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Original Article

COVID-19: Hypernatremia is a significant predictor of mortality

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) pandemic spread rapidly, creating a worrisome scenario worldwide. In hospitalized patients, dysnatremia (hyponatremia and/or hypernatremia) is the most common electrolyte disturbance, reported in 30–40% of cases and associated with a poor prognosis. This study aimed to evaluate the association between dysnatremia and mortality in hospitalized patients infected with SARS-COV-2.

Methods: Retrospective longitudinal study that analyzed data from hospital records of 1,000 patients with COVID-19 (median age, 62.5 years; 57.1% men), including 109 (10.9%) deaths. Kaplan-Meier survival curves and Cox proportional hazard models with Hazard Ratio (HR) with 95% confidence intervals (95%CI) were applied to confirm the association between dysnatremia (hyponatremia and/or hypernatremia) and death.

Results: Hypernatremia was detected in 83 (76.1%) of the patients who died, with a cumulative reduction in survival ($p < 0.01$) and a 2.42-fold increased mortality risk (95%CI: 1.45–2.91). In the multivariable analysis, hypernatremia was the main factor associated with increased mortality (HR: 1.50; 95%CI: 1.23–1.81). Long length of stay (LOS) (HR: 1.54; 95%CI: 1.21–1.78), old age (HR: 1.63; 95%CI: 1.28–1.88), and chronic kidney disease (HR: 1.77; 95%CI: 1.21–3.30) were also associated with death.

Conclusion: Hypernatremia during hospitalization is an important risk factor for poor prognosis and an increased mortality risk. LOS, old age, and chronic kidney disease could also be used for risk stratification in patients with COVID-19.

Keywords: *COVID-19; dysnatremia; hypernatremia; death*

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INTRODUCTION

SARS-CoV-2 is a very transmissible microorganism with a high rate of dissemination in the last two years. SARS-CoV-2 current worldwide pandemic has already affected more than 660 million people with more than 6.7 million deaths. In Brazil, more than 35 million people were infected and presented COVID-19, causing several hospital admissions and more than 695,000 deaths[1].

COVID-19 is a systemic disease with a predominance of respiratory symptoms. Since it is a new disease, other short- and long-term effects have been studied in the current pandemic[2]. A previous study evaluated 24,410 COVID-19 patients and the main symptoms were fever (78.0%), cough (56.0%), and fatigue (31.0%), with 19% of all hospitalized patients requiring non-invasive ventilation and 9% requiring invasive ventilation[3]. Also, a high incidence of pulmonary edema and embolism has been observed as opposed to similar (viral) respiratory tract infections[4,5]. COVID-19-hospitalized patients also seem to present extra-pulmonary manifestations, such as water- and electrolytes-balance disorders[6-8].

Dysnatremia is the most common electrolyte disturbance that has been associated with a worse prognosis for patients hospitalized with COVID-19[9-14]. It was also previously demonstrated that hospitalized patients with community-acquired pneumonia caused by other pathogenic microorganisms presenting

hyponatremia and hypovolemia have a higher mortality risk[12]. Hyponatremia is also a condition with an incidence rate of up to 30% in hospitalized patients presenting poor prognosis in pneumonia outcomes[15-19]. More recently, hypernatremia during hospitalization was associated with a worse prognosis in COVID-19 patients[6,8,12]. This study aimed to evaluate the association of dysnatremia with death in COVID-19-hospitalized patients.

METHODS

Data collection

This is a retrospective longitudinal study carried out in Brazil, in the city of Porto Alegre, at the Hospital Moinhos de Vento. All participants signed an informed consent form and the study was previously approved by the clinical Research Ethics Committee, protocol No. 4.497.118. The study analyzed data from hospital records of 1,000 patients aged over 18 years hospitalized with COVID-19 confirmed by RT-PCR, from March to December 2020. All patients were routinely evaluated for plasma sodium concentration, which varied according to the clinical status and the length of stay (LOS). Patients with at least three sodium analyses were further selected to compare different concentrations, including the first one (performed during hospital admission) and the two presenting the highest and the lowest values during hospitalization. Sodium values were used to define the clinical category of the patient: hyponatremia (< 135 mEql/L), eunatremia (135–145 mEql/L), and hypernatremia (> 140 mEql/L)[17-19].

