Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1080704
J Health Sci Med 2022; 5(3): 799-804

Predictors and outcome of hyponatremia in patients with COVID 19: a single-center experience

Ercan Türkmen[1], Mahmut Altındal[2], Ferah Taran[1], Tuba Kuruoğlu[3], Aydın Deveci[3], Melih Akpunar[4], Seyyid Bilal Açıkgöz[5], Nurhan Köksal[6]

[1]Ondokuz Mayıs University, Faculty of Medicine, Department of Nephrology, Internal Medicine, Samsun, Turkey
[2]Altınbaş University, Faculty of Medicine, Department of Internal Medicine, Division of Nephrology, Istanbul, Turkey
[3]Ondokuz Mayıs University, Faculty of Medicine, Department of Clinical Microbiology and Infectious Diseases, Samsun, Turkey
[4]Ondokuz Mayıs University, Faculty of Medicine, Department of Internal Medicine, Samsun, Turkey
[5]Ondokuz Mayıs University, Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Samsun, Turkey
[6]Ondokuz Mayıs University, Faculty of Medicine, Department of Chest Diseases, Samsun, Turkey

Cite this article as: Türkmen E, Altındal M, Taran F, et al. Predictors and outcome of hyponatremia in patients with COVID 19: a single-center experience. J Health Sci Med 2022; 5(3): 799-804.

ABSTRACT

Aim: Hyponatremia (serum sodium <135 mEq/L) portends a worse prognosis in patients with community-acquired pneumonia. Data regarding the outcome of hyponatremia in hospitalized COVID-19 patients are insufficient and controversial. The present study aimed to identify the predictors of hyponatremia and its impact on clinical outcome measures in hospitalized COVID-19 patients.

Material and Method: We conducted a retrospective study on 787 adult patients with SARS-CoV-2 infection admitted to a university hospital between March 10, 2020, and December 15, 2020, February. Demographic and laboratory features, comorbid diseases, medications, radiology results, and clinical outcome measures of the patients were obtained retrospectively from their medical records.

Findings: One hundred fifty-nine (20.2%) patients out of 787 had hyponatremia. Hyponatremia was mild (sodium: 130 -134 mEq/L) in majority of cases (n=124). The severity of pneumonia (p=0.013) and having diabetes (p < 0.001) were the independent predictors of hyponatremia at the time of admission. The median length of hospital stay (LOS) was longer in patients with hyponatremia than patients with normonatremia (10 days vs. 8 days, p < 0.001). In multivariate analysis, hyponatremia was significantly associated with ICU admission or the need for mechanical ventilation (adjusted OR, 1.72; 95% confidence interval [95% CI], 1.03 to 2.85; p=0.036). The severity of pneumonia, hemoglobin and lactate dehydrogenase levels, neutrophil-to-lymphocyte ratio (NLR), and body temperature were also associated with ICU admission or the need for mechanical ventilation. The oxygen saturation, male sex, serum albumin, NLR, and the ICU admission but not the hyponatremia on admission were significantly related to mortality.

Conclusion: Hyponatremia on admission predicts ICU admission or mechanic ventilation need but not mortality in COVID-19 patients, and it should be considered in risk stratification.

Keywords: Hyponatremia, COVID-19, outcomes

INTRODUCTION

Since it has been officially declared by World Health Organization (WHO) at the beginning of 2020, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has had a significant impact on health and economy worldwide (1-5). Hyponatremia (serum sodium <135 mEq/L), even when mild, was found to be associated with mortality in a diverse spectrum of diseases, including cancer (6-9). Hyponatremia was linked to increased mortality and length of hospital stay in patients with community-acquired pneumonia (10-12). Hyponatremia was related to intensive care unit (ICU) admission and death in patients with SARS-CoV-1 (13). Older age, obesity, comorbid diseases, immunosuppressive use, and some laboratory variables (Lymphocytes count, C-reactive protein, lactate dehydrogenases, ferritin, vs.) have been associated with mortality and a worse outcome in patients with coronavirus disease 2019 (COVID-19) (4,5,14). Studies

Corresponding Author: Ercan Türkmen, ercan.turkmen1907@gmail.com
Received: 08.10.2021 **Accepted:** 07.01.2022

This work is licensed under a Creative Commons Attribution 4.0 International License.

dealing with the impact of hyponatremia on outcomes and mortality in COVID-19 patients revealed conflicting results. The risk stratification is of supreme importance during pandemic given the limited hospital resources; whether hyponatremia at admission should be added to risk stratification tools is unknown. In the present study, conducted in a relatively large cohort of patients hospitalized for COVID-19, we aimed to investigate the association of hyponatremia with in-hospital mortality, length of hospital stay, ICU admission, and the need for mechanical ventilation. We also aimed to examine the risk factors for the development of hyponatremia in COVID-19 patients.

