). While most patients experienced symptoms that were mild to moderate, severe cases frequently required admission to intensive care units

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(ICUs) and invasive mechanical ventilation (3,4) and resulting in various organ injuries, especially kidney injury (5). Therefore, early identification of patients at risk for such adverse outcomes is essential for timely intervention and resource allocation in clinical settings (1,6).

Hyponatremia, defined as a serum sodium concentration below 135 mmol/L (7,8), is a common electrolyte disturbance observed in patients hospitalized with COVID-19 (9,10). Its pathogenesis in COVID-19 is multifactorial, including the effects of systemic inflammation, inappropriate antidiuretic hormone secretion, and organ dysfunction (11,12). Hyponatremia is prevalent among medically hospitalized patients (13) and is linked to poor prognosis, which may reflect disease burden and prognosis in these patients (1,14). This disorder is also linked to a range of negative outcomes, such as extended hospital stays, a higher likelihood of ICU admission, and an increase in in-hospital mortality (15-17).

Several studies have investigated the prognostic value of hyponatremia severity in predicting adverse clinical outcomes in COVID-19. Systematic reviews and meta-analyses indicate that hyponatremia is independently associated with a twofold increase in risk of poor outcomes (1,14). However, the precise role of hyponatremia severity as a stratifying marker remains to be fully elucidated. Understanding this relationship could enhance clinical risk assessment and inform management strategies for patients affected by COVID-19.

Objectives

The objective of this study is to evaluate the association between hyponatremia severity and clinical outcomes in COVID-19 patients, specifically focusing on the risk of ICU admission, need for mechanical ventilation, and mortality. The study aims to determine whether severe or moderate hyponatremia independently predicts worse outcomes.

Patients and Methods

Study design and participants

This retrospective cohort study was conducted on 315 COVID-19 patients diagnosed with hyponatremia who were admitted to Khorshid hospital in Isfahan, Iran, between May and December 2020. Existing medical records were reviewed to assess the relationship between the severity of hyponatremia at hospital admission and subsequent clinical outcomes.

Inclusion and exclusion criteria

This study included hospitalized adult patients diagnosed with COVID-19 confirmed by polymerase chain reaction (PCR) testing, who had serum sodium (Na) levels below 135 mmol/L or mEq/L, meeting the criteria for hyponatremia on admission (7,8,18). Patients who had complete demographic, clinical, and laboratory data were included for analysis. Exclusion criteria comprised patients who received experimental treatments for COVID-19 before admission. Additionally, patients with incomplete medical records or lacking essential baseline data were excluded to ensure data integrity and reliability of results.

Data collection

Data for this retrospective cohort study were collected by reviewing patients' electronic health records and clinical documents using a standardized data extraction form. Trained researchers gathered detailed demographic information, clinical history, laboratory results, and outcome measures from hospital databases and medical documents. The data included patients' age, gender, smoking status, immunosuppressive treatments, and a comprehensive list of comorbidities such as malignancy, organ transplantation, cardiac, respiratory, metabolic, rheumatologic, thyroid, and cerebrovascular diseases. Vital signs measured at admission, including temperature, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), respiratory rate (RR), and oxygen saturation (SPO_2), were recorded. Laboratory results for this study were collected from patients' medical records and hospital laboratory databases, focusing on tests performed within the first 24 hours of admission. The collected laboratory parameters included serum potassium, phosphorus, magnesium, and calcium levels; white blood cell (WBC) count; hemoglobin (Hb) concentration; platelet count; percentage of neutrophils and lymphocytes; blood pH; bicarbonate (HCO3); partial pressure of carbon dioxide (PCO_2); liver enzymes including aspartate aminotransferase (AST) and alanine transaminase (ALT); alkaline phosphatase (ALP); serum albumin; blood glucose; blood urea nitrogen (BUN); serum creatinine; lactate dehydrogenase (LDH); erythrocyte sedimentation rate (ESR); and C-reactive protein (CRP). The outcome measures included ICU admission, the requirement for mechanical ventilation, and mortality status (recovered or died) among COVID-19 patients, with hyponatremia severity categorized as severe or moderate when serum sodium levels were below 130 mEq/L, and mild when levels were between 130 and 134 mEq/L (19). The collected data were used for subsequent statistical analysis to examine the relationship between hyponatremia severity and clinical outcomes in COVID-19 patients.

