

# Hypernatremia increases mortality in patients admitted by COVID-19: A Retrospective longitudinal study with 1000 patients

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## Research Article

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# Abstract

Coronavirus disease 2019 (COVID-19) pandemic spread rapidly and this scenario is concerning worldwide. In hospitalized patients, dysnatremia (hyponatremia and/or hypernatremia) is the most common electrolyte disturbance, being reported in 30–40% of cases and associated with a poor prognosis. This retrospective longitudinal study aimed to evaluate the association of dysnatremia with mortality in hospitalized patients infected with COVID-19. We analyzed data from hospital records of 1000 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. Hypernatremia was detected in 83 (76.1%) of the patients who died, with a cumulative reduction in survival ( $p < 0.01$ ) and an increased risk for death by 2.4 fold (95%CI 1.4–2.9). In the multivariable analysis, hypernatremia was the main factor associated with increased mortality (HR:1.50; 95%CI:1.23–1.81). Other factors also associated with death were 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 kidney disease (HR:1.77; 95%CI:1.21–3.30). Hypernatremia during hospitalization is an important risk factor for poor prognosis and an increased risk (2.4) of mortality. LOS, old age, and kidney disease could also be used for risk stratification in patients with COVID-19.

## Introduction

Severe acute respiratory syndrome – coronavirus 2 (SARS-CoV-2) is a very transmissible microorganism with a high rate of dissemination in the last two years [1]. SARS-CoV2 current worldwide pandemic has already affected more than 295 million people with more than 5 million deaths. In Brazil, more than 22 million people were infected and presented COVID-19, generating a large number of hospital admissions and more than 600,000 deaths [2].

COVID-19 is a systemic disease with a predominance of respiratory symptoms. Since it is a new disease, other short-term and long-term effects have been studied in the current pandemic [3]. A previous study evaluated 24,410 COVID-19 patients and the main symptoms were fever (78%), cough (56%), and fatigue (31%), with 19% of all hospitalized patients requiring non-invasive ventilation and 9% requiring invasive ventilation [4]. Also, a high incidence of pulmonary edema and embolism has been observed as opposed to similar (viral) respiratory tract infections [5,6]. COVID-19 hospitalized patients seem to present extra-pulmonary manifestations too, such as water and electrolytes disorders [7–9].

Dysnatremia (serum sodium level  $> 145\text{mmol/L}$  or  $< 135\text{mmol/L}$ ) is the most common electrolyte disturbance that has been associated with a worse prognosis for hospitalized COVID-19 patients [10–15]. It was also previously demonstrated that hospitalized patients with community-acquired pneumonia (CAP) caused by other pathogenic microorganisms presenting hyponatremia and hypovolemia have a higher risk of death [13]. Hyponatremia is also a disturbance with an incidence rate of up to 30% in hospitalized patients presenting poor prognosis in pneumonia outcome [16–20]. More recently,

hypernatremia during the hospitalization period was associated with a worse prognosis in COVID-19 patients [7,8,13]. The present study aimed to evaluate the association of dysnatremia with a high risk of death in COVID-19 hospitalized patients.

## Methods

### Data Collection

This was 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 this study was approved from Institutional Review Boards of National Health Council of Brazil (approval number 4.497.118). The study analyzed data from hospital records of 1000 patients over 18 years of age, regardless of gender, ethnicity, previous comorbidities, and length of hospital stay hospitalized with COVID-19, confirmed by RT-PCR, between March and December 2020. All patients were routinely evaluated for plasma sodium concentration and the number of the dosages 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 dosages, including the first one (performed in the hospital admission) and the two presenting the highest and the lowest values. Sodium values were used to define the clinical category of the patient: hyponatremia (< 135 mmol/L), eunatremia (135–145 mmol/L), and hypernatremia (> 140 mmol/L) [18,20].