MATERIAL AND METHOD

The present study was designed retrospectively. This study was approved by Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 26.08.2021, Decision No: 2021/408). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients with real-time reverse transcription-polymerase chain reaction (RT-PCR) confirmed SARS-CoV-2 infection who were hospitalized at Ondokuz Mayıs University Hospital between March 10, 2020, and December 15, 2020, were enrolled in this study. Patients under the age of 18 were excluded. Normonatremic (serum sodium level 135-145 mEq/L) and hyponatremic (serum sodium level < 135 mEq/L) patients were included in the study. Hyponatremia was classified as mild (Na 130-134 mEq/L) and moderate-severe (Na < 130 mEq/L). Since hypernatremia could affect mortality, patients with hypernatremia (Na ≥ 146 mEq/L) were excluded. Patients with pseudo-hyponatremia due to elevated serum glucose, triglycerides, or osmotic agents were excluded from the statistical analysis.

The demographic (age, sex) and laboratory features (including serum sodium, potassium, blood urea nitrogen (BUN), creatinine, glucose, alanine aminotransferase (ALT), lactate dehydrogenase (LDH), troponin I, D-dimer, albumin, hemoglobin, white blood cell and lymphocyte counts, mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), platelet counts, C-reactive protein (CRP), procalcitonin); clinical findings (volume status, fever, oxygen saturation) comorbid diseases (diabetes mellitus (DM), hypertension, previous or current malignancy, coronary artery disease (CAD), heart failure, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), any chronic liver disease), all medications (including renin-angiotensin-aldosterone system blockers and diuretics), radiology results, and clinical outcome measures of the patients (in-hospital mortality, length of hospital stay, ICU admission, or ventilator need) were obtained from medical records of the patients. The presence and extent of pneumonia were assessed by thoracic computerized tomography (CT), which was performed at the time of admission in all patients. The severity of pneumonia was classified as none, unilateral or bilateral pneumonia. All patients were treated according to the protocols released by the Turkish Ministry of Health.

Statistical Analysis

Data were analysed by using IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA). Kolmogorov-Smirnov test was used to determine whether the variables showed a normal distribution or not. Normally distributed numerical variables were specified as mean±standard deviation, and the numerical variables not showing normal distribution were expressed as median (Interquartile range, IQR). Categorical data were expressed as numbers and percentages (%). Student's t-test or Mann-Whitney U-test was used to compare between-group differences in numerical variables depending upon normal distribution. The Chi-square test or Fisher's Exact test was performed to assess categorical variables. Multivariate logistic regression models were used to explore the risk factors associated with mortality and the need for ICU or mechanical ventilation. A p-value of less than 0.05 was accepted as statistically significant.

RESULTS

A total of 787 patients were included in the study. One hundred fifty-nine (20.2%) patients had hyponatremia. One hundred twenty-four of hyponatremic individuals (78%) had a mild hyponatremia. The median age was 61 (22) years and 427 patients (54.3%) were female. Hypertension was the most common comorbid disease observed in 309 (39.3%) patients. **Table 1** lists the demographic and clinical features of the patients with hyponatremia and normonatremia. In multivariable analysis, the severity of pneumonia (adjusted OR, 1.66; 95% confidence interval (95% CI), 1.11 to 2.48; p < 0.013) and having diabetes (adjusted OR, 2.40; 95% confidence interval (95% CI), 1.49 to 3.86; p < 0.001) were significantly associated with hyponatremia (**Table 2**). The median length of hospital stay (LOS) was significantly longer in patients with hyponatremia (10 days vs. 8 days, p < 0.001) than patients with normonatremia (**Table 3**). Two hundred twelve (26.9%) patients required either ICU admission or mechanical ventilation. During follow-up, the need for mechanical ventilation was more common in patients with hyponatremia than patients with normonatremia (45.3% vs. 22.3%; p < 0.001). In multivariate analysis, hyponatremia was significantly associated with ICU admission or the need for mechanical ventilation (adjusted OR, 1.72; 95% confidence interval (95% CI),