Statistical analysis

Kolmogorov-Smirnov with Lilliefors correction and Shapiro-Wilk tests were performed to evaluate the normality of the continuous data. All continuous data are presented as median followed by the interquartile range (IQRs), and differences between groups were tested with the Mann-Whitney U and Kruskal-Wallis (with Tukey' post hoc) tests. Categorical variables are reported as numbers (percentage) and a chi-square test was used for study comparisons. Kaplan-Meier survival curves were produced for serum sodium, LOS, and mortality with log-rank Mantel-Cox chi-square distribution. Cox proportional hazard models with covariates were used to assess the association of sodium concentrations with mortality. A priori, confounders considered in the multivariable analysis were LOS, sodium measures (admission, lowest, and highest), sex, age, and comorbidities (heart disease, hypertension, pulmonary diseases, diabetes, chronic kidney disease, cerebrovascular diseases, central nervous system diseases, cancer, and arthritis). Hazard ratio (HR) and 95% confidence intervals (95%CI) were estimated and significance was accepted at p-values < 0.05 for all tests. SPSS program, Version 23.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for data analysis.

RESULTS

Characteristics of COVID-19 patients

This study included 1,000 patients, 571 male (57.1%) and 429 female (42.9%), with a median age of 62.5 years (IQR: 47.0–75.0) and LOS of 8.0 days (IQR: 5.0–14.0). Of these patients, 335 (33.5%) were admitted to the intensive care unit (ICU) and 109 died (52.3% men and 47.7% women). Age and LOS were significantly higher in patients who died (p < 0.01). The most frequent comorbidities were hypertension (46.2%), diabetes (19.1%), pulmonary diseases (17.8%), heart diseases (17.6%), depression (8.7%), cancer (8.6%), chronic kidney disease (7.0%), central nervous system diseases (5.6%), cerebrovascular diseases (5.0%), arthritis (1.6%), and liver diseases (1.1%) (Table 1).

Table 1: Bivariate analysis of the variables between hospitalized patients who survived and those who died from COVID-19.

Characteristic	Total (n = 1000)		Patients who survived (n = 891)		Patients who died (n = 109)		p-values
	n	%	n	%	n	%	
Sex							
Female	429	42.9	377	42.3	52	47.7	0.28
Male	571	57.1	514	57.7	57	52.3	
Median age (IQR)	62.5 (47.0–75.0)		59.0 (45.0–71.0)		85.0 (80.0–91.0)		**< 0.01**
Median length of stay (IQR)	8.0 (5.0–14.0)		8.0 (5.0–12.0)		18.0 (10.0–36.0)		**< 0.01**
Comorbidities							
Heart diseases	176	17.6	127	14.3	49	45.0	**< 0.01**
Hypertension	462	46.2	390	43.8	72	66.1	**< 0.01**
Pulmonary diseases	178	17.8	151	16.9	27	24.8	**0.04**
Diabetes	191	19.1	157	17.6	34	31.2	**< 0.01**
Chronic Kidney diseases	70	7.0	42	4.7	28	25.7	**< 0.01**

Continua...

Tabela 2: Continuação.

Characteristic	Total (n = 1000)		Patients who survived (n = 891)		Patients who died (n = 109)		p-values
	n	%	n	%	n	%	
Liver diseases	11	1.1	9	1.0	2	1.8	0.43
Cerebrovascular diseases	50	5.0	29	3.3	21	19.3	**< 0.01**
CNS diseases	56	5.6	30	3.4	26	23.9	**< 0.01**
Cancer	86	8.6	67	7.5	19	17.4	**< 0.01**
Depression	87	8.7	80	9.0	7	6.4	0.37
Arthritis	16	1.6	12	1.3	4	3.7	0.06

IQR: Interquartile range; CNS: Central nervous systems.

Dysnatremia and death

Analyses of sodium concentrations were performed at three moments: 1) patient admission; 2) lowest sodium concentration during hospitalization; and 3) highest sodium concentration during hospitalization. In this way, we could separately assess the influence of dysnatremia in three different situations, estimating at which time sodium concentrations may influence the most the increase in patient's mortality risk.

In an overall analysis, at admission, 303 (31.2%) cases of hyponatremia, 651 (67.1%) of eunatremia, and 16 (1.6%) of hypernatremia were observed. At the lowest sodium concentration at hospitalization, 506 (51.8%) cases of hyponatremia, 467 (47.8%) of eunatremia, and 4 (0.4%) of hypernatremia were detected. At the highest sodium concentration at hospitalization, 46 (4.7%) cases of hyponatremia, 764 (78.2%) of eunatremia, and 167 (17.1%) of hypernatremia were identified (Figure 1).