### 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 posthoc) 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, length of stay (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, lower, and higher), sex, age, and comorbidities (heart disease, hypertension, pulmonary, diabetes, kidney, cerebrovascular disease, central nervous system disease, 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, Version 23.0 for Windows (SPSS Inc., Chicago, IL, USA), and R software (R Foundation for Statistical Computing, Vienna, Austria; <<http://www.R-project.org>>) were used for data analysis.

## Results

### Baseline Characteristics of COVID-19 patients

This study included 1000 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 ICU and 109 died (52.3% men and 47.7% women;  $p = 0.28$ ). Age and LOS were significantly higher in patients who died ( $p < 0.01$ ). The most common comorbidities were hypertension (46.2%), diabetes (19.1%), pulmonary disease (17.8%), heart disease (17.6%), depression (8.7%), cancer (8.6%), kidney disease (7.0%), central nervous system disease (5.6%), cerebrovascular disease (5.0%), arthritis (1.6%), and liver disease (1.1%). Hypertension, diabetes, pulmonary disease, heart disease, cancer, kidney disease, central nervous system disease, and cerebrovascular disease were significantly more frequent in patients who died than in those who survived (Table 1).

Table 1

Bivariate analysis of the characteristics between survived and dead patients with COVID-19 included in this study

Variables	Total (n = 1000)		Survived (n = 891)		Dead (n = 109)		p-values
	n	%	n	%	n	%	
Sex							
<i>Female</i>	429	42.9	377	42.3	52	47.7	0.28
<i>Male</i>	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)		<b>&lt; 0.01</b>
Median length of stay (IQR)	8.0 (5.0–14.0)		8.0 (5.0–12.0)		18.0 (10.0–36.0)		<b>&lt; 0.01</b>
Comorbidities							
<i>Heart disease</i>	176	17.6	127	14.3	49	45.0	<b>&lt; 0.01</b>
<i>Hypertension</i>	462	46.2	390	43.8	72	66.1	<b>&lt; 0.01</b>
<i>Pulmonary disease</i>	178	17.8	151	16.9	27	24.8	<b>0.04</b>
<i>Diabetes</i>	191	19.1	157	17.6	34	31.2	<b>&lt; 0.01</b>
<i>Chronic Kidney disease</i>	70	7.0	42	4.7	28	25.7	<b>&lt; 0.01</b>
<i>Liver disease</i>	11	1.1	9	1.0	2	1.8	0.43
<i>Cerebrovascular disease</i>	50	5.0	29	3.3	21	19.3	<b>&lt; 0.01</b>
<i>CNS disease</i>	56	5.6	30	3.4	26	23.9	<b>&lt; 0.01</b>
<i>Cancer</i>	86	8.6	67	7.5	19	17.4	<b>&lt; 0.01</b>
<i>Depression</i>	87	8.7	80	9.0	7	6.4	0.37
<i>Arthritis</i>	16	1.6	12	1.3	4	3.7	0.06
IQR: Interquartile range.							
CNS: Central Nervous Systems.							

## Association between dysnatremia and death

Hypernatremia was significantly more frequent in deaths than in survivors in the three measurements (6.7% vs 1.0% on admission, 3.7% vs 0.0% at the lowest concentration, and 76.1% vs 9.7% at the highest concentration,  $p < 0.01$ ) (**Table S1**). In the quantitative analysis, sodium concentrations were statistically higher in patients who died than in survivors at admission (median: 138.0, IQR: 135.0–145.0 vs median: 137.0; IQR: 135.0–139.0,  $p = 0.04$ , **Table S2**) and at the highest concentration (median: 148.0, IQR: 146.0–

153.0 vs median: 140.0; IQR: 138.0–142.0,  $p < 0.01$ , Fig. 1, **Table S2**), respectively. However, there was no significant difference between low sodium concentrations among patients who died compared with those who survived (median: 135.0, IQR: 132.0–137.0 vs median: 135.0, IQR: 133.0–137.0;  $p = 0.80$ ) (**Table S2**).

