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Araştırma

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Association of Hypophosphatemia with Morbidity and Mortality in Patients with COVID-19

COVID-19'lu Hastalarda Hipofosfateminin Morbidite ve Mortalitesi ile İlişkisi

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ABSTRACT

Background and Objective: In critical cases, electrolyte disturbances such as hypophosphatemia have been shown to be associated with mortality and in our study, we aimed to examine the relationship between hypophosphatemia, a symptom disorder with COVID-19, and death.

Material and Methodology: This study is a retrospective, cross-sectional investigation that encompasses patients diagnosed with COVID-19 and subsequently admitted for treatment at our hospital. Based on their serum phosphate levels, the patients were bifurcated into two distinct categories: those with serum phosphate levels below 2.5 mg/dl, classified as hypophosphatemic, and those with levels above this benchmark, categorized as non-hypophosphatemic. The comparisons drawn between these two cohorts were facilitated using a range of statistical methodologies, and the resulting findings were subsequently analyzed and interpreted within this framework.

Results: Compared to the hypophosphatemia group, the diagnoses of DM (p<0.001) and CKD (p=0.015) were statistically significantly higher in the group without hypophosphatemia. A statistically significant difference was found between phosphorus groups and mortality and length of stay (p<0.001). In addition, age and length of hospitalization were found to be statistically significantly higher in those who died compared to those who were alive (p<0.001; p=0.002).

Conclusion: Hypophosphatemia has been shown to be associated with mortality in patients with COVID-19, as in many studies and in our study, and it may be a biomarker in predicting severe disease.

Key Words: COVID-19, Phosphorus, Diabetes Mellitus, Mortality

ÖZET

Amaç: Kritik hastalıklarda hipofosfatemi gibi elektrolit bozukluklarının mortalite ile ilişkisi gösterilmiştir. Biz de çalışmamızda COVID-19'lu hastalarda bir elektrolit bozukluğu olan hipofosfateminin mortalite ile ilişkisini incelemeyi amaçladık.

Yöntemler: Bu retrospektif kesitsel çalışma, hastanemizde COVID-19 tanısı alıp, yatarak tedavi gören hastaları içermektedir. Hastalar, serum fosfor düzeylerine göre iki gruba ayrılmıştır: serum fosfor düzeyi 2.5 mg/dl'nin altında olanlar (hipofosfatemi) ve bu seviyenin üzerinde olanlar (hipofosfatemi olmayanlar). İki grup arasındaki karşılaştırmalar, çeşitli istatistiksel yöntemler kullanılarak yapılmış ve sonuçlar bu veriler ışığında değerlendirilmiştir.

Bulgular: Hipofosfatemi grubuyla karşılaştırıldığında, hipofosfatemi olmayan grupta DM (p<0,001) ve KBY (p=0,015) tanıları istatistiksel olarak anlamlı yüksekti. Fosfor grupları ile mortalite ve yatış süresi arasında da istatistiksel olarak anlamlı farklılık saptandı (p<0.001). Ayrıca yaş ve yatış süreleri sağ olanlara kıyasla exitus olanlarda istatistiksel olarak anlamlı yüksek bulundu (p<0.001; p=0.002).

Sonuç: Hipofosfatemi yapılan birçok çalışmada ve bizim çalışmamızda da olduğu gibi COVID-19'lu hastalarda mortalite ile ilişkisi gösterilmiştir ve şiddetli hastalığı öngörmede bir biyobelirteç olabilir.

Anahtar Kelimeler: COVİD-19, Fosfor, Diyabetis Mellitus, Mortalite

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Introduction

The COVID-19 epidemic, Coronavirus disease 2019 (COVID-19), which caused a respiratory pandemic for the first time in the world, has infected more than 139 million people today and caused the death of approximately 3 million people [1,2]. In many studies, it has been shown that COVID-19 causes diseases and complications in the cardiovascular, gastrointestinal (GI) and urogenital systems as well as the respiratory system [2]. COVID-19 virus infection can cause electrolyte disorder and fluid imbalance in the body by affecting the gastrointestinal and urogenital system, and this situation can be dangerous and fatal if not controlled [2]. Electrolyte and acid-base imbalances occupy an important place in many serious diseases, as well as in COVID-19 disease, which causes severe viral pneumonia together with acute respiratory distress syndrome (ARDS) from asymptomatic infection [2-4].

In a small number of studies, it has been shown that electrolyte disorders such as hyponatremia, hypokalemia, hypochloremia, and hypocalcemia are among common electrolyte disorders that increase mortality and morbidity in patients [1,4,5]. In acute critical illnesses, patients may become prone to serum phosphorus disorders [6]. Hypophosphatemia, especially observed in critically ill patients, is a common electrolyte disorder associated with numerous side effects [7]. The prevalence of hypophosphatemia reported in critical illnesses varies between 10% and 80% in different studies [6].

Especially hypophosphatemia, which is among the sepsis findings, is also associated with high morbidity and mortality in Covid-19 disease [6-7]. In Covid-19 infection, hypophosphatemia develops as a result of hypovolemia, tissue hypoxia, septic systemic inflammation (cytokine storm), heart failure, rhabdomyolysis, and immune complex deposition [8]. Hypophosphatemia is potentially life-threatening, as phosphate is one of the main intracellular anions required in numerous biological processes [8-9].

