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ARAŞTIRMA / RESEARCH

Effects of hypokalemia on clinical outcomes in hospitalized patients with Covid-19 pneumonia

Hastanede yatan Covid-19 pnömoni hastalarında hipokaleminin klinik sonuçlara etkileri

Bülent Kaya[1], Saime Paydaş[1], Tolga Kuzu[1], Ömer Demiroğlu[2], Sevinç Püren Yücel[3], Mustafa Balal[1], Yeşim Taşova[4]

[1]Çukurova University Faculty of Medicine, Department of Nephrology, [3]Department of Biostatistics, [4]Department of Infectious Diseases, Adana, Turkey
[2]Aksaray University Education and Research Hospital, Department of Internal Medicine, Aksaray, Turkey

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Abstract

Purpose: We investigated the effects of hypokalemia on clinical outcomes in hospitalized patients with Covid-19 pneumonia.

Materials and Methods: In this single-center retrospective study, we recorded characteristics of hospitalized covid-19 pneumonia patients and laboratory test results on the first hospital day. Duration of hospitalization, requiring intensive care including mechanical ventilation and survival, were determined.

Results: Our study included 185 patients and of them 111 male (60% male) patients with mean age of 64 ± 14.5 (23-90). Patients were grouped as hypokalemic (16.8%) and normokalemic patients (83.2%). The number of diabetic patients was higher in the normokalemic group. Serum total protein and albumin levels were lower in hypokalemic group, while alkaline phosphatase, gamma-glutamyl transpeptidase, total bilirubin, direct bilirubin, blood pH and bicarbonate level were higher. In multiple logistic regression analyses, alkalosis increased risk of hypokalemia 5.73 times. Duration of hospitalization, requirement of intensive care and hospital mortality were similar in hypokalemia and normokalemia patients.

Conclusion: In patients with Covid-19 pneumonia, hypokalemia has been found to be quite common as high as 16.8% at the first presentation. Hypokalemia was related to metabolic alkalosis but unrelated to the duration of hospitalization, requirement of intensive care including mechanical ventilation and hospital mortality.

Keywords: Covid-19 pneumonia, hypokalemia, mortality

Öz

Amaç: Çalışmamızda hastanede yatan Covid-19 pnömonili hastalarda hipokaleminin klinik sonuçlar üzerindeki etkilerini araştırdık.

Gereç ve Yöntem: Tek merkezli retrospektif çalışmada, hastanede yatan covid-19 pnömonili hastaların demografik ve klinik özellikleri ile birlikte hastanenin ilk günündeki laboratuvar sonuçları kaydedildi. Hastaların hastanede yatış süreleri, mekanik ventilasyon dahil yoğun bakım gereksinimi ve sağ kalım süreleri belirlendi.

Bulgular: Çalışmamıza yaş ortalaması 64 ± 14.5 (23-90) olan 111 erkek (% 60) olmak üzere 185 hasta dahil edildi. Hastalar hipokalemik (%16.8) ve normokalemik (%83.2) olarak 2 gruba ayrıldı. Diyabetik hasta sayısı normokalemik grupta daha fazlaydı. Hipokalemik grupta serum total protein ve albümin düzeyleri daha düşük, alkalen fosfataz, gama-glutamil transpeptidaz, total bilirubin, direkt bilirubin, kan pH'sı ve bikarbonat düzeyi daha yüksekti. Çoklu lojistik regresyon analizinde alkaloz hipokalemi riskini 5.73 kat artırdı. Hastanede yatış süresi, yoğun bakım gereksinimi ve hastane mortalitesi hipokalemi ve normokalemi hastalarında benzerdi.

Sonuç: Covid-19 pnömoni hastalarında ilk başvuruda hipokalemi %16.8 gibi oldukça yüksek oranda bulunmuştur. Hipokalemi metabolik alkaloz ile ilişkiliydi ancak hastanede kalış süresi, mekanik ventilasyon dahil yoğun bakım gereksinimi ve hastane mortalitesi ile ilişkili değildi.