## **Length of stay (LOS) and sodium concentration**

LOS was evaluated concerning sodium concentrations. On 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 (**Table S3**). 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) hypernatremia (**Table S3**). 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 (Fig. 2, **Table S3**). Patients with hypernatremia had higher LOS at admission and the highest sodium concentration ( $p < 0.01$ ) (Fig. 2). However, patients with hyponatremia had significantly more LOS in the evaluation of lower sodium concentrations (**Table S3**).

## **Changes in sodium concentration, LOS, and risk of death**

In the Kaplan Meier analysis, the three sodium concentrations were evaluated (admission, lower and higher concentrations) concerning the LOS. On admission, hypernatremia was present in 7 deaths (6.7%), of which showed a cumulative reduction in survival that lasted 72 days ( $p = 0.05$ ). In the analysis with the lower sodium concentrations, hypernatremia was present in 4 deaths (3.7%), of which they presented a cumulative reduction in survival that lasted only 10 days ( $p < 0.01$ ). In the analysis with higher sodium concentrations, hypernatremia was present in 83 deaths (76.1%), of which presented a cumulative reduction in survival that lasted 127 days ( $p < 0.01$ ) (**Table S4**), being the most robust analysis, indicating that hypernatremia significantly reduces survival and significantly increased the cumulative risk by 2.4 fold (95%CI: 1.4–2.9,  $p < 0.01$ ) (Fig. 3).

## **Hypernatremia, the longer length of stay, older age, and kidney disease are associated independently with COVID-19 mortality**

In the multivariate analysis by Cox regression, the variables independently 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 kidney disease (HR: 1.77; 95%CI: 1.21–3.30;  $p < 0.01$ ) (Table 2). These factors show great potential as predictors of mortality, increasing the probability of death by 50% for hypernatremia, 54% for longer LOS, 63% for older age, and 77% for kidney disease.

Table 2  
Multivariable associations of risk factors with in-hospital mortality among COVID-19 patients

Variables	Wald Chi-Square	Hazard Ratio	lower CI95%	Higher CI95%	<i>p</i> -values
<b>Sodium concentration (higher)</b>	<b>21.61</b>	<b>1.50</b>	<b>1.23</b>	<b>1.81</b>	<b>&lt; 0.01</b>
Sodium concentration (admission)	0.10	1.00	0.95	1.05	0.99
Sodium concentration (lower)	0.01	1.00	0.94	1.06	0.92
<b>Length of stay (LOS)</b>	<b>15.29</b>	<b>1.54</b>	<b>1.21</b>	<b>1.78</b>	<b>&lt; 0.01</b>
Sex male	0.40	0.87	0.56	1.34	0.53
<b>Age (scale)</b>	<b>60.78</b>	<b>1.63</b>	<b>1.28</b>	<b>1.88</b>	<b>&lt; 0.01</b>
Comorbidities					
Heart disease	1.84	1.38	0.87	2.18	0.17
Hypertension	0.00	1.01	0.64	1.58	0.98
Pulmonar	1.40	1.33	0.83	2.14	0.24
Diabetes	0.44	1.17	0.74	1.84	0.51
<b>Kidney</b>	<b>67.41</b>	<b>1.77</b>	<b>1.21</b>	<b>3.30</b>	<b>&lt; 0.01</b>
Cerebrovascular disease	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 <i>p</i> -values are highlighted in bold.					
CNS: Central Nervous System.					

## Discussion

Dysnatremia is associated with increased mortality in patients with pneumonia caused by COVID-19 [8]. In the present study, hypernatremia was associated with a 50% higher risk of mortality in multivariate analysis in patients admitted by COVID-19. We evaluated 1,000 patients hospitalized with COVID-19 and detected that hypernatremia was largely frequent, affecting 76.1% of individuals who died. Our results are consistent with those of other relevant investigations to date [7,13–15,21].

The sodium levels 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 65 years but in

almost 4.8% of those older than 75 years admitted to the hospital [22]. In a retrospective study involving 8,441 older patients admitted to the ICU, approximately 3.6% had hypernatremia on admission, and 15.3% developed hypernatremia during hospitalization; the mortality rate in those admitted with hypernatremia was approximately 33.3%, while patients without hypernatremia had a mortality rate of 18.1% [23].