1.03 to 2.85; p=0.036). The median length of hospital stay, the need for mechanical ventilation or ICU admission, and the mortality rate did not differ significantly between patients with mild hyponatremia and moderate to severe hyponatremia (serum Na < 130). Other important factors independently associated with ICU admission or need for mechanical ventilation were severity of pneumonia, hemoglobin and LDH levels, neutrophil-to-lymphocyte ratio (NLR), and body temperature (**Table 4**). Overall, 102 of 787 (13%) patients died in hospital. The patients with hyponatremia had a higher mortality rate compared to patients with normonatremia (24.5% vs. 10%; p < 0.001). Nevertheless, in multivariate analyses, oxygen saturation, male sex, serum albumin, NLR, and the ICU admission but not the hyponatremia were significantly associated with mortality (**Table 5**).

Table 2. Univariate and multivariate analysis of factors associated with hyponatremia

	Univariate		Multivariate	
Variable	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Age (years)	1.02 (1.01-1.04)	<0.001	1.01 (0.99-1.02)	0.589
Sex (male)	1.61 (1.13-2.31)	0.009	1.32 (0.81-2.13)	0.263
Diabetes mellitus (yes)	2.60 (1.79-3.79)	<0.001	2.40 (1.49-3.86)	<0.001*
CAD (yes)	1.80 (1.10-2.93)	0.018	1.07 (0.55-2.07)	0.840
CKD (yes)	1.91 (1.15-3.17)	0.013	1.24 (0.64-2.41)	0.532
Fever (yes)	1.44 (1.09-2.06)	0.045	1.29 (0.81-2.06)	0.283
Oxygen saturation	0.96 (0.94-0.98)	<0.001	0.99 (0.96-1.02)	0.598
Pneumonia severity classified as none, unilateral, bilateral	1.77 (1.33-2.37)	<0.001	1.66 (1.11-2.48)	0.013*
Albumin	0.44 (0.31-0.61)	<0.001	0.76 (0.47-1.23)	0.256
Hemoglobin	0.94 (0.86-1.01)	0.106	1.06 (0.94-1.20)	0.340
NLR	1.03 (1.02-1.05)	<0.001	1.01 (0.99-1.03)	0.265
CRP	1.01 (1.00-1.01)	<0.001	1.00 (1.00-1.01)	0.209
Procalcitonin	1.06 (1.02-1.11)	0.005	1.01 (0.97-1.05)	0.555
LDH	1.00 (1.00-1.00)	0.003	1.00 (0.99-1.00)	0.752
D-dimer	1.25 (1.00-1.00)	0.248	1.00 (1.00-1.00)	0.166

CAD: Coronary artery disease; CKD: Chronic kidney disease; NLR: Neutrophil to lymphocyte ratio; CRP: C-reactive protein; LDH: Lactate dehydrogenase; OR: Odds ratio; (95% CI): 95% Confidential interval; *p<0.05: Statistically significant parameters

Table 4. Risk factors for intensive care unit admission or mechanical ventilation need in COVID-19 patients

	ICU admission or mechanical ventilation need			
	Univariate		Multivariate	
Variable	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Hyponatremia	2.80 (1.90-4.13)	<0.001	1.72 (1.04-2.86)	0.036*
Procalcitonin	1.08 (1.03-1.13)	0.003	0.98 (0.94-1.01)	0.134
CRP	1.01 (1.01-1.01)	<0.001	1.00 (1.00-1.01)	0.051*
NLR	1.07 (1.05-1.09)	<0.001	1.03 (1.00-1.05)	0.035*
Pneumonia severity	3.80 (2.31-6.26)	<0.001	1.66 (1.09-2.45)	0.018*
Body temperature	2.03 (1.40-2.89)	<0.001	1.55 (1.17-2.06)	0.002*
LDH	1.00 (1.00-1.00)	<0.001	1. 00 (1.00-1.00)	0.006*
Hemoglobin	0.76 (0.70-0.83)	<0.001	0.84 (0.75-0.95)	0.005*