Anahtar kelimeler: COVİD-19, Hipokalemi, Mortalite

Yazışma Adresi/Address for Correspondence: Dr. Bülent Kaya, Çukurova University Faculty of Medicine, Department of Nephrology, Adana, Turkey E-mail: bulentkaya32@gmail.com
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INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) first appeared in China in November 2019 and has spread all over the world[1,2]. SARS-CoV-2 enters the cell by using ACE-2 (Angiotensin-converting enzyme-2) receptors and thus causes dysfunctions in many organs such as the lung, kidney, intestine, heart, and brain with these receptors[3,4]. Lungs are the primary target organ in Covid-19[5]. The disease may be mild or hospitalization may be required due to severe lung involvement[6]. During the treatment of patients, mechanical ventilation and intensive care may be required due to serious complications such as sepsis, acute respiratory distress syndrome (ARDS), and shock[6-9]. In the later stages of the disease, an uncontrolled increase in cytokines causes organ dysfunction which leads to morbidity and mortality[4]. Advanced age, diabetes mellitus (DM), cardiovascular disease, malignancy, renal failure, chronic lung disease, and using immunosuppressive medications increase the risk of developing Covid-19 and complications[8,10,11].

According to the clinical severity of the disease patients are treated with antiviral drugs, IL-2 antagonists, and corticosteroids, although no drug has been shown to be effective against SARS-CoV-2[6,12]. In patients with severe disease, fatal complications such as cytokine release syndrome, hemophagocytosis, sepsis ARDS and the need for mechanical ventilation may develop[7,13]. Electrolyte disturbances such as hypokalemia, hyponatremia, and hypophosphatemia may also occur during Covid-19[14]. Many clinical conditions such as anorexia, vomiting, gastroenteritis, high fever and hyperventilation, may cause these disorders.

Hypokalemia is one of the electrolyte disorders seen in Covid-19 patients, and it has been associated with the severity of the disease as well as the need for mechanical ventilation[15]. But there are also studies reporting that it is not related to the need for intensive care and death[16,17]. Hypokalemia can lead to increased mortality with various complications such as cardiac arrhythmia, respiratory muscle weakness, and ileus.

In our study, we investigated the relationship between hypokalemia detected at first admission in patients hospitalized for Covid-19 pneumonia with disease activity, duration of hospitalization, need for intensive care, and/or mechanical ventilation, and mortality.

MATERIALS AND METHODS

Sample

In our study, patients aged 18-90 years who were hospitalized for Covid-19 pneumonia in Çukurova University Medical Faculty Hospital between 30.12.2020 and 15.03.2021 were retrospectively analyzed. All patients diagnosed with COVID-19 pneumonia, hospitalized, and serum potassium <5.5 mg/dl were included in the study. Patients with hyperkalemia (serum K> 5.5 mg/dl) were not included in the study. The patients in the study were obtained from patients who were admitted to the hospital consecutively. Patients admitted to Covid-19 services were evaluated by the doctors in this department. At the first admission of the patient's age, gender, chronic diseases, medications, and laboratory findings were recorded. Seven patients were excluded from the study due to hyperkalemia (K>5.5 mg/dl). The remaining 185 patients were included in the study and the patients were divided into 2 groups as normokalemic and hypokalemic. Our study was approved by Çukurova University Ethics Committee with the decision of 107/37, dated 22/01/2021. Consent was obtained from the participants.

Procedure

The duration of hospitalization, the need for intensive care, requiring mechanical ventilation, survival and during-to-death of the patients were recorded. The goal of our study was to determine the prevalence of hypokalemia in Covid-19 pneumonia patients who were admitted to the hospital for the first time, as well as the impact of hypokalemia on intensive care, mechanical ventilation, and survival.