In a previous study that evaluated 111,545 sodium measures, hypernatremic and hyponatremic patients showed higher LOS than eunatremic. The mortality rates of hyponatremic and hypernatremic inpatients were 19% and 48%, respectively. Disease severity as measured by LOS and mortality indicated these critical limits should not be broadened [24]. Hypernatremia has detrimental effects on various physiologic functions and was shown to be an independent risk factor for increased mortality in COVID-19 patients [25]. These results are in agreement with our findings, where hypernatremia and older age were associated with mortality by COVID-19.

Additionally, longer LOS, older age, and kidney disease were significant predictors for death. The association between hypernatremia, kidney disease, and higher LOS with mortality by COVID-19 was previously shown in a previous multicentric cohort that evaluated 4,664 patients [8]. These associations were observed in the present study, allowing a clinical characterization of COVID-19 patients in southern Brazil, reproducing the findings of risk factors for mortality. 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 [14].

In this COVID-19 cohort, hypernatremia and kidney disease were associated independently with mortality. Previous studies showed that is indirect and direct adverse consequences of high dietary sodium on the kidney. In patients with kidney disease, dietary sodium may have pivotal effects on hypertension control, proteinuria, immunosuppressant therapy, the efficacy of antiproteinuric pharmacologic therapy, and maintaining an optimal volume status. Dietary sodium intake is an important factor in patients with all stages of chronic kidney disease, counting those receiving dialysis therapy or those who have received a kidney transplant [25–28].

Many studies confirmed that both dysnatremia were independently associated with poor prognosis in patients hospitalized by COVID-19 [7,8,28,29]. Interestingly, in patients hospitalized with COVID-19, was detected that admittance hyponatremia was frequent; affecting more than 20% of patients, for a total of 957 subjects, and hypernatremia was found in only 3.7%, a total of 174 subjects [8]. Another study, including 488 subjects with COVID-19, found an incidence of 24.6% of hyponatremia and 5.3% of hypernatremia [13]. Also, hypernatremia detected two days after admission and exposure to hypernatremia at any time point during hospitalization were associated with a 2.34-fold and 3.05-fold increased risk of death, respectively, compared to eunatremia. Hyponatremia at admission was linked with a 2.18-fold increase in the likelihood of needing ventilatory support [13]. 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 assess the effect of hypernatremia treatment on the prognosis. Finally, the serum sodium was not corrected for glycemia. The main advantage of the study is a large number of patients were included, all of whom were admitted with RT-PCR-confirmed COVID-19. Also, all patients were followed-up throughout the entire period of hospitalization. In addition, all sodium measurements during follow-up were considered, computing the highest and lowest sodium values. In this sense, the stratification of patients on arrival at the hospital (considering clinical and laboratory tests, for example) 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 [1,28].

In conclusion, hypernatremia during hospitalization is an important risk factor for poor prognosis, being associated independently with a greater risk of mortality. Also, the other factors associated with COVID-19 mortality were longer LOS, older age, and kidney disease. Serum sodium values, longer LOS, older age, and kidney disease could be used for risk stratification in patients with COVID-19. Physicians treating COVID-19 should be made aware that patients with dysnatremia are at a higher risk for death than those presenting with eunatremic. Intervention studies would be needed to ascertain whether correction of dysnatremia could improve clinical evolution.

## Declarations

### Authorship

Jonas M. Wolf, Franciele P. Berlesi, Tiane C. dos Santos, Andressa B. Glaeser, Juçara G. Maccari, and Luiz A. Nasi designed the study. Jonas M. Wolf performed the statistical analyses. Jonas M. Wolf, Franciele P. Berlesi, Tiane C. dos Santos, Andressa B. Glaeser, Vagner R. Lunge, Juçara G. Maccari, and Luiz A. Nasi wrote the first draft of the manuscript and contributed to the literature review and discussion of results. All authors contributed to and have approved the final manuscript.