ICU: Intensive care unit; CRP: C-reactive protein; NLR: Neutrophil to lymphocyte ratio; LDH: Lactate dehydrogenase; OR: Odds ratio; (95% CI): 95% Confidential interval. *p<0.05: Statistically significant parameters

Table 1. Comorbidities, demographic and clinical characteristics of hypo- and normonatremic patients

	Hyponatremia (n=159)	Normonatremia (n=628)	p
	n (%)		
Sex (male)	101 (63.5)	326 (76.3)	0.009*
Diabetes mellitus	61 (38.4)	121 (19.3)	<0.001*
Hypertension	69 (43.4)	240 (38.2)	0.232
Malignancy	19 (11.9)	49 (7.8)	0.096
CAD	27 (17)	64 (10.2)	0.017*
Heart failure	12 (7.5)	26 (4.1)	0.073
CKD	25 (15.7)	56 (8.9)	0.012*
COPD	13 (8.2)	58 (9.2)	0.677
RAAS blocker	51 (32.1)	170 (27.0)	0.210
Diuretic use	47 (29.6)	141 (22.4)	0.098
Thiazide	27 (17)	93 (14.8)	
Furosemide	22 (13.8)	61 (9.7)	
Spironolactone	6 (3.8)	12 (1.9)	
Pneumonia on CT			<0.001*
None	14 (8.8)	137 (21.8)	
Unilateral	4 (2.5)	35 (5.6)	
Bilateral	141 (88.7)	457 (72.7)	
	Median (IQR)		
Age, years	60 (22)	64 (21)	<0.001*
Fever‡ (%)	66 (41.5)	208 (33.1)	0.047*
Hemoglobin, gr/dL	12 (2.6)	12.7 (2.9)	0.029*
White blood cell, 10^3/mm³	7.2 (5.5)	6.3 (3.7)	0.001*
Lymphocyte, 10^3/mm³	0.98 (0.87)	1.20 (0.82)	0.007*
MPV, fL	10.1 (1.4)	10.2 (1.1)	0.919
NLR	6.73 (10.18)	3.59 (5.74)	<0.001*
Platelet, 10^3/mm³	225 (110)	204 (111)	0.397
Oxygene saturation, %	94 (8)	96 (5.0)	<0.001*
CRP, mg/dL	89.1 (117.3)	34.8 (89.2)	<0.001*
Procalcitonin, ng/mL	0.22 (0.35)	0.08 (0.11)	<0.001*
LDH, IU/L	347 (233)	275 (170)	<0.001*
D-dimer, ng/mL	1109 (1917)	568 (869)	<0.001*
Troponin I, ng/mL	0.1 (0.0)	0.1 (0.0)	0.301
Glucose, mg/dL	128 (81)	123 (68)	0.371
BUN, mg/dL	17.7 (16.2)	16.9 (14.7)	0.090
Creatinine, mg/dL	0.95 (0.55)	0.97 (0.48)	0.629
Sodium, mEq/L	132 (3)	139 (4)	<0.001*
Potassium, mEq/L	4.3 (0.8)	4.3 (0.7)	0.676
ALT, IU/L	25 (26)	22 (25)	0.053
	Mean±SD		
Albumin, gr/dL	3.3±0.6	3.6±0.6	<0.001*

IQR: Interquartile range; SD: Standard deviation, CAD: Coronary artery disease; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; RAAS: Renin-angiotensin-aldosterone system; MPV: Mean platelet volume; NLR: Neutrophil to lymphocyte ratio; LDH: Lactate dehydrogenase; CRP: C-reactive protein; BUN: Blood urea nitrogen; ALT: Alanine aminotransferase; Fever‡>37.5 °C; CT: Computerized tomography; *p<0.05: Statistically significant parameters

Table 3. Outcome stratified by serum sodium level

	Hyponatremia (n=159)	Normonatremia (n=628)	p
Length of hospital stay, day	10 (9)	8 (8)	<0.001*
ICU admission or ventilator need, n (%)	72 (45.3)	140 (22.3)	<0.001*
Death, n (%)	39 (24.5)	63 (10.0)	<0.001*