Covid-19 was diagnosed with a positive SARS-CoV-2 PCR test in the nasal swab. Indications for hospitalization for Covid-19 pneumonia include arterial oxygen saturation of less than 93% in room air or tachypnea (respiratory rate ≥ 24/min) or lung involvement greater than 50% with thorax CT. Requirements for intensive care due to Covid-19 pneumonia include arterial oxygen saturation <90% or PaO2 <70 mmHg, despite 5 L/min oxygen therapy or tachypneic (respiratory rate ≥ 30/min) or hypotension (systolic blood pressure <90 mmHg).

The normal potassium level in the serum is 3.5-5.5 mg/dl. Hypokalemia was defined as serum potassium

level <3.5 mg/dl at the time of the first admission to the hospital.

Statistical analysis

All analyses were performed using IBM SPSS Statistics Version 20.0 statistical software package. Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation and as median and minimum-maximum where appropriate. Chi-square test was used to compare categorical variables between the groups. The normality of distribution for continuous variables was confirmed with the Kolmogorov-Smirnov test. For comparison of continuous variables between two groups, the Student's t-test or Mann-Whitney U test was used depending on whether the statistical hypotheses were fulfilled or not. The stepwise backward logistic regression analysis was performed to determine significant predictors of hypokalemia. All significant variables in the univariate analysis, as well as clinically important variables (gender, age, and diuretic treatment) were included in the logistic regression analysis. For logistic regression analysis, pH were categorized into three groups: normal (pH:7.35-7.45), acidosis (pH<7.35) and alkalosis (pH>7.45). For univariate analysis, event-free survival was calculated by Kaplan-Meier method and log rank test was performed. The statistical level of significance for all tests was considered to be 0.05.

RESULTS

Our study included 185 patients (111, 60% male) with a mean age of 64 14.5 (23-90). According to serum potassium levels, the patients were categorized into two groups: hypokalemic (31, 16.8%), and normokalemic (154, 83.2%). The number of DM patients was higher in the normokalemic group (p=0.014). (Table 1).

Table 1. Demographic and clinical characteristics of hypokalemic and normokalemic patients (n=185)

	Hypokalemic (n=31, 16.8 %)	**Normokalemic (n=154, 83.2 %)**	**p value**
Age(year)[a]	63.5±15.5 63.0(27-89)	64.1±14.3 66.5(23-90)	0.807
Male[b]	14(45.2)	97(63.0)	0.099
Female[b]	17(54.8)	57(37.0)	
Smoking [b]	4(12.9)	29(18.8)	0.596
DM[b]	5(16.1)	64(41.6)	0.014
HT[b]	20(64.5)	101(65.6)	0.909
CAD[b]	11(35.5)	59(38.3)	0.926
HF[b]	3(9.7)	23(14.9)	0.578
CRF[b]	3(9.7)	32(20.8)	0.235
COPD[b]	4(12.9)	16(10.4)	0.925
Malignancy[b]	2(6.5)	2(1.3)	0.131
Thiazide[b]	11(35.5)	43(27.9)	0.530
Furosemide[b]	1(3.2)	19(12.3)	0.206
ACE/ARB[b]	14(45.2)	67(43.5)	0.865
Favipravir[b]	17(54.8)	96(62.3)	0.562
Death[b]	3(9.7)	16(10.4)	0.905
Alive[b]	28(90.3)	138(89.6)	
MVI Yes[b]	5(16.1)	14(9.1)	0.326
MVI No[b]	26(83.9)	140(90.9)	
ICN Yes[b]	6(19.4)	29(18.8)	0.946
ICN No[b]	25(80.6)	125(81.2)	
DH(day)[a]	10.7±4.9 10.0(2-20)	10.9±6.1 9.0(1-31)	0.794

[a] Data are expressed as mean±standart deviation, median (min-max), [b] Data are expressed as frequency (%).
Note: Bold values indicate statistical significance (p<0.05).
Abbreviations= DM: diabetes mellitus, HT: hypertension, CAD: Coronary artery disease, HF: Heart Failure, CRF: Chronic renal failure, COPD: chronic obstructive pulmonary disease, ACE: Angiotensin converting enzyme inhibitor, ARB: Angiotensin-2 receptor blocker MVI: The need for mechanical ventilation, ICN: The need for intensive care, DH: Duration of hospitalization