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### Conflicts of interest

The authors declare no conflicts of interest.

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## Figures

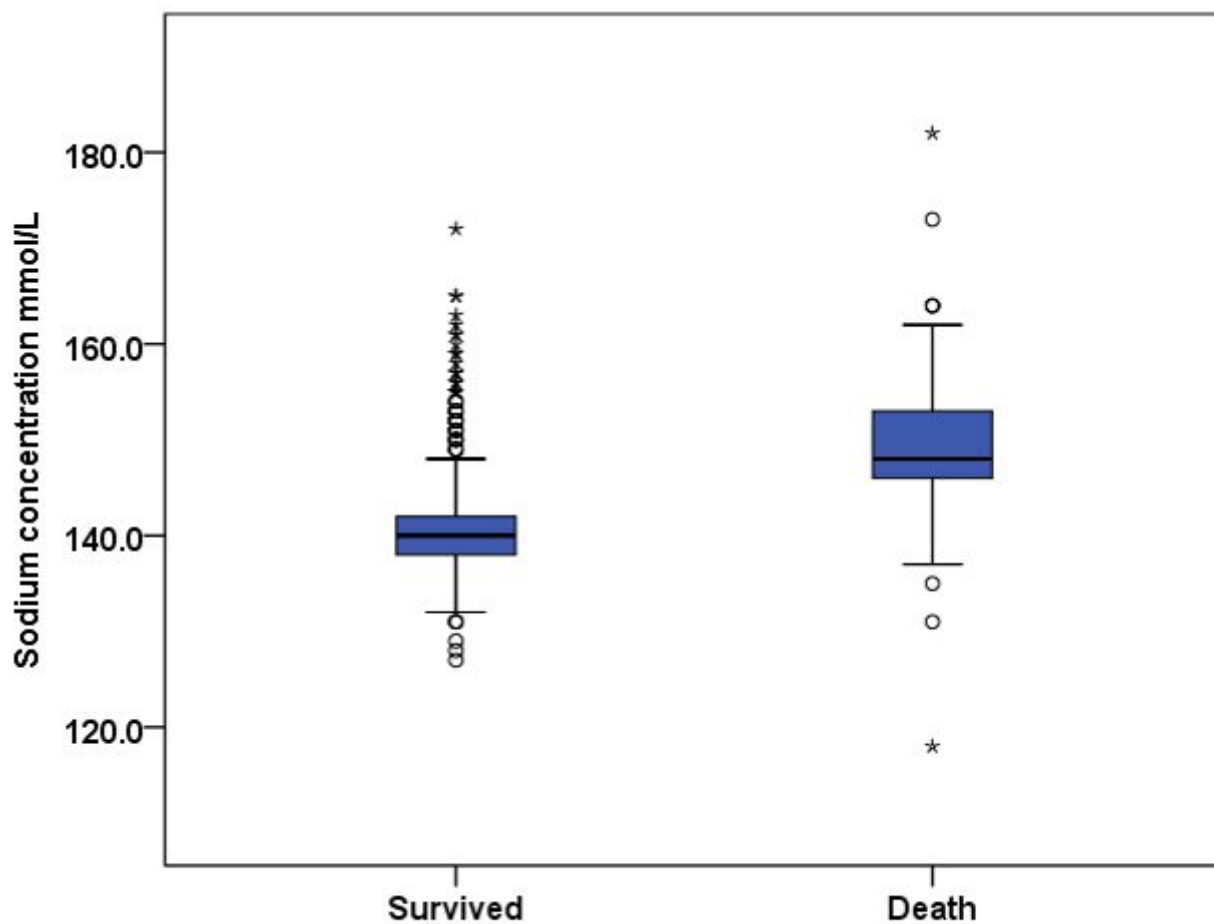


Figure 1

Comparison between sodium concentrations in survived and death in patients with COVID-19.