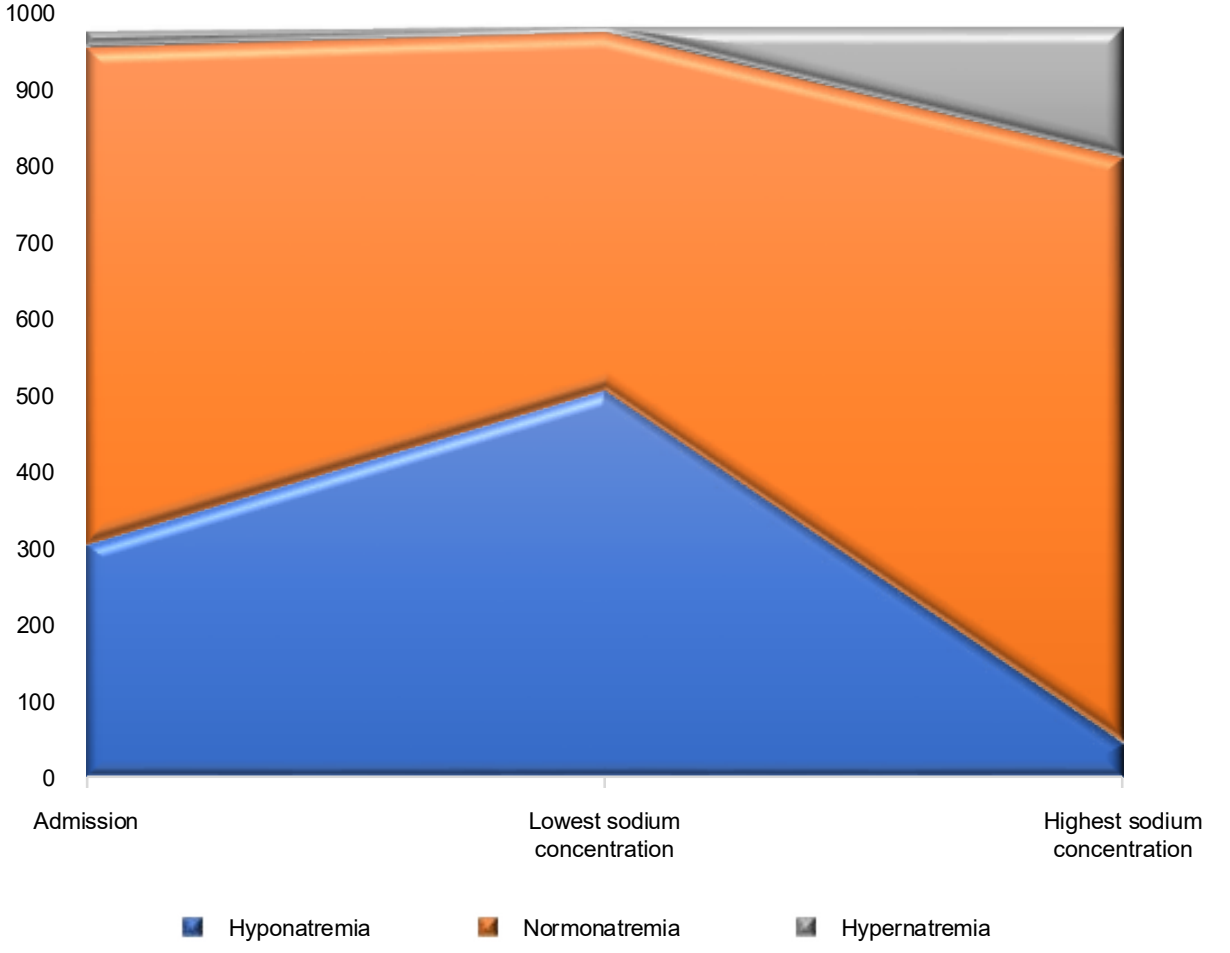

Figure 1: Overall absolute frequency of sodium concentration considering the three measurements performed in this study: at admission, lowest concentration, and highest concentration during hospitalization.

Hypernatremia was more frequent in patients who died than in survivors in admission (6.7% vs 1.0%) and during hospitalization (3.7% vs 0.0% at the lowest concentration, and 76.1% vs 9.7% at the highest concentration, $p < 0.01$) (Table 2). In the quantitative analysis, sodium concentrations were higher in patients who died than in survivors at admission (median: 138.0, IQR: 135.0–145.0 vs 137.0; IQR: 135.0–139.0, $p = 0.04$, Figure 2A) and at the highest concentration (median: 148.0, IQR: 146.0–153.0 vs 140.0; IQR: 138.0–142.0, $p < 0.01$, Figure 2C), respectively. However, there was no significant difference between the lowest sodium concentrations among patients who died compared with those who survived (median: 135.0, IQR: 132.0–137.0 vs 135.0, IQR: 133.0–137.0; $p = 0.80$) (Figure 2B).

