Araştırma Makalesi
Research Article

Hyponatremia: More than just an electrolyte for COVID-19 patients

HİPONATREMİ: COVID-19 HASTALARINDA ELEKTROLİTTEN DAHA FAZLASI

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ABSTRACT

Aim: Hyponatremia is the most common electrolyte disturbance among infections, especially with pneumonia. Here, we aimed to analyze the presence of hyponatremia among COVID-19 patients along with its relation to the in-hospital mortality.

Materials and methods: The patients were divided into two groups COVID-19 negative and positive and also with and without pneumonia. The association between hyponatremia and in-hospital mortality from any cause was evaluated with univariate and multivariate cox regression model.

Results: A total of 636 patients, a mean age of 50± 18 years, 48 % of the female with a median duration of hospitalization of 5.5 (IQR, 2,11) days were included. Of those 553 (87%) were detected COVID-19 PCR positive and 298 (47%) of those with pneumonia. The median serum sodium concentration was lower in COVID-19 PCR positive patients [134 (IQR, 130,137) mEq/L] compared to negatives [139 (IQR, 136, 140) mEq/L] (p<0.001). The median serum sodium levels were significantly lower in patients with pneumonia [136 (IQR, 133.138) mEq/L] than without pneumonia [139 (IQR, 137, 145) mEq/L] (p<0.001). All deaths occurred in patients with pneumonia [(n=40 (13.4%)]. Hyponatremia was significantly associated with in-hospital mortality on unadjusted (OR, 3.85, 95%CI: 1.73, 8.53, P<0.001) and adjusted [OR, 3.58, 95% CI: 1.58, 8.1, P=0.002] Cox models.

Conclusion: Hyponatremia at admission is prevalent and an independent risk factor for in-hospital mortality among COVID-19 patients particularly those with pneumonia. It might be an important laboratory clue for these patients' diagnosis and survivals.

Keywords: COVID-19, hyponatremia, pneumonia, in-hospital mortality

ÖZ

Amaç: Hiponatremi özellikle pnömonisi olan hasta grubunda sık rastlanan bir elektrolit anomalisidir. Biz bu çalışmada, COVID-19 pozitif hasta grubunda hiponatremi sıklığı ile mortalite arasındaki ilişkiyi değerlendirmeyi hedefledik.

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Metod: Hastalar COVID-19 PCR pozitif, negatif ve COVID-19 PCR pozitif hastalar ise kendi içinde pnömoni olan ve olmayanlar olarak gruplara ayrıldı. Hiponatremi ve mortalite arasındaki ilişki tek değişkenli ve çok değişkenli COX regresyon analizi ile incelendi.

Sonuç: Ortalama yaşı 50± 18 yıl olan 636 hasta çalışmaya dahil edildi. Hastaların % 48'i kadın ve ortanca hastanede yatış süreleri ise 5,5 (IQR, 2,11) gündü. Hastaların 553 (% 87) 'ünde COVID-19 PCR pozitif, ve pozitif hastaların 298'inde (%47) pnömoni saptandı. Ortanca serum sodyum konsantrasyonu COVID-19 PCR pozitif [134 (IQR, 130,137) mEq/L] hastalarda, negatif [139 (IQR, 136, 140) mEq/L] ($p<0.001$) olan hastalara göre düşük saptandı. COVID-19 PCR pozitif hasta grubu içinde pnömoni hasta grubunda [136 (IQR, 133,138) mEq/L]serum sodyum konsantrasyonu pnömoni olmayan[139 (IQR, 137, 145) mEq/L] ($p<0.001$) gruba göre istatistiksel olarak anlamlı düzeyde düşük saptandı Tüm ölümler pnömoni ile başvuran hasta grubunda izlendi [(n=40 (%13.4)]. Hiponatremi hem tek değişkenli (OR, 3.85, % 95 CI: 1.73, 8.53, $P<0.001$) hem de çok değişkenli [OR, 3.58, 95%CI: 1.58, 8.1, $P=0.002$] Cox regresyon modelinde mortalite için bağımsız bir risk faktörü olduğu görüldü.

Tartışma: Hastaneye başvuran COVID-19 PCR pozitif hastalarda özellikle pnömoni saptanan grupta hiponatremi sık görülmekte ve mortalite için bağımsız bir risk faktörü olarak izlenmektedir. Bu hasta grubunda prognozun belirlenmesi açısından hiponatremi önemli bir laboratuvar parametresi olarak görev yapabilir.