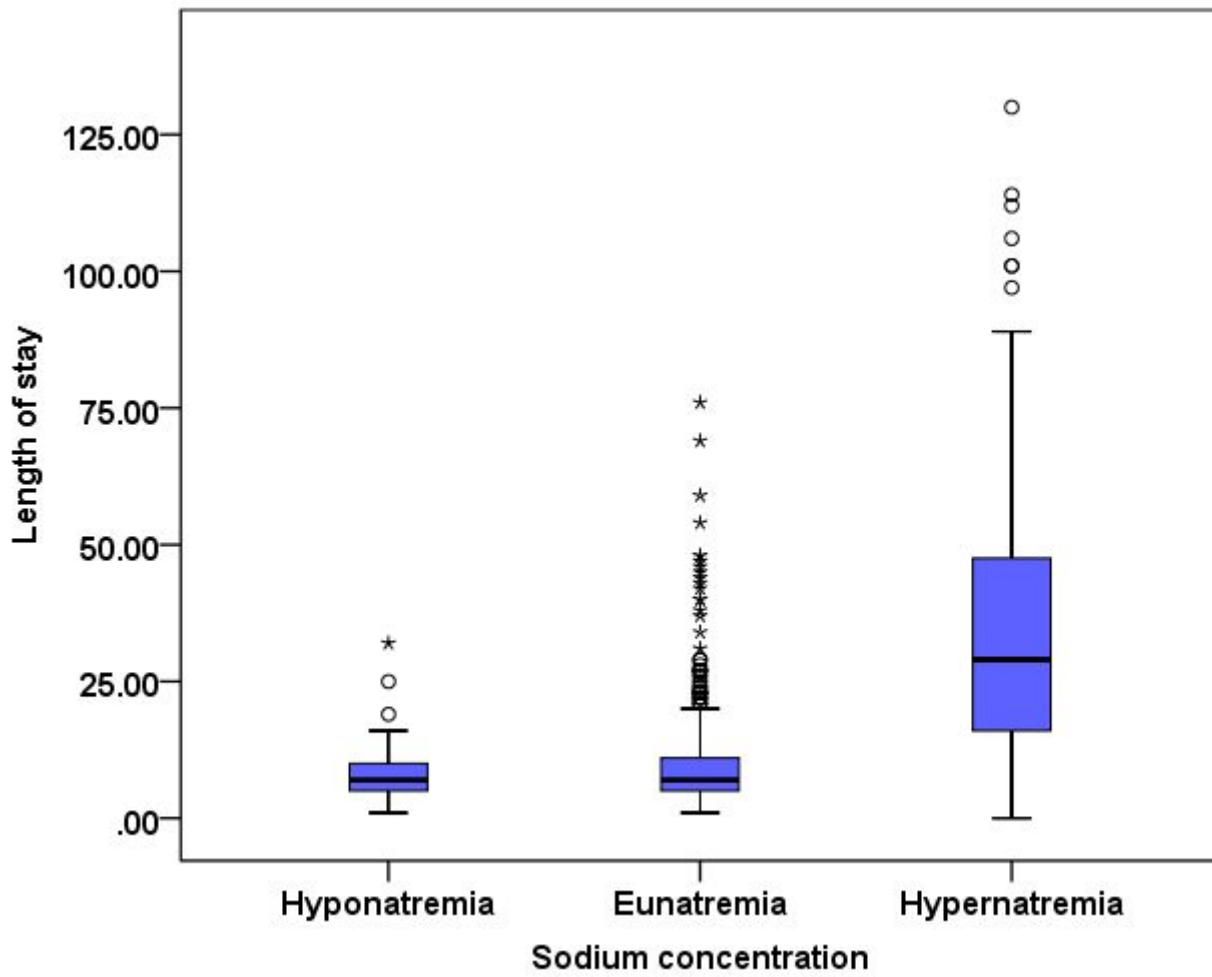


Figure 2

Comparison between sodium concentrations and length of stay in patients with COVID-19.