ICU: Intensive care unit; *p<0.05: Statistically significant parameters

Table 5. Risk factors for mortality in COVID-19 patients

Variable	Mortality			
	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Sex (male)	1.36 (0.89-2.08)	0.157	2.30 (1.07-4.96)	0.034*
Hyponatremia	2.92 (1.87-4.55)	<0.001	1.45 (0.75-2.80)	0.268
Procalcitonin	1.11 (1.05-1.18)	<0.001	1.05 (0.99-1.12)	0.084
CRP	1.01 (1.01-1.01)	<0.001	1.00 (1.00-1.01)	0.135
NLR	1.06 (1.04-1.09)	<0.001	1.03 (1.00-1.06)	0.035*
Albumin	0.15 (0.10-0.24)	<0.001	0.34 (0.17-0.71)	0.004*
Oxygen saturation	0.90 (0.87-0.92)	<0.001	0.95 (0.91-0.99)	0.017*
LDH	1.00 (1.00-1.00)	<0.001	1.00 (1.00-1.00)	0.637
Hemoglobin	0.79 (0.72-0.87)	<0.001	0.88 (0.76-1.03)	0.122
ICU admission	14.88 (9.24-23.85)	<0.001	8.08 (3.65-17.87)	<0.001*

CRP: C-reactive protein; NLR: Neutrophil to lymphocyte ratio; LDH: Lactate dehydrogenase; ICU: Intensive care unit; OR: Odds ratio; (95% CI): 95% Confidential interval. *p<0.05: Statistically significant parameters

DISCUSSION

In the present study, we examined the predictors of hyponatremia on admission and its outcome in patients hospitalized for COVID-19. Our findings showed that diabetes mellitus and the severity of pneumonia were the independent predictors of the development of hyponatremia at the time of admission. Additionally, although we have not found a correlation between increased mortality and hyponatremia, we have documented that hyponatremia was associated with longer in-hospital stay and a higher incidence of ICU admission or ventilator need.

Hyponatremia is the most common electrolyte abnormality in hospitalized patients. It is identified in 30% of patients with community-acquired pneumonia (11,15). Although previous smaller studies had reported a higher incidence of hyponatremia in patients with COVID-19, more recent and more extensive studies had revealed a lower incidence that ranges from 20% to 45% (16-21). Leong et al. (13) have documented a similar incidence of hyponatremia (29%) in previous SARS epidemic in Hong Kong. We have found hyponatremia in 159 patients (20.2%), most of whom had mild hyponatremia in line with the previous reports.

The pathogenic mechanisms for the development of hyponatremia in patients with community-acquired pneumonia remain uncertain. Inappropriate ADH secretion stimulated by pain, hypovolemia, nausea, and certain medications has been postulated causative factors. The International Health Outcome Predictive Evaluation for COVID-19 (HOPE-COVID-19) registry found that chronic kidney disease, bilateral pneumonia, tachypnea, male sex, and at age ≥ 70 years were associated with hyponatremia (17). Similar to our findings, a French study revealed that pulmonary lesions on the thoracic CT-scan performed during admission were significantly more extensive in the hyponatremic patients with COVID-19 compared to the normonatremic group (22). Inflammation and increased IL-6 levels have been linked with non-osmotic ADH secretion (23). Bernie et al. (24,25) documented an inverse relationship between IL-6 levels and serum Na. IL-6 levels were available only for a limited number of patients in our study, so we did not include them in statistical analysis. Although we have found significantly higher serum levels of inflammatory markers including CRP, procalcitonin, and NLR in patients with hyponatremia than the normonatremic group, these markers were not associated with hyponatremia in multivariate analysis.

In the present study, we noted that the patient group with hyponatremia had a longer length of hospital stay than the normonatremic group. The former group needed ICU admission and mechanical ventilation more frequently. In a longitudinal retrospective cohort study, Tzoulis et al. (18) documented that hyponatremia at admission was linked with a 2.2-fold increase in the likelihood of needing ventilator support but not associated with length of hospital stay in patients with COVID-19. Similar to our findings, Atilla et al. (19) found that hyponatremia was associated with length of hospital stay, need for mechanical ventilation, and ICU admission in COVID-19 patients. In a retrospective, multicenter, observational cohort study of 4645 COVID-19 patients from New York, investigators concluded that hyponatremia was associated with increased risk of encephalopathy and mechanical ventilation. Comorbid diseases, serum creatinine, D-dimer, procalcitonin, ferritin, IL-6 levels, lymphocyte, and neutrophil numbers have been linked with the severity and the prognosis of COVID-19 infection (3,26-30). We believe that risk stratification is essential in the efficient use of hospital resources during the pandemic. We suggest that hyponatremia at the time of admission could be added to risk stratification tools for predicting clinical outcomes in COVID-19 patients.