Outcomes

The primary outcome of this study is the association between hyponatremia severity and major adverse clinical outcomes in COVID-19 patients, including ICU admission, need for mechanical ventilation, and mortality. Secondary outcomes include the evaluation of hyponatremia severity potential role as a prognostic indicator for the management of COVID-19 patients.

Statistical analysis

The data analysis was performed using the Statistical Package for Social Sciences (SPSS) version 27 (IBM Corp, USA). Levene's test was utilized to assess the equality of variances, and the Kolmogorov-Smirnov test was applied to evaluate the normality of quantitative variables. Differences in frequency distribution between groups were examined using the independent t-test for quantitative data and the chi-square test for qualitative variables. Both univariate and multivariate logistic regression analyses were conducted to investigate the association between hyponatremia severity and clinical outcomes such as ICU admission, need for mechanical ventilation, and mortality. Odds ratio (OR) with 95% confidence intervals (CIs) were calculated to determine the predictive strength of hyponatremia for adverse clinical outcomes in COVID-19 patients. A *P* value less than 0.05 was considered statistically significant for all tests.

Results

In Table 1, the baseline demographic and comorbidity characteristics of patients were compared across groups defined by ICU admission, mechanical ventilation status, and mortality. The analysis showed no significant differences in age or gender distribution between these groups. Smoking status was slightly higher in ICU-admitted patients; however, it did not reach statistical significance, as well as in the two other variables of mechanical ventilation status and mortality. Among comorbidities, malignancy was more prevalent in patients who required mechanical ventilation and in those who died, showing a significant association. Other comorbidities such as cardiac disease, organ transplantation, respiratory disease, diabetes, thyroid disease, and cerebrovascular diseases did not differ significantly across the groups based on ICU admission, ventilation, or death outcomes. Rheumatologic diseases showed a higher presence among mechanically ventilated patients and those who died, with both associations being statistically significant. The presence of hypertension was significantly greater in the patients who were admitted to the ICU compared to those who were not (Table 1).

The comparative analysis of patients' baseline clinical and laboratory data revealed differences related to ICU admission, mechanical ventilation, and mortality. Vital signs at admission showed that SBP tended to be higher among mechanically ventilated patients, while DBP was notably lower in those who died. Respiratory rate was elevated in patients admitted to the ICU and those who died, and oxygen saturation was significantly lower across all three groups; ICU admission, mechanical ventilation, and mortality. Heart rate and body temperature did not show considerable differences. Laboratory findings indicated that patients admitted to the ICU or requiring mechanical ventilation exhibited higher WBC counts and neutrophil percentages alongside lower lymphocyte percentages. Hemoglobin levels were generally lower in more severe cases, including those needing ventilation, ICU admission, and those who died. Calcium levels were

Table 1. Comparative analysis of patients' baseline demographic and comorbidities characteristics by ICU admission, ventilation status, and mortality