Table 2: Bivariate analysis of the sodium concentration between patients who survived and those who died with COVID-19 in hospitalized patients.

Sodium concentration	Patients who survived (n = 891)		Patients who died (n = 109)		*p*-values
	n	%	n	%	
Admission concentration (n = 970)					
Hyponatremia	274	31.6	29	27.9	**< 0.01**
Eunatremia	583	67.3	68	65.4	
Hypernatremia	9	1.0	7	6.7	
Lowest concentration (n = 977)					
Hyponatremia	442	50.9	64	58.7	**< 0.01**
Eunatremia	426	49.1	41	37.6	
Hypernatremia	0	0	4	3.7	
Highest concentration (n = 977)					
Hyponatremia	43	5	3	2.8	**< 0.01**
Eunatremia	741	85.4	23	21.1	
Hypernatremia	84	9.7	83	76.1	

Significant *p*-values are highlighted in bold.

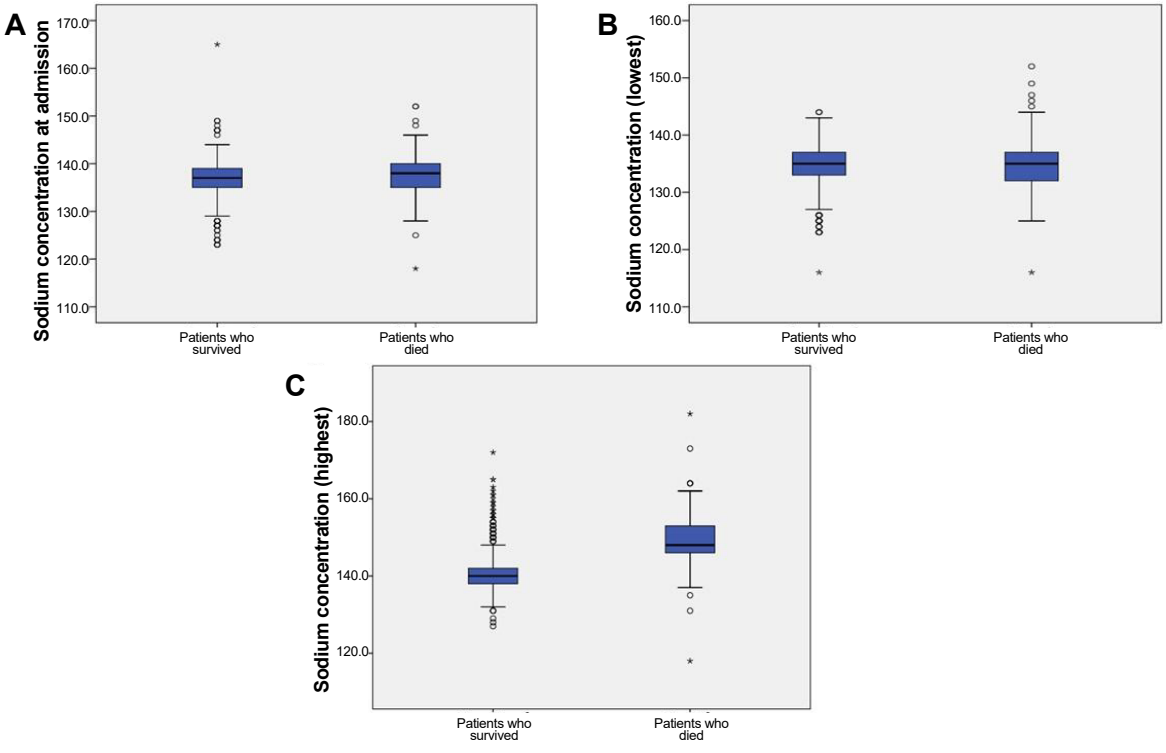

Figure 2: Comparison between sodium concentrations in patients who survived and died. A: Sodium concentrations at admission ($p = 0.04$); B: Lowest sodium concentration during hospitalization ($p = 0.80$). C: Highest sodium concentration during hospitalization ($p < 0.01$).