Table 2. Laboratory results of patients (n=185)

Mean ±SD	Hypokalemic (n=31, 16.8 %)	Normokalemic (n=154, 83.2 %)	p value
Glucose, mg/dl	143.1±72.3 118(82-469)	165.7±111.2 134(68-990)	0.298
BUN, mg/dl	20.6±15.2 15(5-70)	25.6±22.2 18(4.7-136.8)	0.129
Creatinin, mg/dl	1.0±1.3 0.8(0.3-8.1)	1.3±1.4 0.8(0.3-9.0)	0.124
Total protein, g/L	60.6±8.5 60(46.0-75.7)	64.4±6.6 65(45.0-82.7)	0.027
Albumin, g/L	30.5±6.1 30(19.6-40.6)	33.7±4.9 34(16.1-47.0)	0.002
Uric acid, mg/dl	4.6±2.0 3.9(1.6-7.9)	5.8±2.6 5.1(2.5-15.7)	0.085
AST, U/L	52.4±40.0 37(15-187)	40.8±28.6 32(12-225)	0.134
ALT, U/L	37.1±29.1 29(7-125)	29.2±27.8 21(5-253)	0.071
ALP, U/L	95.4±43.7 90(35-240)	76.4±31.9 67.5(35-250)	0.013
GGT, U/L	63.1±38.1 55(6-181)	51.3±59.6 32(8-419)	0.002
Total Bilirubin, mg/dl	0.6±0.3 0.6(0.2-1.6)	0.5±0.3 0.5(0.0-1.8)	0.017
Direct Bilirubin, mg/dl	0.1±0.1 0.1(0.0-0.4)	0.1±0.0 0.1(0.0-0.5)	0.023
Sodium, mmol/L	134.3±9.1 135(108-151)	133.8±5.8 133(111-163)	0.143
Potassium, mmol/L	3.1±0.2 3.2(2.3-3.4)	4.2±0.4 4.2(3.5-5.5)	<0.001
Chloride, mmol/L	97.1±9.3 99(71-117)	98.5±6.0 98(82-135)	0.430
Magnesium, mg/dl	1.9±0.4 1.9(1.3-3.3)	1.9±0.4 1.9(0.9-3.1)	0.905
Calcium, mg/dl	8.5±0.5 8.7(7.0-9.3)	8.7±0.6 8.8(6.7-10.0)	0.146
Phosphorus, mg/dl	2.8±1.0 2.6(1.3-4.9)	3.3±1.0 3.2(1.5-6.8)	0.065
WBC, 103/µl	8.627±4.088 8(3-19)	8.023±4.194 6.94(1.6-3.07)	0.464
Lymphocyte,µl	864±413 800(260-2100)	965±473 820(290-3300)	0.352
Hemoglobin, g/dl	12.1±2.3 12.3(8.0-17.4)	12.8±2.0 13.0(6.6-17.1)	0.111
Platelet, 103/µl	210±75.9 188(43-384)	223±94.5 201(87-643)	0.813
Platelet / Lymphocyte	0.2±0.1 0.2(0.0-0.7)	0.2±0.1 0.2(0.0-1.2)	0.488
CRP/ Lymphocyte	0.1±0.1 0.1(0.0-0.7)	0.1±0.1 0.0(0.0-0.7)	0.199
D-dimer, mg/l	1.3±1.1 0.9(0.2-4.5)	1.4±1.6 0.9(0.1-9.0)	0.755
Ferritin, mg/dl	531.7±552.1 404(81-2320)	447.4±456.5 288.6(6.5-2500)	0.194
Fibrinogen, mg/dl	563.5±192.7	533.4±152.3	0.340