We have found a relatively high in-hospital mortality (13%) rate for the entire cohort. The data considering the association of increased mortality and hyponatremia in COVID-19 patients are controversial (17-21). Our results revealed a higher mortality rate in patients with hyponatremia than patients with normonatremia. However, hyponatremia was not found to be an independent predictor of mortality in multivariate analysis. Nevertheless, most of our patients had mild hyponatremia, and our results regarding mortality and hyponatremia relationship in COVID-19 patients should be interpreted in the appropriate context.

Although we included a relatively large number of patients from a single center in our study and analyzed the effect of multiple factors besides hyponatremia

on clinical outcome measures, several limitations of our study deserve mention. First, the study design was retrospective. Second, we did not include the patients in the hyponatremia group if they were normonatremic at admission but developed hyponatremia during hospitalization. Third, we could only document volume status and the exact cause of hyponatremia in a minority of cases, given the study's retrospective nature and the lack of urine studies and serum osmolality. Finally, follow-up serum Na levels were not included in the analysis.

CONCLUSION

Our results indicated that hyponatremia is quite common among hospitalized patients with COVID-19. We have shown that hyponatremia was associated with more extended in-hospital stay and a higher incidence of ICU admission or ventilator need. Diabetes and the severity of pneumonia were found to be the independent predictors of hyponatremia in COVID-19 patients. We suggest that hyponatremia at the time of admission could be added to risk stratification tools in patients hospitalized for COVID-19.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 26.08.2021, Decision No: 2021/408).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in china: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020; 323: 1239-42.
2. COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med 2021; 47: 60-73.
3. Suleyman G, Fadel RA, Malette KM, et al. Clinical characteristics and morbidity associated with coronavirus disease 2019 in a series of patients in Metropolitan Detroit. JAMA Netw Open 2020; 3: e2012270.
4. Bellan M, Patti G, Hayden E, et al. Fatality rate and predictors of mortality in an Italian cohort of hospitalized COVID-19 patients. Sci Rep 2020; 10: 20731.
5. Kim L, Garg S, O'Halloran A, et al. Risk factors for intensive care unit admission and in-hospital mortality among hospitalized adults identified through the US coronavirus disease 2019 (COVID-19)-associated hospitalization surveillance network (COVID-NET). Clin Infect Dis 2021; 72: 206-14.
6. Fucà G, Mariani L, Lo Vullo S, et al. Weighing the prognostic role of hyponatremia in hospitalized patients with metastatic solid tumors: the HYPNOSIS study. Sci Rep 2019; 9: 12993.
7. Sun L, Hou Y, Xiao Q, Du Y. Association of serum sodium and risk of all-cause mortality in patients with chronic kidney disease: A meta-analysis and sysematic review. Sci Rep 2017; 7: 15949.
8. Kovesdy CP, Lott EH, Lu JL, et al. Hyponatremia, hypernatremia, and mortality in patients with chronic kidney disease with and without congestive heart failure. Circulation 2012; 125: 677-84.
9. Sato N, Gheorghiade M, Kajimoto K, et al; ATTEND Investigators. Hyponatremia and in-hospital mortality in patients admitted for heart failure (from the ATTEND registry). Am J Cardiol 2013; 111: 1019-25.
10. Tokgöz Akyil F, Akyil M, Çoban Ağca M, et al. Hyponatremia prolongs hospital stay and hypernatremia better predicts mortality than hyponatremia in hospitalized patients with community-acquired pneumonia. Tuberk Toraks 2019; 67: 239-47.
11. Nair V, Niederman MS, Masani N, Fishbane S. Hyponatremia in community-acquired pneumonia. Am J Nephrol 2007; 27: 184-90.
12. Ravioli S, Gygli R, Funk GC, Exadaktylos A, Lindner G. Prevalence and impact on outcome of sodium and potassium disorders in patients with community-acquired pneumonia: A retrospective analysis. Eur J Intern Med 2021; 85: 63-7.
13. Leong HN, Chan KP, Oon LL, et al. Clinical and laboratory findings of SARS in Singapore. Ann Acad Med Singap 2006; 35: 332-9.
14. Nurlu N, Ozturk OO, Cat A, Altunok ES, Gumus A. Could some laboratory parameters predict mortality in COVID-19? Clin Lab 2021; 67.
15. Krüger S, Ewig S, Giersdorf S, et al. CAPNETZ study group. Dysnatremia, vasopressin, atrial natriuretic peptide and mortality in patients with community-acquired pneumonia: results from the german competence network CAPNETZ. Respir Med 2014; 108: 1696-705.
16. Aggarwal S, Garcia-Telles N, Aggarwal G, Lavie C, Lippi G, Henry BM. Clinical features, laboratory characteristics, and outcomes of patients hospitalized with coronavirus disease 2019 (COVID-19): Early report from the United States. Diagnosis (Berl) 2020; 7: 91-6.
17. Ruiz-Sánchez JG, Núñez-Gil IJ, Cuesta M, et al. Prognostic impact of hyponatremia and hypernatremia in COVID-19 pneumonia. A HOPE-COVID-19 (Health Outcome Predictive Evaluation for COVID-19) Registry Analysis. Front Endocrinol (Lausanne) 2020; 11: 599255.
18. Tzoulis P, Waung JA, Bagkeris E, et al. Dysnatremia is a predictor for morbidity and mortality in hospitalized patients with COVID-19. J Clin Endocrinol Metab 2021; 106: 1637-48.
19. Atila C, Sailer CO, Bassetti S, et al. Prevalence and outcome of dysnatremia in patients with COVID-19 compared to controls. Eur J Endocrinol 2021; 184: 409-18.
20. Frontera JA, Valdes E, Huang J, et al. Prevalence and impact of hyponatremia in patients with coronavirus disease 2019 in New York City. Crit Care Med 2020; 48: 1211-7.
21. Hirsch JS, Uppal NN, Sharma P, et al. Prevalence and outcomes of hyponatremia and hypernatremia in patients hospitalized with COVID-19. Nephrol Dial Transplant 2021; 36: 1135-8.