Length of stay (LOS) and dysnatremia

LOS was evaluated regarding sodium concentrations. At admission, the LOS had medians of 10.0 (IQR: 6.0–16.0) for hyponatremia, 7.0 (IQR: 5.0–13.0) for eunatremia, and 13.0 (IQR: 7.5–35.0) for hypernatremia (Figure 3A). At the lowest sodium concentration, the LOS was 11.0 (IQR: 7.0–21.0) for hyponatremia, 7.0 (IQR: 4.0–10.0) for eunatremia, and 7.5 (IQR: 2.5–10.5) for hypernatremia (Figure 3B). At the highest sodium concentration, the LOS was 7.0 (IQR: 5.0–10.0) for hyponatremia, 7.0 (IQR: 5.0–11.0) for eunatremia, and 29.0 (IQR: 16.0–48.0) for hypernatremia (Figure 3C). Patients with hypernatremia had longer LOS and the highest sodium concentration ($p < 0.01$). However, patients with hyponatremia had longer LOS in the evaluation of lowest sodium concentrations (Figure 3B).

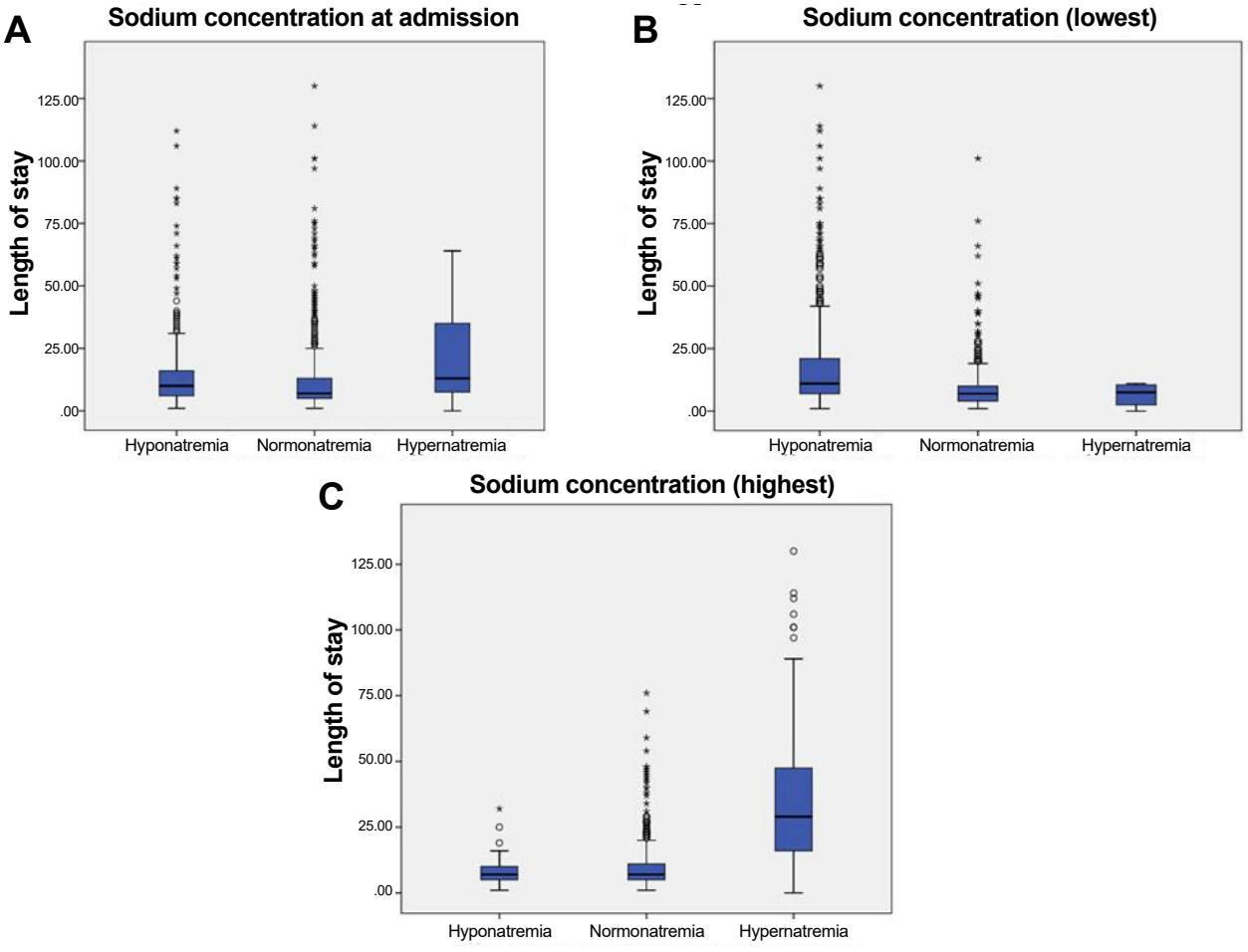

Figure 3: Comparison between sodium concentrations and length of stay. A: Sodium concentrations at admission ($p < 0.01$); B: Lowest sodium concentration ($p < 0.01$); C: Highest sodium concentration ($p < 0.01$).