Anahtar Kelimeler: COVID-19, Hiponatremi, pnömoni, mortalite

Hyponatremia, defined as serum sodium concentration below 135 mEq/L, is the most common type of electrolyte imbalance in hospital settings (1). Hyponatremia would extend with various clinical manifestations, such as hypovolemic, euvolemic, and hypervolemic conditions. This imbalance might occur as a result of several conditions including endocrine and nutritional abnormalities, cardiovascular disease, renal or liver pathologies, and common infectious conditions (2).

In the general population, community-acquired pneumonia associated with viral infections is the most common condition presented with hyponatremia (3). The main viral pathogens are influenza, parainfluenza viruses, adenovirus, and respiratory syncytial virus. Previous studies have reported that hyponatremia was independently associated with the disease severity, hospital duration, and mortality in viral agent-associated pneumonia (4).

Since late 2019, 298.915.721 confirmed COVID-19 (Coronavirus disease-2019) cases and 5.469.303 deaths related to SARS-COVID-19 have been reported worldwide. Among those reports, hyponatremia has been detected in patients who had longer in-hospital stays and also patients who presented with pneumonia in different countries but the pathogenetic interrelation is still inconclusive (5).

Here in this retrospective cohort, we aimed to analyze the presence of hyponatremia among COVID-19 patients along with its relation to in-hospital mortality.

MATERİAL AND METHODS

Study Population

We have retrospectively obtained all baseline clinical and laboratory variables from the patients who were admitted and hospitalized to our pandemic clinic with the suspicion of COVID-19 infection, between 24 March to 31 December 2020. The obtained variables as follows: COVID-19 RNA polymerase chain reaction (COVID-19 PCR) test results, age, gender, date of admission, comorbidities such as diabetes, hypertension, chronic kidney disease, cardiovascular disease, medications, serum sodium concentration (mEq/L), serum

creatinine (mg/dL), serum calcium (mg/dL), phosphorus (mg/dL), potassium (mEq/L), albumin (g/dL), total protein (g/dL), fasting glucose (mg/dL), complete blood count, c-reactive protein (mg/L), ferritin (ng/mL) and fibrinogen (mg/dL) levels.

All patients were evaluated, diagnosed, and treated according to the national COVID-19 guidelines reported by the Ministry of Health. All admitted patients were divided into two groups COVID-19 negative and positive and also another group with pneumonia and without pneumonia among covid-19 PCR positive patients. Pneumonia was documented by high-resolution computed chest tomography. Young patients aged less than 18 years old and patients with moderate to advanced chronic kidney disease (stage 3-4-5) were excluded from the analysis. All demographic and laboratory data, hospital stay, and outcomes were recorded from the patient's medical files.

Hyponatremia was defined as serum sodium concentration below 135 mEq/L. Only baseline laboratory results were included in the statistical analyses since the effects of the treatments would conflict with the impact of COVID-19 infection on electrolyte levels.

The study was approved by the Gazi University Clinical Research Ethics Committee and also the Ministry of Health Scientific Research Committee (number:2022-115 date: 07.12.2021)

Statistical Analysis

We performed all analyses using SPSS version 24 (IBM Corp., Armonk, N.Y., USA). A two-sided p-value <0.05 value was considered significant. All values are expressed as mean ◎ SD or median with interquartile range (IQR) depending on their distribution and categorical variables as frequencies and proportions. Differences between binary groups were assessed using either parametric (Student t test) or nonparametric (Mann–Whitney U test) tests for quantitative variables and Chi-square tests for categorical variables. Group comparisons were performed in two subgroups. The first was created as COVID-19 PCR negative versus positive patients and the second group as COVID-19 PCR positive patients with and without pneumonia.

The correlation between serum sodium level and duration of hospitalization was assessed with spearman correlation analysis.

The association between hyponatremia and in-hospital mortality from any cause was evaluated using the Kaplan-Meier method with a log-rank test as well as a univariate and multivariate cox regression model. All other admissions clinical and laboratory parameters were included in both univariate and multivariate cox regression analysis. The adjusted variables selected for the multivariate cox model were a priori selected by 10 events per-variable rule to prevent over-fitting, hence multivariate cox regression model was adjusted by age, gender, diabetes mellitus, and coronary heart disease.

RESULTS

The variables of 636 patients with a mean age of 50± 18 years, 48 % of female, with a median duration of hospitalization of 5.5 (IQR, 2,11) days were included in the analyses. A total of 40 (6%) death occurred due to sepsis. The demographical and laboratory characteristics were depicted in Table 1.