22. De Carvalho H, Letellier T, Karakachoff M, et al. Hyponatremia is associated with poor outcome in COVID-19. J Nephrol 2021; 34: 991-8.
23. Mastorakos G, Weber JS, Magiakou MA, Gunn H, Chrousos GP. Hypothalamic-pituitary-adrenal axis activation and stimulation of systemic vasopressin secretion by recombinant interleukin-6 in humans: potential implications for the syndrome of inappropriate vasopressin secretion. J Clin Endocrinol Metab 1994; 79: 934-9.
24. Berni A, Malandrino D, Parenti G, Maggi M, Poggesi L, Peri A. Hyponatremia, IL-6, and SARS-CoV-2 (COVID-19) infection: may all fit together? J Endocrinol Invest 2020; 43: 1137-9.
25. Berni A, Malandrino D, Corona G, et al. Serum sodium alterations in SARS CoV-2 (COVID-19) infection: impact on patient outcome. Eur J Endocrinol 2021; 185: 137-44.
26. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med 2020; 58: 1021-8.
27. Imam Z, Odish F, Gill I, et al. Older age and comorbidity are independent mortality predictors in a large cohort of 1305 COVID-19 patients in Michigan, United States. J Intern Med 2020; 288: 469-76.
28. Alwafi H, Naser AY, Qanash S, et al. Predictors of length of hospital stay, mortality, and outcomes among hospitalised COVID-19 patients in Saudi Arabia: A Cross-Sectional Study. J Multidiscip Healthc 2021; 14: 839-52.
29. Liao D, Zhou F, Luo L, et al. Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study. Lancet Haematol 2020; 7: 671-8.
30. Bannaga AS, Tabuso M, Farrugia A, et al. C-reactive protein and albumin association with mortality of hospitalised SARS-CoV-2 patients: a tertiary hospital experience. Clin Med (Lond) 2020; 20: 463-7.