Dysnatremia, LOS, and probability of death

In the Kaplan Meier analysis, the three sodium concentrations were evaluated (admission, lowest and highest concentrations) concerning the LOS. On admission, hypernatremia was present in seven out of 16 deaths (43.8%), showing a cumulative reduction in survival (log-rank Mantel-Cox = 5.88; $p = 0.05$) (Figure 4A). In the analysis with the lower sodium concentrations, hypernatremia was present in four out of four deaths (100%), which presented a cumulative reduction in survival (log-rank Mantel-Cox = 152.66; $p < 0.01$) (Figure 4B). In the analysis with higher sodium concentrations, hypernatremia was present in 83 out of 167 deaths (49.7%), presenting a cumulative reduction in survival (log-rank Mantel-Cox = 21.71; $p < 0.01$) (Figure 4C). Thus, as the most robust analysis, it indicates that hypernatremia significantly reduces survival and significantly increased the cumulative risk by 2.42 fold (95%CI: 1.45–2.91, $p < 0.01$) (Figure 5C).

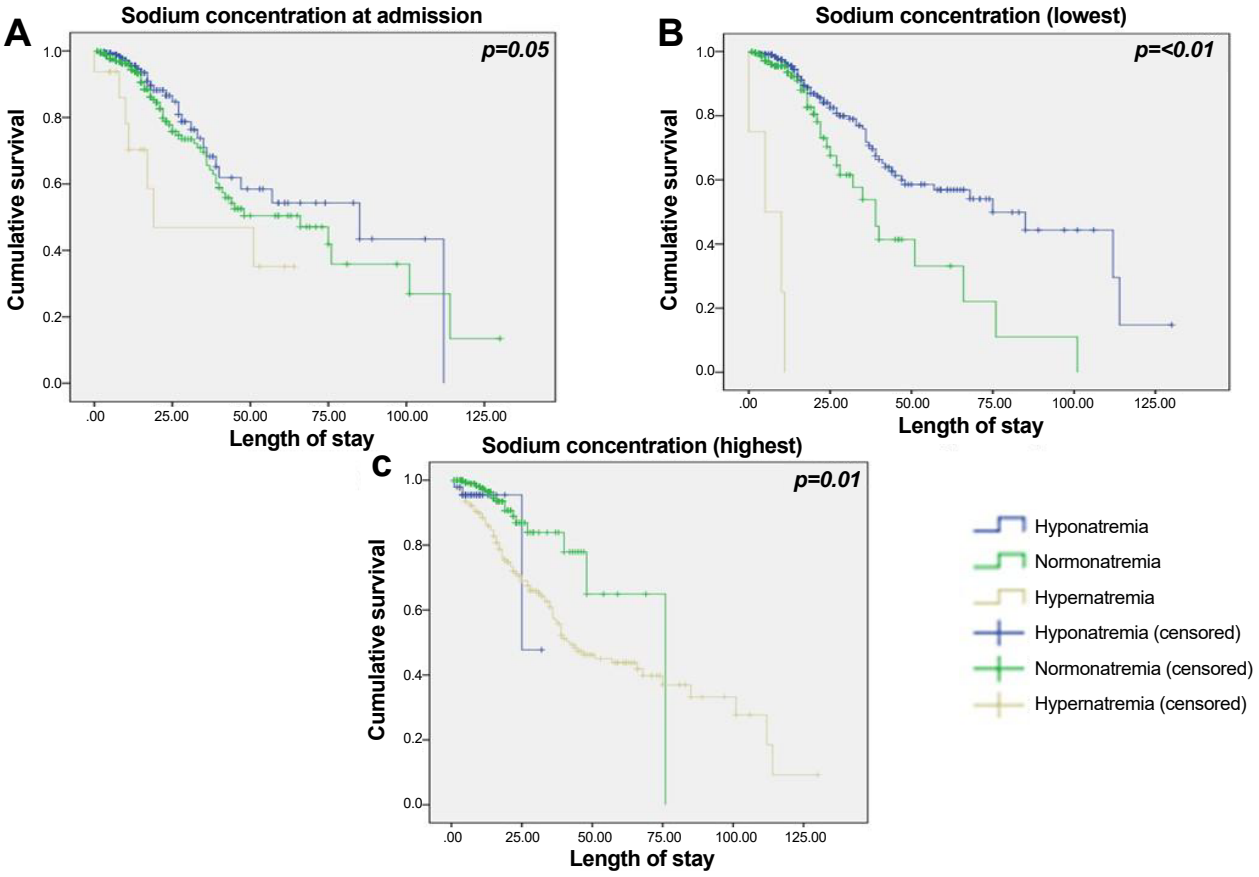

Figure 4: Cumulative survival based on serum sodium concentrations and length of stay. Kaplan-Meier curve showing probability of survival based on serum sodium status. A: Sodium concentrations at admission (p = 0.05); B: Lowest sodium concentration (p < 0.01); C: Highest sodium concentration (p < 0.01).

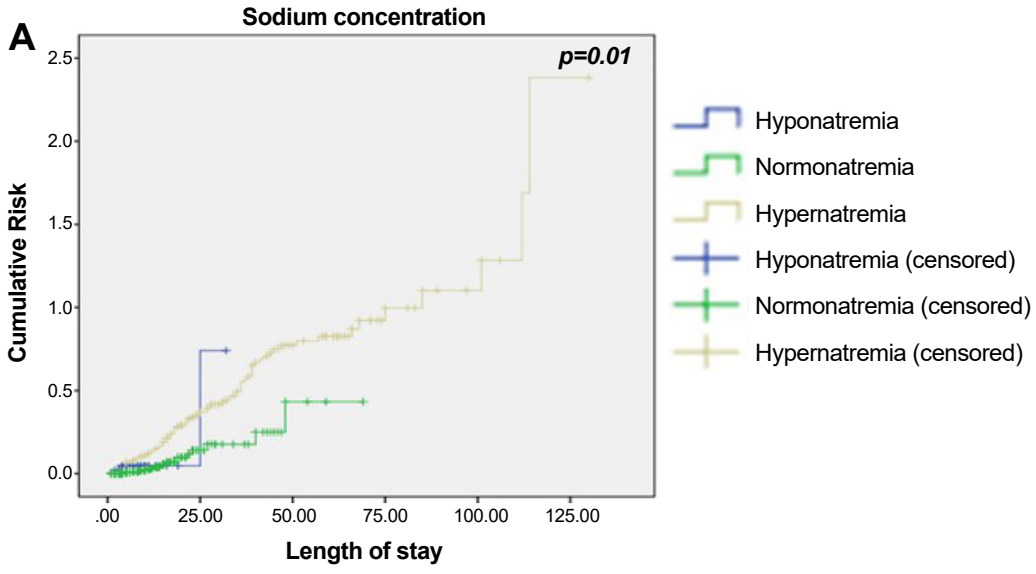

Figure 5: Cumulative risk based on serum sodium concentrations and length of stay. Kaplan-Meier curve showing probability of risk based on serum sodium in high concentrations.