	554(180-1136)	506.5(50-950)	
LDH, U/L	430±384 340(142-2352)	366.1±175.6 320(119-1384)	0.494
CRP, mg/L	110.0±95.6 94(7.8-501)	98.7±82.2 79.6(1.4-474)	0.507
Procalcitonin, ng/ml	0.6±1.0 0.2(0.0-5.5)	0.4±1.1 0.1(0.0-8.1)	0.235
Troponin, ng/l	26.5±47.0 12.1(1.0-245)	22.2±46.2 9.8(0.9-310)	0.545
INR	1.1±0.2 1.0(0.8-1.6)	1.0±0.1 1.0(0.8-2.1)	0.943
PT, min.	14.0±3.0 13.0(10.3-21)	13.3±2.7 12.9(10.2-27)	0.330
APTT, min.	28.5±5.7 28(19.7-40)	27.8±5.0 27(18.1-45)	0.492
TSH, mIU/l	1.1±0.8 0.8(0.2-2.8)	1.3±1.1 1.0(0.0-5.9)	0.701
pH	7.4±0.1 7.4(7.2-7.5)	7.3±0.0 7.4(7.2-7.4)	0.001
HCO3, mmol/l	27.3±7.1 26.4(12.0-42)	23.2±4.6 23.9(2.0-31)	0.019
PCO2, mmHg	38.6±8.5 40.3(22.0-52)	38.7±6.5 39(23.0-56)	0.951

Note: Data are expressed as mean±standart deviation, median (min-max). Bold values indicate statistical significance (p<0.05). BUN: blood urea nitrogen, CRP: C-reactive protein

Table 3. Results of survival analyses according to hypokalemia (n=185)

	Total of Events (n/n)	Event-free Survival (day) Mean	Event-free Survival (day) Median	p value
Hypokalemic	31/3	18.3(21.7-26.9)	-	0.688
Normokalemic	154/16	24.4(21.7-27.1)	25.0(20.6-29.3)	

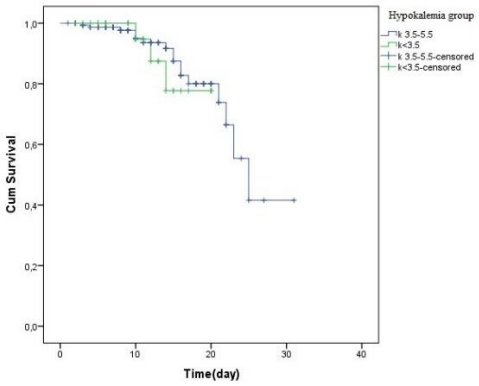

Figure 1. Event-free survival curves according to hypokalemia (n=185)

Associations between hypokalemia and laboratory characteristics of patients are summarized in Table 2. The hypokalemic group had lower levels of serum total protein (p=0.027) and albumin (p=0.02), and higher levels of alkaline phosphatase (p=0.013), gamma glutamyl transpeptidase (p=0.002), total bilirubin (p=0.017), direct bilirubin (p=0.023), serum bicarbonate (p=0.019) and higher blood pH (p=0.001) (Table 2).

Factors affecting hypokalemia were evaluated using multiple logistic regression analysis. According to the backward procedure, pH levels were found to be the only significant risk factor associated with hypokalemia. The risk of hypokalemia is increased 5.73 times in patients with alkalosis. The duration of hospitalization, requirements for intensive care and mechanical ventilation, and hospital mortality were not different in hypokalemic and normokalemic patients. (Table 1). Although mean event-free survival (EFS) was shorter in cases with hypokalemic compared with normokalemic (18.3 vs. 24.4 days), the difference was not statistically significant (p=0.688) (Table 3 and Figure 1).

DISCUSSION

In patients hospitalized for Covid-19 pneumonia, the frequency of hypokalemia was found 16.8% at first admission to the hospital. The duration of hospitalization, requirement for intensive care, mechanical ventilation need, death, and EFS were not different in hypokalemia and normokalemic patients. The only factor that found the risk of hypokalemia was alkalosis.