Table 1: Demographic and laboratory characteristics of the whole study population

	N=636
Age (years, mean±sd)	50±18
Gender (n, %)	
Female	304 (48%)
Male	332 (52%)
Comorbidities (n, %)	
Diabetes Mellitus	153 (24 %)
Hypertension	132 (21 %)
Chronic Kidney Disease	52 (8%)
Coronary Hearth Disease	67 (11%)
Medicine (n, %)	
ACE inh	56 (9%)
ARB	62 (10%)
Calcium Channel Blockers	65 (10%)
Furosemide	26 (4%)
Thiazide	51 (8%)
LABORATORY ANALYSIS	
Glucose (mg/dL)	112 (97,135)
BUN (mg/dL)	14 (11, 19)
Creatinine(mg/dL)	0.8 (0.6, 1)
Sodium (mEq/L)	137±6
Potassium (mEq/L)	4.1±0.5
Calcium (mg/dL)	9.3±0.6
Phosphorus (mg/dL)	3.4±0.8
Albumin (g/dL)	3.9±0.7
Total protein (g/dL)	6.9±0.7
Urine density	1013±64
Haemoglobin (g/dL)	13±2
WBC (uL)	13300 (12000, 14400)
Neutrophil (uL)	4370 (3230,6390)
Lymphocyte (uL)	1400 (920, 2000)
C-reactive protein (mg/L)	17 (3, 80)
Ferritin (ng/mL)	121 (34,331)
Fibrinogen (mg/dL)	399 (291, 524)
COVID PCR (N, %)	
Negative	83 (13%)
Positive	553 (87%)
Covid pneumonia	298 (47%)
Exitus	40 (6 %)
Discharge from hospital	596 (94 %)
Duration of hospitalization (days, median, min-max)	5.5 (1,54)

ACE INH; Angiotensin-converting enzyme (ACE) inhibitors, **ARB;** Angiotensin-II receptor blockers, **BUN**; Blood urea nitrogen, **WBC;** White Blood Cell

Among 636 patients 553 (87%) were detected COVID-19 PCR positive and 298 (47%) of those were diagnosed with viral pneumonia. The mean sodium concentration was 137±6 mE/L among the whole study population. Diabetes mellitus was the most common comorbidity with a percentage of 24 %, followed by hypertension with a percentage of 21 %. Pneumonia was present in 54% of 553 COVID-19 PCR-positive patients (n=298). There was a statistically significant negative correlation between serum sodium levels and duration of hospitalization (r spearman -0,372, p<0.001) among the whole study population. A total of 40 (6%) deaths occurred during follow-up.

The comparison of variables between COVID-19 PCR-positive and negative patients was summarized in Table 2.

Table 2: The comparison of baseline parameters between COVID 19 positive versus negative patients

	COVID 19 Positive (n=553)	**COVID 19 Negative (n=83)**	**P Values**
Gender (n, %)			
Female	274 (49,5%)	30 (36,1%)	
Male	279 (50,5%)	53 (63,9%)	**0.01**
Age (years, mean±sd)	50±18	51±17	0.63
Diabetes Mellitus (n, %)	140 (25%)	13 (16 %)	**0,05**
Coronary Heart Disease (n, %)	52 (9.4 %)	15 (18.2%)	**0.02**
Hypertension (n, %)	108 (20 %)	24 (29 %)	**0.05**
Chronic Kidney Disease (n, %)	45 (8%)	7 (8%)	0.83
Antihypertensive Medicine (n,%)			
ACE inh	42 (8%)	14 (17%)	**0.01**
ARB	56 (10%)	6 (7%)	0.55
Thiazide	44 (8%)	7 (8%)	0.83
Furosemide	20 (4%)	6 (7 %)	0.13
Calcium channel blockers	56 (10%)	9 (11%)	0.84
Laboratory			
Glucose (mg/dL)	111 (97,135)	114 (96, 137)	0.79
Bun (mg/dL)	14 (11,19)	14(11,19)	0.78
Creatinine (mg/dL)	0.80 (0.66, 0.99)	0.76 (0.63, 0.93)	0.17
Sodium (mEq/L)	134(130, 137)	139 (136, 140)	**<0.01**
Potassium (mEq/L)	4.1 (3.8,4.4)	4.0 (3.8, 4.4)	0.61
Calcium (mg/dL)	9.3 (8.9,9.7)	9.4(9.1,9.7)	0.20
Phosphorus (mg/dL)	3.3 (2.9, 3.8)	3.3 (2.8, 4.0)	0.85
Albumin (g/dL)	4.1 (3.6,4.5)	4.0 (3.5,4.4)	0.25
Total protein (g/dL)	7.0 (6.6, 7.4)	6.9(6.5, 7.4)	0.10
Urine density	1019(1009, 1023)	1018 (1010, 1026)	0.75
Haemoglobin (g/dL)	13 (12, 14)	13 (12,14)	0.71
WBC (uL)	6635 (5072, 8685)	9140 (6630, 12160)	**<0.01**
LYMPHOCYTE (uL)	1375 (920, 1987)	1570 (1050, 2150)	0.24
C-reactive protein (mg/L)	48 (8,132)	15 (3,78)	**<0.01**
Ferritin (ng/mL)	121 (33,329)	118 (37, 401)	0.67
Fibrinogen (mg/dL)	398 (290, 520)	418 (293, 640)	0.18
Exitus (n, %)	40 (7,2 %)	-	**<0.01**