Factors associated with COVID-19 death

In the multivariate analysis, the variables associated with mortality were: hypernatremia (HR: 1.50; 95%CI: 1.23–1.81; $p < 0.01$), longer LOS (HR: 1.54; 95%CI: 1.21–1.78; $p < 0.01$), older age (HR: 1.63; 95%CI: 1.28–1.88; $p < 0.01$), and chronic kidney disease (HR: 1.77; 95%CI: 1.21–3.30; $p < 0.01$) (Table 3). These variables were predictors of mortality, increasing the probability of COVID-19 death.

Table 3: Cox regression of risk factors with in-hospital mortality among COVID-19 patients.

Characteristic	Wald Chi-Square	Hazard Ratio	Lowest 95%CI	Highest 95% CI	*p*-values
Sodium (highest concentration during hospitalization)	**21.61**	**1.50**	**1.23**	**1.81**	**< 0.01**
Sodium (sodium concentration at admission)	0.10	1.00	0.95	1.05	0.99
Sodium (lowest concentration during hospitalization)	0.01	1.00	0.94	1.06	0.92
Length of stay (LOS)	**15.29**	**1.54**	**1.21**	**1.78**	**< 0.01**
Male sex	0.40	0.87	0.56	1.34	0.53
Age (scale)	**60.78**	**1.63**	**1.28**	**1.88**	**< 0.01**
Comorbidities					
Heart diseases	1.84	1.38	0.87	2.18	0.17
Hypertension	0.00	1.01	0.64	1.58	0.98
Pulmonary diseases	1.40	1.33	0.83	2.14	0.24
Diabetes	0.44	1.17	0.74	1.84	0.51
Kidney diseases	**67.41**	**1.77**	**1.21**	**3.30**	**< 0.01**
Cerebrovascular diseases	0.92	1.28	0.77	2.14	0.34
CNS	0.76	1.27	0.74	2.19	0.38
Cancer	0.21	1.09	0.63	1.87	0.77
Arthritis	0.28	1.15	0.40	3.35	0.79

Significant *p*-values are highlighted in bold. CNS: Central nervous system.