Our study found that in patients with Covid-19 pneumonia, the frequency of hypokalemia at the time of the first admission to the hospital was quite high. Hypokalemia in Covid-19 patients can be caused by a variety of factors. The renin-angiotensin-aldosterone (RAS) system is one of the most significant determinants of serum potassium levels[18]. Hypokalemia can be caused by the interaction between SARS-CoV-2 and RAS. ACE-2 receptors are present in abundance in the kidneys and mediate the entry of SARS-CoV-2 into cell[3]. Mechanisms of renal damage may occur through direct viral injury due to SARS-CoV-2, hypoxic injury, complement activation, endothelial damage, and microthrombi, hypovolemia, renal tubular injury and sepsis[19]. This damage may result in renal tubular potassium loss. In Covid-19 patients, inadequate oral intake due to nausea and vomiting, as well as increased potassium loss due to diarrhea, can also lead to hypokalemia. Hypokalemia may be develop by diuretics used to treat hypervolemia and hypertension[20]. In our patients, there was no relationship between hypokalemia and diuretics. Since diuretics are often used in combination with ACE or ARB inhibitors, their serum potassium-lowering effects may not appear.

Blood gas abnormalities are one of the factors that affect serum potassium levels[21]. Alkalosis may reduce serum potassium levels by causing serum potassium to enter the cell[21]. In our study, we found that alkalosis increased the risk of hypokalemia by 5.73 times. In these patients, vomiting and diuretics may contribute to metabolic alkalosis. In addition, respiratory acidosis due to extensive lung parenchyma involvement due to pneumonia and metabolic alkalosis may develop to compensate for respiratory acidosis.

The effect of hypokalemia on the severity of the disease and the need for intensive care in Covid-19 patients is controversial. In our study, there was no relationship between hypokalemia and laboratory parameters such as CRP, lymphocyte count, fibrinogen, D-dimer, and ferritin, which are indicators of disease severity. Several previous studies have reported that hypokalemia was not associated with the risk of transfer to intensive care and death, as in our study[16,17]. Contrary to these results, hypokalemia was associated with disease severity in 429 patients, and hypokalemia was associated with disease severity and the need for mechanical ventilation in 306 patients[15,22]. According to these studies, this relationship may be due to negative effects such as hypokalemia-induced myocardial dysfunction, ventricular arrhythmia, and respiratory muscle dysfunction[15]. Comprehensive studies involving more patients are needed to evaluate this issue.

In patients with hypokalemia, serum albumin and total protein levels were lower, while total bilirubin, direct bilirubin, ALP, and GGT levels were higher. Acute hepatocellular damage caused by SARS-Cov-2 has been associated with mild transaminase and bilirubin elevations as well as a decrease in serum albumin levels, which may be attributed to direct viral infection, cytokine release syndrome, systemic inflammation, or hypoxic liver damage[23]. These disorders may be due to the simultaneous effects of SARS-CoV-2 on the liver and kidneys. Besides, antiviral drugs can cause both increased liver enzymes and tubular damage in the kidneys.

Our study had some limitations. We could not detect how long after the onset of the disease they applied to the hospital and the first symptoms and signs of the disease. We could not measure urine potassium levels. We could not clearly determine the duration of antiviral drugs used in the days before applying to our hospital. Our knowledge about the treatments used during hospitalization is also limited. Also, our number of patients is insufficient.

In conclusion, our study found that hypokalemia is quite common at first admission in patients hospitalized for Covid-19 pneumonia, and the most important factor associated with hypokalemia was alkalosis. Hypokalemia was not associated with duration of hospitalization, need for intensive care, EFS, and death. More comprehensive studies are required to clarify this issue.

Yazar Katkıları: Çalışma konsepti/Tasarımı: BK, MB, SPY; Veri toplama: TK, ÖD, SPY; Veri analizi ve yorumlama: BK, SP, SPY; Yazı taslağı: BK, MB; İçeriğin eleştirel incelenmesi: SP, MB, YT; Son onay ve sorumluluk: BK, SP, TK, ÖD, SPY, MB, YT; Teknik ve malzeme desteği: ÖD; Süpervizyon: SP, YT; Fon sağlama (mevcut ise): yok.

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