ACE INH; Angiotensin-converting enzyme (ACE) inhibitors, **ARB;** Angiotensin-II receptor blockers, **BUN**; Blood urea nitrogen, **WBC;** White Blood Cell

The comorbidities of diabetes mellitus, coronary heart disease, and hypertension were more common in positive patients compared to negatives (p=0.05, p=0.02, p=0.05 respectively). There were no statistically significant differences in serum creatinine, potassium, calcium, phosphorus, albumin, total protein, urine density hemoglobin, ferritin, and fibrinogen concentrations in group comparisons (Table 2). The median WBC account was statistically significantly lower (p<0.01) and the median C-reactive protein level was higher (p<0.01) in COVID-19 PCR positive patients compared to the negatives (p<0.01). The median serum sodium concentration was statistically significantly lower in COVID-19 PCR positive patients compared to negatives [134 (IQR, 130,137) mEq/L in COVID-PCR positives versus 139 (IQR, 136, 140) mEq/L negatives (p<0.001)]

We have created another group of patients with and without pneumonia among COVID-19 PCR-positive patients. All comparison analyses were depicted in Table 3.

Table 3: The comparison of baseline parameters among the Covid 19 patients with pneumonia versus without pneumonia

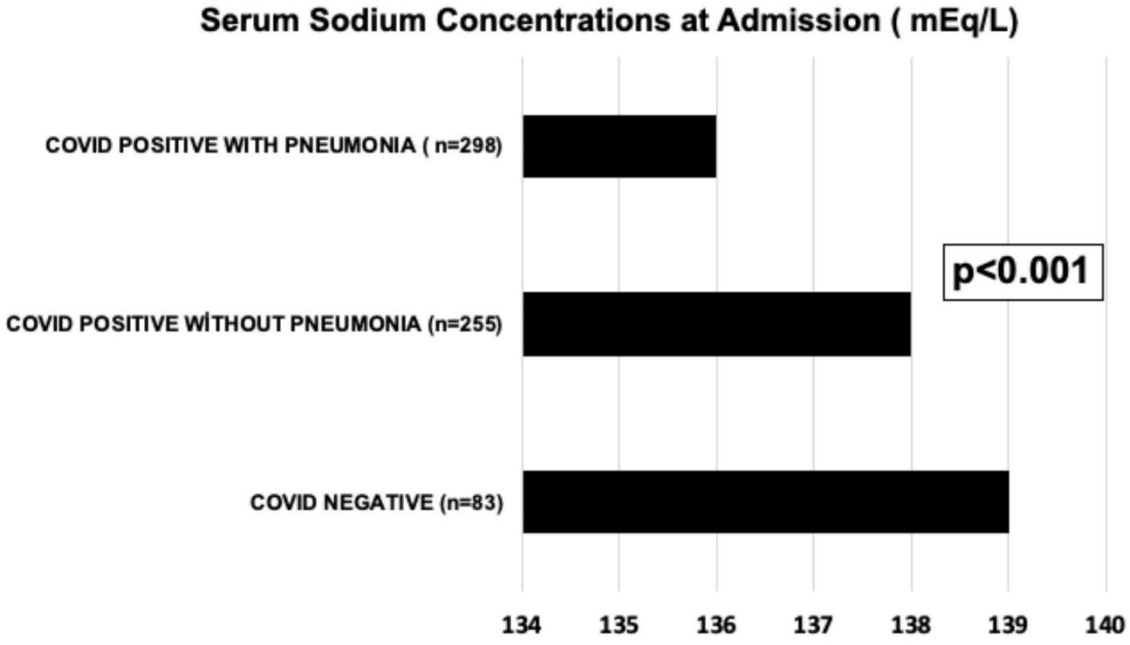
	Patients with pneumonia (n=298)	**Patients without Pneumonia (n=255)**	**P Values**
Gender (n, %)			
Female	128 (43%)	146 (57%)	
Male	170 (57%)	109 (43%)	**<0.01**
Age (years, mean±sd)	60±16	38±12	**<0.01**
Diabetes Mellitus (n, %)	127 (42%)	13 (5%)	**<0.001**
Coronary Heart Disease (n, %)	44 (15%)	8 (3%)	**<0.001**
Hypertension (n, %)	92 (31%)	16 (6%)	**<0.001**
Chronic Kidney Disease (n, %)	36 (12%)	9 (4%)	**<0.001**
Antihypertensive Medicine (n,%)			
ACE inh	34 (11%)	8 (3%)	**<0.001**
ARB	51 (17%)	5 (2%)	**<0.001**
Thiazide	39 (13%)	5 (2%)	**<0.001**
Furosemide	20 (7%)	-	**<0.001**
Calcium channel blockers	51 (17%)	5(2%)	
Laboratory			
Glucose (mg/dL)	120(104,157)	101 (91,116)	**<0.001**
BUN (mg/dl)	17(13,23)	12 (10,15)	**<0.001**
Creatinine (mg/dl)	0.9 (0.7, 1.1)	0.74(0.62,0.87)	**<0.001**
Sodium (meq/L)	136 (133,138)	139 (137,145)	**<0.001**
Potassium (meq/L)	4.0 (3.7, 4.3)	4.1 (3.9,4.3)	**<0.001**
Calcium (mg/dl)	9.0(8.7,9.3)	9.6 (9.4, 9.9)	**<0.001**
Phosphorus (mg/dl)	3.2 (2.7,3.7)	3.5 (3.1,3.9)	**<0.001**
Albumin (g/dl)	3.6 (3.3, 4.0)	4.5 (4.2,4.7)	**<0.001**
Total protein (g/dl)	6.8(6.3,7.9)	7.3 (6.9,7.6)	**<0.001**
Urine density	1020 (1012, 1028)	1014(1008,1020)	**<0.001**
Haemoglobin (d/dl)	12.7 (11.3,13.9)	13.7 (12.8, 15.0)	**<0.001**
WBC (uL)	5790 (4460,8225)	7195 (5785, 8820)	**<0.001**
Lymphocyte (uL)	1000(690,1372)	1915 (1470,2417)	**<0.001**
C-reactive protein (mg/L)	64 (20.3,115.7)	2.9 (1.7,5.4)	**<0.001**
Ferritin (ng/mL)	257 (122,523)	33 (15,90)	**<0.001**
Fibrinogen (mg/dL	496 (419,600)	292 (245, 342)	**<0.001**
Exitus (n, %)	40 (13,4 %)	-	**<0.001**