Variables	ICU admission			Mechanical ventilation			Death		
	No (n= 207)	Yes (n= 108)	*P* value	No (n=279)	Yes (n=36)	*P* value	No (n=289)	Yes (n= 26)	*P* value
Demographic characteristics									
Age (years)	62.66 (15.49)	62.99 (16.28)	0.865	62.74 (15.80)	63 (15.48)	0.928	62.4 (15)	66.6 (14)	0.190
Age ≥ 60 years (No, %)	65 (60.19%)	131 (63.29%)	0.593	175 (62.72%)	31 (58.33%)	0.601	179 (61.9)	17 (65.3)	0.723
Sex - Female (No, %)	76 (36.71%)	37 (34.26%)	0.664	102 (36.56%)	11 (30.56%)	0.486	105 (36.3)	8 (30.7)	0.574
Smoking status (No, %)	32 (15.46%)	24 (22.22%)	0.138	49 (17.56%)	7 (19.44%)	0.785	50 (17)	6 (23)	0.465
Comorbidities									
Malignancy	3 (1.45%)	5 (4.63%)	0.089	5 (1.79%)	3 (8.33%)	0.014	5 (1.7)	3 (11.5)	0.002
Organ transplantation	4 (1.93%)	1 (0.93%)	0.491	5 (1.79%)	0 (0%)	0.413	5(100)	0 (0)	a
Immunosuppressive treatment	6 (2.90%)	1 (0.93%)	0.267	6 (2.15%)	1 (2.78%)	0.816	6 (2)	1 (3.8)	0.553
Cardiac disease	46 (22.22%)	32 (29.63%)	0.144	66 (23.66%)	12 (33.33%)	0.207	70 (24.2)	8 (30.7)	0.453
Hypertension	71 (34.30%)	51 (47.22%)	0.027	103 (36.92%)	19 (52.78%)	0.068	109 (37.7)	13 (50)	0.217
Respiratory disease	44 (21.26%)	24 (22.22%)	0.843	58 (20.79%)	10 (27.78%)	0.334	62 (21.4)	6 (23)	0.841
Diabetes	80 (38.65%)	44 (40.74%)	0.712	112 (40.14%)	12 (33.33%)	0.431	114 (39.4)	10 (38.4)	0.922
Rheumatologic diseases	3 (1.45%)	2 (1.85%)	0.787	3 (1.08%)	2 (5.56%)	0.045	3 (1)	2(7)	0.009
Thyroid diseases	18 (8.70%)	6 (5.65%)	0.315	20 (7.17%)	4 (11.11 %)	0.408	22(7.6)	2 (7.6)	0.981
Cerebrovascular diseases	16 (7.73%)	6 (5.56%)	0.473	19 (6.81%)	3 (8.33%)	0.737	16(6.5)	3 (11.5)	0.345

ICU: Intensive care unit. Data are presented as number %) for categorical and mean (standard deviation [SD]) for quantitative variables. Categorical variables were analyzed using the chi-square test, while quantitative variables were analyzed using the independent t-test. a: all (not applied for statistical).

Table 2. Comparative analysis of patients' baseline clinical and laboratory data by ICU admission, ventilation status, and mortality