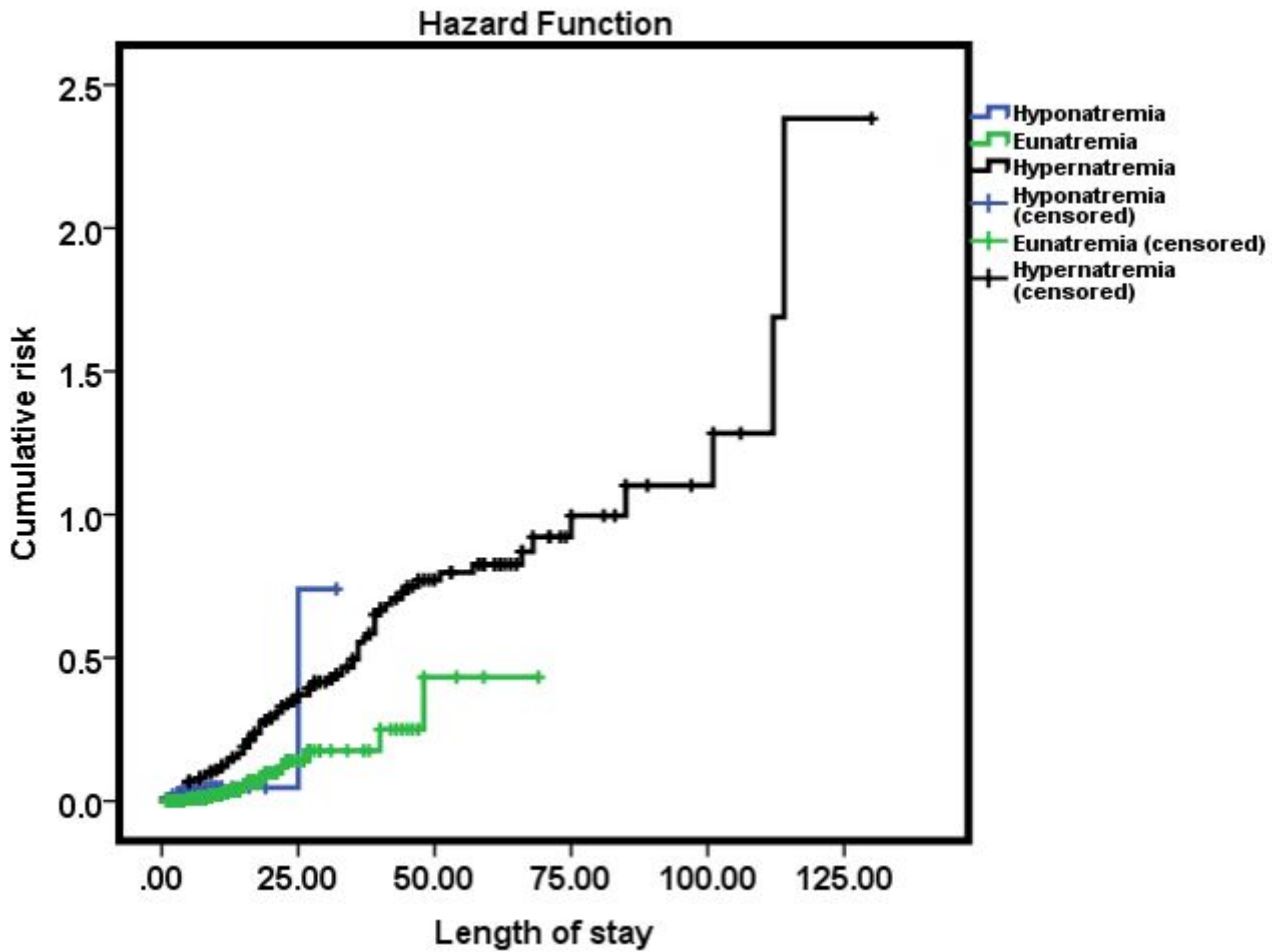


Figure 3

Kaplan-Meier curve showing probability of death risk based on serum sodium status in patients with COVID-19.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [TableS1.docx](#)
- [TableS2.docx](#)
- [TableS3.docx](#)
- [TableS4.docx](#)