ACE INH; Angiotensin-converting enzyme (ACE) inhibitors, **ARB;** Angiotensin-II receptor blockers, **BUN;** Blood urea nitrogen, WBC; White Blood Cell

All comorbidities were more common in patients with pneumonia. The patients with pneumonia were older than those without pneumonia (60±16 vs 38±12, p<0.01). The median creatinine concentration was statistically significantly higher (p<0.01) and median serum sodium levels were significantly lower in patients with pneumonia compared to those without pneumonia [136 (IQR, 133.138) mEq/L with pneumonia versus 139 (IQR, 137, 145) mEq/L without pneumonia (p<0.001)]. All deaths occurred among patients with pneumonia [(n=40 (13.4 %)].

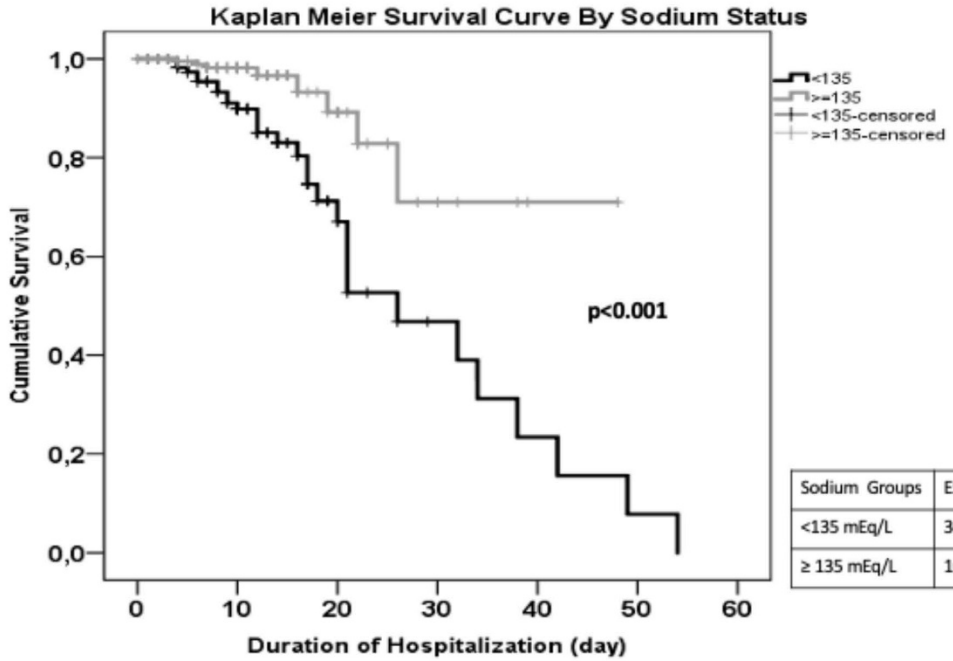
When we analyze the baseline serum sodium concentrations between COVID-19 positive with and without pneumonia and COVID-19 negative patients, a sequential decrease was observed between group comparisons (Figure 1).