Variables	ICU admission			Mechanical ventilation			Death		
	No (n = 207)	Yes (n = 108)	*P* value	No (n = 279)	Yes (n = 36)	*P* value	No (n = 289)	Yes (n = 26)	*P* value
Vital signs at admission									
SBP (mm Hg)	128.24 (17.50)	131.57 (20.27)	0.134	128.64 (17.53)	135.13 (24.53)	0.041	129.44 (18.3)	128.8 (20.6)	0.874
DBP (mm Hg)	77.02 (10.82)	75.60 (12.63)	0.298	76.72 (11.02)	75.13 (14.61)	0.436	80 (70-80)	70 (60-80)	0.016
RR (breaths/min)	23.08 (4.80)	24.81 (6.12)	0.006	23.40 (5.05)	25.77 (6.97)	0.063	23 (5)	26 (6)	0.010
HR (beats/min)	94.49 (13.66)	94.87 (15.26)	0.825	94.70 (13.88)	94.02 (16.75)	0.783	94 (85-103)	92 (82-110)	0.794
Temp (°C)	38.20 (3.66)	38.02 (0.84)	0.623	38.18 (3.18)	37.84 (.81)	0.524	38.17 (3.1)	37.8 (0.7)	0.646
O_2 Sat (%)	86.92 (6.06)	80.41 (11.20)	<0.001	85.53 (8.09)	78.19 (10.78)	<0.001	85.23 (8.3)	78.7 (10.6)	<0.001
Laboratory parameters									
Potassium (mmol/L)	4.05 (0.5)	4.11 (0.55)	0.367	4.06 (.55)	4.12 (.59)	0.546	4.06 (0.55)	4.18 (0.63)	0.282
Phosphorus (mg/dL)	2.91 (.67)	2.89 (.79)	0.784	2.88 (.69)	3.07 (.87)	0.137	2.9 (0.69)	2.9 (0.99)	0.673
Magnesium (mg/dL)	1.90 (.30)	1.86 (.25)	0.253	1.89 (.29)	1.84 (.21)	0.345	1.9 (0.29)	1.8 (0.23)	0.091
Calcium (mg/dL)	8.34 (.59)	8.41 (.60)	0.349	8.34 (.58)	8.56 (.65)	0.032	8.37 (0.6)	8.36 (0.6)	0.893
WBC (10^3/µL)	6.49 (3.25)	8.26 (4.52)	<0.001	6.75 (3.24)	9.81 (6.25)	<0.001	6.95 (3.5)	8.78 (5.6)	0.019
Hemoglobin (g/dl)	13.27 (1.67)	12.79 (2.25)	0.036	13.24 (1.80)	12.04 (2.30)	<0.001	13.18 (1.8)	12.3 (2.2)	0.026
Platelet (10^3/µL)	185.5 (72.07)	201.09 (84.95)	0.084	190.33 (72.64)	195.25 (105.78)	0.715	190.7 (74.3)	192 (103)	0.921
Neutrophil (%)	75.12 (9.27)	80.28 (9.81)	<0.001	76.23 (9.59)	81.97 (9.69)	<0.001	76.6 (9.5)	80 (11.2)	0.082
Lymphocyte (%)	18.13 (8.45)	13.86 (8.43)	<0.001	17.22 (8.62)	12.37 (7.90)	<0.001	16.8 (8.4)	14.74 (10.6)	0.237
pH	7.37 (.21)	7.36 (.08)	0.854	7.37 (.18)	7.33 (.10)	0.174	7.37 (0.18)	7.33 (0.11)	0.246
HCO_3 (meq/L)	26.18 (3.69)	26.50 (4.29)	0.485	26.26 (3.69)	26.51 (5.37)	0.718	26.2 (3.7)	26.9 (5.4)	0.417
PCO_2 (mm Hg)	42.80 (8.37)	41.58 (9.97)	0.253	42.46 (8.74)	41.77 (10.57)	0.665	42.4 (8.7)	41.2 (11)	0.513
AST (U/L)	38.67 (14.02)	42.16 (14.90)	0.042	39.48 (14.33)	42.86 (14.77)	0.181	39.87 (14.53)	39.8 (13.1)	0.992
ALT (U/L)	32.96 (17.05)	33.98 (14.49)	0.597	33.17 (16.49)	34.38 (13.94)	0.673	33.3 (16.4)	32.3 (13.3)	0.763
ALP (U/L)	161.05 (57.51)	166.0 (59.37)	0.473	161.13 (56.0)	175.27 (71.77)	0.165	161.7 (56.5)	174 (73.4)	0.327
Albumin (g/dL)	3.90 (0.50)	3.70 (0.44)	<0.001	3.86(.49)	3.62 (0.50)	0.006	3.86 (0.49)	3.5 (0.43)	<0.001
Blood glucose (mg/dL)	141.62 (53.07)	154.40 (47.73)	0.037	144.08 (51.55)	160.88 (50.09)	0.068	144.6 (51.6)	161.5 (49.8)	0.118
BUN (mg/dL)	17.06 (4.90)	18.01 (4.42)	0.082	17.2 (4.86)	18.84 (3.59)	0.053	17.2 (4.8)	18.4 (3.36)	0.223
Creatinine (mg/dL)	0.97 (.17)	1.01 (.18)	0.085	.98 (.17)	1.03 (.20)	0.092	0.98 (0.17)	1 (0.2)	0.261
LDH (U/L)	756.63 (616.2)	792.75 (301.79)	0.563	759.90 (550.98)	839.63 (314.45)	0.391	758.3 (541.9)	887.1 (350)	0.237
ESR (mm/hr)	52.25 (22.95)	59.36 (27.33)	0.015	53.57 (22.68)	63.33 (36.25)	0.024	54.8 (24.1)	52.9 (31.2)	0.713
CRP (mg/L)	69.60 (45.50)	65.05 (45.15)	0.396	68.50 (44.92)	64.44 (49.18)	0.612	68.2 (44.3)	66.2 (55.9)	0.839