DISCUSSION

In this study, we observed an association between hypernatremia and a 50% higher mortality risk in multivariate analysis in patients admitted to hospital due to COVID-19. We evaluated several patients hospitalized with COVID-19 and detected that hypernatremia was largely frequent, affecting 76.1% of individuals who died. Our results are consistent with the literature to date[6,12-14,20].

Sodium level disturbance is the most common electrolyte abnormality in clinical practice. Clinical data reported that hypernatremia is present in approximately 2.0% of patients older than 60 years and in almost 4.8% of those older than 70 years admitted to the hospital[21]. In a retrospective study of 8,441 older patients admitted to the ICU, approximately 3.6% had hypernatremia at admission, and 15.3% developed hypernatremia during hospital stay; the mortality rate in those admitted with hypernatremia was approximately 33.3%, while patients without hypernatremia had a 18.1% mortality rate[22]. Hypernatremia has detrimental effects on various physiologic functions and was shown to be a risk factor for increased mortality in COVID-19 patients[20].

Additionally, longer LOS, older age, and chronic kidney disease were significant variables associated with death. The association between hypernatremia, chronic kidney disease, and longer LOS with mortality by COVID-19 was previously shown in a cohort study that evaluated 4,664 patients[7]. We detected these associations in this study, allowing a clinical characterization of COVID-19 patients in Southern Brazil. On the other hand, hyponatremia could indicate pulmonary involvement, whereas hypernatremia is associated with prolonged LOS and the need for intensive care/mechanical ventilation, particularly when resulting from prior hyponatremia[13].

Hypernatremia and chronic kidney disease independently with mortality. Previous studies showed that are indirect and direct adverse consequences of high dietary sodium on the kidney. In patients with chronic kidney disease, dietary sodium may have pivotal effects on hypertension control, proteinuria, immunosuppressant therapy, efficacy of antiproteinuric pharmacologic therapy, and maintaining an optimal volume status. Dietary sodium intake is an important

factor in patients with chronic kidney disease, including those receiving dialysis therapy or those who have received a kidney transplant[23-27].

Many studies confirmed that dysnatremia was associated with poor prognosis in patients hospitalized due to COVID-19[6,7,28-30]. Interestingly, patients hospitalized with COVID-19 frequently presented hyponatremia at admission; affecting more than 20% of patients, while hypernatremia was found in only 3.7%[7]. Another study found a 24.6% incidence of hyponatremia and 5.3% of hypernatremia in patients hospitalized with COVID-19. Also, hypernatremia detected two days after admission and exposure to hypernatremia at any time during hospitalization were associated with an increased mortality risk, compared to eunatremia. Hyponatremia at admission was linked with a 2.18-fold increase in the likelihood of needing ventilatory support[12]. These results showed the pivotal importance of sodium measures in patients hospitalized, including COVID-19 patients, mainly in ICU patients.

This study has important limitations. This is a retrospective study and the consequential relationship between dysnatremia and mortality cannot be asserted. It is also not possible to evaluate the effect of hypernatremia treatment on the prognosis. Finally, the serum sodium was not corrected for glycemia. The large number of patients is the main advantage of this study, all of whom were hospitalized with RT-PCR-confirmed COVID-19. Also, we followed-up all patients during the entire hospitalization. In addition, we considered all sodium measurements during follow-up, computing the highest and lowest sodium values. Thus, the stratification of patients on arrival at the hospital (considering clinical and laboratory tests) makes it possible to identify those who are at greater risk of an unfavorable clinical outcome and makes it possible to improve monitoring and availability of resources for them[28,30].

In conclusion, hypernatremia during hospitalization is an important risk factor for poor prognosis, which is independently associated with a greater mortality risk. Physicians treating COVID-19 should be aware that patients with hypernatremia are at a higher risk for death than those with eunatremic.

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Conflicts of interest

The authors declare no conflicts of interest.

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