Figure 1: The comparison of serum sodium concentrations of the study population



As shown in Figure 2, there was a statistically significant difference in hospital mortality between the patients with normal serum sodium levels (Na≥ 135mEq/L) and the patients with low serum sodium levels (Na<135 mEq/L) (p<0.001). At follow-up, a total of 40 (13.4 %) patients died among COVID-PCR positive patients with pneumonia whereas none without pneumonia group (Table 3).

Figure 2: Kaplan Meier Survival Curve according to the patients' sodium status



Sodium Groups	Exitus (n)	P value
<135 mEq/L	30	<0.001
≥ 135 mEq/L	10	

The results of univariate cox proportional hazard model showed that having older age [unadjusted odds ratio (OR): 1.03, 95% confidence interval (CI): 1.00, 1.06 , P = 0.01], viral pneumonia [OR, 5.54 , 95%CI: 1.90, 15.5 , P<0.001], higher serum phosphorus levels [OR, 1.42 , 95%CI: 1.05, 1.92 , P=0.02] and having serum sodium levels under 135mEq/L [OR, 3.85 , 95%CI: 1.73, 8.53 , P<0.001] were statistically significantly associated with any cause of in-hospital mortality (Table 4).

Table 4: Factors associated with overall mortality among the whole study population (univariate and multivariate cox regression analyses)

	Univariate		**Multivariate***	
	Beta (95 %CI)	**P values**	**Beta (95 %CI)**	**P values**
Gender (n, %, male)	0.77 /0.38, 1.56)	0.48	**-**	**-**
Age (years, mean±sd)	1.03 (1.00,1.06)	**0.01**	-	-
Diabetes Mellitus (n, %)	1.51 (0.77,2.90)	0.22	**-**	**-**
Coronary Heart Disease (n, %)	2.03 (0.97, 4.20)	**0.06**	**-**	**-**
Hypertension (n, %)	1.29 (0.65, 2.58)	0.45	1.39 (0.65, 2.97)	0.38
Chronic Kidney Disease (n, %)	1.90(0.88, 4.12)	0.10	1.66 (0.76, 3.63)	0.19
Viral Pneumonia (n,%)	5.54 (1.90, 15.5)	**<0.001**	5.95 (1.95, 18.1)	**0.002**
Antihypertensive Medicine (n,%)				
ACE inh	0.74 (0.26, 2.10)	0.57	0.58 (0.20, 1.72)	0.33
ARB	0.71 (0.25,2.04)	0.53	0.60 (0.19, 1.88)	0.38
Thiazide	2.18 (0.82,5.77)	0.11	1.77 (0.63, 5.01)	0.27
Furosemide	0.62 (0.14,2.76)	0.53	0.47 (0.10, 2.07)	0.32
Calcium channel blockers	0.92 (0.41, 2.04)	0.85	0.77 (0.33, 1.79)	0.54
Laboratory				
Glucose (mg/dL)	1.00(0.99,1.01)	0.61	0,99 (0,98, 1.00)	0.70
BUN (mg/dL)	1.01 (0.99,1.02)	0.11	1.0 (0.99, 1.02)	0.38
Creatinine (mg/dL)	1.04 (0.90,1.21)	0.55	1.04 (0.88, 1.23)	0.60
Sodium (mEq/L)	0.89 (0.82, 0.96)	**0.004**	0.90 (0.84, 0.97)	**0.001**
Potassium (mEq/L)	1.27 (0.74, 2.18)	0.37	1.41 (077, 2.56)	0.25
Calcium (mg/dL)	1.02 (0.61,1.68)	0.93	0.96 (0.57, 1.6)	0.88
Phosphorus (mg/dL)	1.42 (1.05, 1.92)	**0.02**	1.35 (0.99, 1.84)	0.05
Albumin (g/dL)	0.63 (0.40,1.01)	**0.05**	0.76 (10.45, 1.26)	0.29
Total protein (g/dL)	0.66 (0.40, 1.08)	0.10	0.73 (0.44, 1.24)	0.25
Urine density	0.99 (0.99, 1.00)	0.08	0.99 (0.99, 1.00)	0.28
Haemoglobin (d/dL)	0.86 (0.73, 1.01)	0.06	0.86 (0.72, 1.02)	0.09
WBC (uL)	1.00 (1.00, 1.00)	0.98	1.00 (1.00, 1.00)	0.28
Lymphocyte (uL)	1.00 (0.99, 1.00)	0.60	1.0 0.99, 1.00)	0.59
C-reactive protein (mg/L)	1.00(0.99,1.00)	0.21	1.00(0.99, 1.00)	0.39
Ferritin (ng/mL)	1.00 (1.00, 1.00)	0.89	1.00 (0.99, 1.00)	0.34
Fibrinogen (mg/dL	1.00 (0.99, 1.00)	0.68	1.00 (0.99, 1.00)	0.89
Hyponatremia (NA<135 mEq/L)	3.85 (1.73, 8,53)	**<0.001**	3.58 (1.58, 8.1)	**0.002**