ICU: Intensive care unit, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, RR: Respiratory rate, HR: Heart rate, Temp: Temperature, O_2 Sat: Oxygen saturation, HCO3: Bicarbonate, PCO2: Partial pressure of carbon dioxide, WBC: With blood cells, AST: Aspartate aminotransferase, ALT: Alanine transaminase, ALP: Alkaline phosphatase, BUN: Blood urea nitrogen, LDH: Lactate dehydrogenase, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein.
Data are presented as number (%) for categorical and Mean (standard deviation [SD]) for quantitative variables. Categorical variables were analyzed using the chi-square test, while quantitative variables were analyzed using the independent t-test.

significantly higher in ventilated patients. Liver enzyme AST was slightly elevated in ICU patients, whereas ALT and ALP levels were not markedly different. Albumin levels were decreased in all groups with worse outcomes, while blood glucose trends showed some elevation in more critical patients. Other markers, such as BUN, creatinine, LDH, ESR, and CRP, had varied results, with ESR level higher among those admitted to the ICU and mechanically ventilated. Acid-base parameters, including pH, bicarbonate, and partial PCO2, did not show significant differences (Table 2).

The frequency distribution of patients with hyponatremia, classified as either mild or severe/moderate, showed significant differences according to ICU admission, mechanical ventilation status, and mortality. Patients admitted to the ICU had a higher proportion of severe or moderate hyponatremia compared to those not admitted. Similarly, patients who required mechanical ventilation were more likely to have severe or moderate hyponatremia than those who did not need ventilation. This pattern was also observed among patients who died, with a greater prevalence of severe or moderate hyponatremia compared to survivors. These findings suggest a significant association between the severity of hyponatremia and critical illness outcomes, including ICU admission, the necessity for mechanical ventilation, and mortality risk (Table 3).

The logistic regression analysis demonstrated a significant association between hyponatremia severity and adverse clinical outcomes. Severe or moderate hyponatremia was linked with increased odds of ICU admission compared to mild hyponatremia, with an unadjusted OR of 2.69, suggesting that patients with severe or moderate hyponatremia had about 2.69 times higher odds of being admitted to the ICU than patients with mild hyponatremia. When we adjusted variables for confounders (age, gender, hypertension, RR, O_2sat (oxygen saturation), WBC, Hb, AST, albumin, blood glucose, and percentage of lymphocytes and neutrophils), this OR decreased to 2.05. The association was even stronger for mechanical ventilation, where severe or moderate hyponatremia increased the odds substantially, with an unadjusted OR of 10.12. By adjusting for these confounders, such as age, gender, SBP, WBC, HB, albumin, O_2sat, presence of malignancy, lymphocyte and neutrophil percentage, and ESR, the OR decreased to 9.40, indicating the relationship is weaker once these confounding factors are considered. Regarding mortality, severe or moderate hyponatremia was associated with the highest increase in risk, demonstrating an unadjusted OR of 12.56 and an adjusted OR of 13.30 following adjusting for confounders, including age, gender, DBP, RR, WBC, HB, albumin, and the presence of organ transplantation. These results highlight that severe or moderate hyponatremia is a significant independent predictor of ICU admission, necessary for mechanical ventilation, and mortality of COVID-19 patients (Table 4).

Discussion

Our results demonstrated that COVID-19 patients with moderate to severe hyponatremia experienced significantly worse clinical outcomes, including higher rates of ICU admission, increased need for mechanical ventilation, and elevated mortality risk. These results are consistent with those reported in previous studies, including a systematic review and meta-analysis by Khidir et al of 23 studies encompassing COVID-19 patients showed hyponatremia conferred nearly a twofold increased risk of mortality (OR 1.97), ICU admission (OR 1.91), and assisted ventilation (OR 2.04), corroborating the prognostic role of hyponatremia severity observed in our cohort (20). Another comprehensive meta-analysis conducted by Akbar et al, including data from 11,493 patients across eight studies, demonstrated a significant association between hyponatremia and adverse outcomes in COVID-19 patients. Their analysis showed that patients with low serum sodium levels experienced higher risks of severe disease manifestations, prolonged hospitalization, and increased mortality, highlighting hyponatremia as an important prognostic indicator in this population (1). A retrospective study conducted by Rehman et al reported that hyponatremia detected at hospital admission in COVID-19 patients is significantly associated with poorer clinical outcomes. Furthermore, the presence of hyponatremia was found to be a useful predictor not only for the severity of the disease but also for estimating the length of hospital stay, thereby serving as a practical prognostic indicator in managing COVID-19 patients

Table 3. Frequency distribution of patients with hyponatremia (severe or moderate/mild) according to ICU admission, ventilation status, and mortality

Variable		Hyponatremia status					
		Mild		Severe or moderate		Total number	*P* value*
		N	%	N	%		
ICU admission	No	151	72.9	56	27.1	207	<0.001
	Yes	54	50	54	50	108	
Mechanical ventilation	No	198	71.00	81	29.00	279	<0.001
	Yes	7	19.4	29	80.6	36	
Death	No	201	69.6	88	30.4	289	<0.001
	Yes	4	15.4	22	84.6	26	

ICU: Intensive care unit. *Chi-square.

Table 4. The association of hyponatremia (severe or moderate/mild) status with ICU admission, ventilation status, and mortality using binary logistic regression in COVID-19 patients

Hyponatremia Status		*P* value	OR	95% CI	
				Lower	Upper
ICU admission					
Unadjusted	Mild			Ref (1)	
	Severe/moderate	<0.001	2.69	1.65	4.38
Adjusted	Mild			Ref (1)	
	Severe/moderate	0.012	2.05	1.72	3.61
Mechanical ventilation					
Unadjusted	Mild			Ref (1)	
	Severe/moderate	<0.001	10.12	4.26	24.05
Adjusted	Mild			Ref (1)	
	Severe/moderate	<0.001	9.40	3.47	25.49
Death					
Unadjusted	Mild			Ref (1)	
	Severe/moderate	<0.001	12.56	4.20	37.53
Adjusted	Mild			Ref (1)	
	Severe/moderate	<0.001	13.30	4.18	12.29

ICU: Intensive care unit, OR: Odds ratio, CI: Confidence interval, Ref: Reference.

(21). Another retrospective analysis similarly linked hyponatremia with higher ICU admissions and oxygen requirement, and increased disease severity, underscoring its value as an early marker of prognosis (18). A large-scale territorial study in Hong Kong examining 53,415 COVID-19 patients revealed that those with hyponatremia experienced increased 30-day mortality (9.7% versus 5.7%), prolonged hospitalization, and more ICU admissions (7.0% versus 3.3%) (19). Moreover, a cohort study by De Carvalho et al confirmed these associations in COVID-19 patients, finding that hyponatremia was an independent predictor of adverse outcomes with an adjusted OR of 2.77 (95% CI, 1.26–6.15) (22).

The pathophysiological mechanisms underlying the association between hyponatremia severity and COVID-19 outcomes involve multiple interconnected pathways that intensify with increasing electrolyte imbalance severity. The syndrome of inappropriate antidiuretic hormone secretion represents the most commonly reported mechanism, which occurs through COVID-19-induced cytokine storm, particularly elevated interleukin-6 (IL-6) levels that stimulate non-osmotic vasopressin release (23). As hyponatremia severity progresses from mild to moderate and severe forms, these inflammatory cascades become more pronounced, leading to greater physiological derangement (14). The severity-dependent relationship observed in our study reflects the dose-response nature of these pathophysiological processes, where moderate to severe hyponatremia indicates more extensive systemic involvement and greater inflammatory burden. Studies have demonstrated that hyponatremia correlates with more extensive pulmonary lesions on computed tomography (CT) imaging, suggesting that electrolyte severity parallels the degree of organ dysfunction (20, 24). The neurological complications associated with severe hyponatremia, including encephalopathy and cerebral edema and seizures, compound the already compromised neurological status in severe COVID-19 patients, potentially contributing to the observed higher mortality rates and increased need for intensive interventions in those with moderate to severe electrolyte imbalances (14, 25).