ACE INH; Angiotensin-converting enzyme (ACE) inhibitors, **ARB;** Angiotensin-II receptor blockers, BUN; Blood urea *nitrogen*, **WBC;** White Blood Cell

*Adjusted by age, gender, diabetes mellitus, coronary heart disease

Coronary artery disease history was also associated with in-hospital mortality with marginal statistical significance [OR, 1.90, 95%CI: 0.88, 4.12, P=0.06]. Although diabetes mellitus, hypertension, and chronic kidney disease were found like risk factors for in-hospital mortality, these associations did not reach statistical significance (Table3). Both normal serum sodium levels [OR, 0.89, 95%CI: 0.82, 0.96, P=0.004] and higher serum

albumin levels [OR, 0.63, 95%CI: 0.40 , 1.01 , P=0.05] were protective with marginal statistical significance in unadjusted cox analysis. Multivariable cox model adjusted by age, gender, diabetes mellitus, and coronary heart disease revealed that viral pneumonia [OR, 5,95, 95%CI: 1.95, 18.1, P=0.002] and serum sodium levels lower than 135 mEq/L [OR, 3.58, 95%CI: 1.58, 8.1, P=0.002] were independently associated with in-hospital mortality (Table 4).

DISCUSSION

Our study aimed to evaluate the relationship between hyponatremia and COVID-19 positivity along with the presence of pneumonia and all-cause in-hospital mortality in COVID-19 patients. Our goal was to enhance the literature knowledge about the importance of sodium disturbances regarding the prediction of worse outcomes in this new but wide group of patients. Our results showed that hyponatremia was more prevalent in COVID-19-positive patients, especially with viral pneumonitis and hyponatremia leads to a higher risk of death.

Addressing the electrolyte disturbances, one of the earliest reports from Agarwal et al showed that hyponatremia is a frequent abnormality among COVID-19-positive patients(6). Similar to this article, our study has shown that hyponatremia was more common in patients who had COVID-19 PCR positivity compared to the negatives. This co-occurrence might be explained by simply inadequate dietary intake or loss of fever or diarrhea due to the infection by itself. However, other possible mechanistic relations should be taken into account, such as a possible direct renal tubular epithelial injury due to the viral infection (7) or cytokine-induced impairment of the kidney, which resulted in acute kidney injury and dysfunction of the proximal tubule(8). However, our study is not able to give any information about the cause-effect relationship, since we only analyzed the baseline levels of patients. But with this model, we have excluded the possible effect of treatments for infection on electrolyte levels. Taken all previous reports and our findings together one can suggest that hyponatremia might be an important clue for the diagnosis of COVID-19 infection (9)

Irrespective of the hyponatremia etiology, we have found that it manifests more frequently in patients with viral pneumonia. In one previous report, hyponatremia was significantly associated with viral pneumonia due to the COVID-19 infection (10). In another study from China, it has been documented that among 1254 COVID-19 PCR-positive patients, 9.9% of those had serum sodium levels under 135 mEq/L and the presence of hyponatremia was associated with older age, comorbidities, and pneumonia (11). When we look back on our comparison analyses, all patients with pneumonia were older and have more comorbidities along with medication that might affect electrolyte levels compared to those without pneumonia. Despite all, our cohort is relatively younger than previous reports even patients with viral pneumonitis and diuretic usage is in a lesser degree which might exclude the possible high-level impact of diuretic usage and also a metabolic effect of being elder (12) on serum sodium concentration. Although patients with pneumonia had both moderately increased serum creatinine levels and mildly lower serum albumin levels compared to those without pneumonia, those levels were not predisposing for hypervolemic hyponatremia of nephrotic or hepatic etiology. Another potential explanation of hyponatremia in this group of patients is cardiac dysfunction suggested as an increased expression of angiotensin-converting enzyme-2 that acts as a viral receptor for SARS-Cov-2 and cardiac diseases (11). In one way the upregulation of ACEII leads to hyponatremia and in the other way, it increases the intracellular virus transport which concomitantly results in the progression of the primary disease along with hyponatremia(13). In this present study, we were unable to obtain detailed cardiac evaluation regarding any kind of cardiac failure of the patients at admission which limits us to concluding this possible association between hyponatremia and cardiac hemodynamic disturbance. Another cause of hyponatremia is the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

The numerous COVID-19 infection-induced comorbidities such as pneumonia, respiratory failure, and stroke might contribute to SIADH(3). In our cohort, hyponatremia was more profound in the patients with pneumonia, and urine-specific gravity was found higher than in the patients without pneumonia which might be a

clue for SIADH. Since we did not collect the data on urine osmolality or urine sodium excretion level at admission, it restricts the clinical diagnosis of SIADH in our patients to make a clear association.

Another finding in our study is that serum sodium concentration was negatively correlated with in-hospital stay. This finding is not unique, as several previous studies have documented the relationship between hyponatremia and longer duration of hospitalization in different clinical settings (5). Severe pneumonia, need for mechanical ventilation, and need for intensive care unit are more frequent in hyponatremic patients which delays their discharge from the hospital (14, 15).

The most important goal of this current study is to evaluate the possible association between hyponatremia and any cause of in-hospital mortality among COVID-19 patients. In this present study, a multivariable Cox proportional hazards model identified several prognostic markers for 50 -day in-hospital mortality. In univariate analysis, older age, having coronary heart disease, having pneumonia, higher serum phosphorus, lower serum albumin levels, and hyponatremia were significantly associated with any cause of in-hospital mortality. Multivariable analysis adjusted by age, gender, diabetes, and coronary heart disease, only pneumonia and hyponatremia were independently associated with in-hospital mortality. Previously, Carvalho et al reported that hyponatremia was significantly associated with a longer duration of hospitalization, more need for artificial ventilation, and death compared to normo-natremic COVID-19 patients (16). Berni et al have also found a close association between hyponatremia and in-hospital mortality in a small group of patients (17). However, in another prospective study, no significant relationships were found between sodium disturbance and death (18). A different study by Ruiz-Sanchez et al found that hyponatremia was associated with longer hospital stay, but not mortality, contrary, hypernatremia is independently associated with mortality (10). In our study, we excluded the patients who have serum sodium concentration over 145 mEq/L which are few in our cohort. This limits us to conclude another important sodium disturbance in these patients. Those results were similar to another report from Turkey which assessed sodium disturbances and poor outcomes (19). Similar to our findings another research from Turkey, Emektar et al reported that hyponatremia was more common in pneumonia patients and strongly associated with COVID-19 disease severity. However, this study did not include mortality data (20).

The most significant limitation of our study is the lack of urine output levels and osmolality and urine sodium concentrations which restricts us to evaluate etiology at least in clinical settings. Second, as we depicted previously, we wanted to study only admission levels of sodium to exclude the possible effect on therapies for infection, however final electrolyte changes before discharge or exitus would give us repetitive information about how electrolyte dynamic changes affect poor outcomes in this population. Despite all, to the best of our knowledge, this is the third study from Turkey on this topic, which distinguishes mortality analysis from previous Turkish report by Emektar et al. Our results are also different from another report by Akyil et al by establishing the close association between hyponatremia and early in-hospital mortality (19).

CONCLUSION

The COVID-19 pandemic and its effects on metabolism are still under exploration and any kind of effect of the virus would be served to the medical literature. Hyponatremia seems like a frequent electrolyte abnormality among COVID-19 patients and is more prevalent in those with pneumonia. It might be an important laboratory clue for the diagnosis of these patients. It is very important to establish and treat hyponatremia, since its close association with worse outcomes. Further researches have to be carried out to explore its possible association with response to the treatment, morbidity, in-hospital duration, and mortality.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

SMD, EY, UBD conceived and designed the study, EY, HSO, and PAY obtained the study data, SMD analyzed

the data, SMD, UBD interpreted the results of the analysis, SMD and UBD drafted the manuscript and all authors approved the final version of the manuscript.

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