Overall, our findings demonstrating worse clinical outcomes in COVID-19 patients with moderate to severe hyponatremia compared to mild hyponatremia are strongly supported by existing literature and represent an important advancement in our understanding of electrolyte disturbances as prognostic indicators in COVID-19. The consistent evidence across multiple populations and healthcare systems establishes hyponatremia as a reliable biomarker for risk stratification, with the severity gradient providing additional clinical utility for identifying patients at the highest risk for ICU admission, mechanical ventilation, and mortality. These findings have immediate clinical implications for healthcare providers, supporting the use of admission sodium levels as a simple, readily available prognostic tool that can inform treatment decisions and resource allocation, particularly in resource-constrained settings where more sophisticated biomarkers may not be accessible. Future research should focus on whether early correction of moderate to severe hyponatremia can improve clinical outcomes and whether hyponatremia severity should be incorporated into existing COVID-19 severity scoring systems to enhance their predictive accuracy.

Conclusion

In conclusion, the results clearly indicate that in COVID-19 patients, severe or moderate hyponatremia is strongly associated with adverse clinical outcomes, including higher likelihoods of ICU admission, need for mechanical ventilation, and mortality. The ORs from logistic regression highlight that patients with severe or moderate hyponatremia have significantly increased risks compared to those with mild hyponatremia, even after adjusting for multiple potential confounders. These findings underscore the importance of monitoring and managing hyponatremia severity as part of comprehensive care in COVID-19, as it serves as a robust prognostic indicator of worsening disease and poor patient outcomes. Given the substantial impact on critical care requirements and mortality, early identification and appropriate intervention for hyponatremia could be pivotal in improving clinical management and reducing mortality in this population.

Limitations of the study

This study has several limitations inherent to its retrospective cohort design. The reliance on pre-existing medical records may have resulted in incomplete or inaccurate data collection, potentially introducing information bias. Selection bias is also possible, as only patients with complete records and baseline data were included, which may limit the generalizability of the findings. Additionally, the inability to control for all potential confounding variables due to missing or inconsistent data could affect the accuracy of associations between hyponatremia severity and clinical outcomes. The single-center setting of the study may further restrict the external validity of the results. Finally, causal relationships cannot be definitively established due to the observational nature of the study.

Acknowledgments

The authors gratefully acknowledge the dedicated support and cooperation of the staff and management at Khorshid Hospital in Isfahan, Iran, whose assistance and access to essential facilities were invaluable for the successful completion of this study. We also extend our sincere appreciation to Isfahan Endocrine and Metabolism Research Center and Isfahan University of Medical Sciences officials for their approval, expert guidance, and unwavering support throughout the research process.

Authors' contribution

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Conflicts of interest

The authors declare no conflict of interest.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of generative artificial intelligence (AI) and AI-assisted technologies in the writing process

While preparing this work, the authors utilized AI (Perplexity.ai) to refine grammar points and language style. Subsequently, they thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

The research was conducted under the tenets of the Declaration of Helsinki. This study was conducted at Khorshid Hospital and is part of the research project (No. 299077), approved by the ethics committee of Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, under the ethical code of IR.MUI.MED.REC.1399.462 (https://ethics.research.ac.ir/EthicsProposalView.php?id=147206) and approval date on September 6, 2020. Correspondingly, written informed consent was taken from all participants before any intervention. Besides, the authors have ultimately observed ethical issues (including plagiarism, data fabrication, and double publication).

Funding/Support

The funding was supported by the Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran (Grant #299077).

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