During the course of critical illnesses, electrolyte disturbances such as hypophosphatemia frequently occur and have been shown to significantly impact mortality rates [6, 7]. Interestingly, such disturbances are often overlooked in our clinical practice or considered secondary in diagnostic and treatment processes. However, recent research has indicated that hypophosphatemia could potentially have a substantial effect on a patient's overall health status and prognosis.

The COVID-19 pandemic has broadly reshaped the focus of medical research, with many investigators trying to understand the biological and physiological changes caused by the disease [1,4,5]. In this context, our study aims to examine the possible impact of hypophosphatemia, an electrolyte disturbance that COVID-19 may induce, on mortality rates.

The fundamental rationale for this study is to understand the potential influence of electrolyte disturbances on clinical progression and mortality rates in COVID-19 patients. Through this study, we aim to gain more insight into the effect of hypophosphatemia associated with COVID-19 on mortality and to apply this knowledge in our clinical practices. Our hypothesis is that hypophosphatemia in COVID-19 patients has a significant effect on mortality rates. If this hypothesis is confirmed, it could be suggested that strategies maintaining electrolyte balance could play a crucial role in the management of COVID-19.

Materials and Methods

Study Design and Patients

This study, consisting of 673 RT–PCR positive COVID-19 hospitalized patients is a retrospective cross-sectional study conducted at Bakırköy Dr. Sadi Konuk Training and Research Hospital.

Patients were tested for SARS-CoV-2 according to the epidemiological and clinical criteria specified in the National Guideline for the Diagnosis and Treatment Protocol for SARS CoV-2 Infection circulated by the Ministry of Health of the Republic of Turkey. Nasopharyngeal and oropharyngeal specimens were collected from patients once and samples were tested for SARS-CoV-2 using real-time RT-PCR at our hospital. Informed consent was obtained from each subject before the study. Bakirkoy Dr. Sadi Konuk Training and Research Hospital Medical Research Ethics Committee approved the study. Work was done to protect patient privacy and in accordance with the Declaration of Helsinki. (Ethical approval date:30/04/2020, Approval number: 2020-09-15). Necessary permissions were obtained from the hospital administration for the study.

Data were obtained from patient files and hospital registry system. Demographic characteristics of patients (age, gender), RT-PCR result (+/-), radiological findings, laboratory findings (leukocyte, platelet, lymphocyte, hemoglobin, hematocrit, neutrophil, eosinophil counts, and urea, creatinine, albumin, lactate dehydrogenase (LDH)), C-reactive protein (CRP), ferritin, procalcitonin, fibrinogen, prothrombin time (PT), activated partial thromboplastin time (APTT), D-Dimer, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine kinase (CK) , co-morbid diseases (diabetes mellitus, hypertension, ischemic heart disease, etc.), COVID-19 treatments, need for intensive care, length of stay were recorded, and complications and survival of the patients in the hospital were also evaluated.

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Statistical Analysis

SPSS 25.0 package program was used for data analysis in the study. Descriptive data on the socio-demographic information of the participants are given in the form of frequency tables (N and %). Data belonging to continuous variables are given as mean±SD.

When the data of the study were analysed in terms of normality assumptions, Kolmogorov-Smirnov values were determined as p>0.05. Independent t test, one of the parametric tests, was used to determine whether there was a significant difference between various variables and mortality and phosphorus groups. ROC analysis results of phosphorus values predicting mortality are given. Chi Square test or Fisher's Exact test was used to compare categorical variables. Finally, the results of Multivariate Logistic Regression on Mortality Presence of Various Clinical Factors are given. p<0.05 was considered statistically significant.

Results

A total of 673 COVID-19 patients were included in this study and were divided into two groups, hypophosphatemia and non-hypophosphatemia, according to their serum phosphorus level at presentation. Values of serum phosphorus level below 2.5 mg/dl were considered as hypophosphatemia. The mean age of the patients was 61.72±12.79 years.

Of the patients, while 64.2% (n=432) were male, 35.8% (n=241) were female (Table 1). The mean hospital stay at the time of admission was 16.98±11.01 days (Table 1).

Diabetes mellitus was the most common comorbidity with 66.1%(n=445) of the patients included in the study. (Table 1)

Compared to the hypophosphatemia group, DM (p<0.001) and CKD (p=0.015) were found to be statistically higher in the group without hypophosphatemia. (Table 2)

Table 1. Distributions of Descriptive Information Pertaining to Patients

		N	%
Gender	Female	241	35,8
	Male	432	64,2
Phosphorus	Low	362	53,8
	Normal-High	311	46,2
Mortality	Ex	178	26,4
	Discharge	495	73,6
		Mean±SD	**Median (min-max)**
Age		61,72±12,79	63,00 (18,00-97,00)
Hospitilazition		16,98±11,01	11,01 (2,00-104,00)
Phosphorus		2,47±0,78	0,78 (0,40-8,50)
		Absent N (%)	**Present N (%)**
Hypertension		308 (45,8)	365 (54,2)
Diabetes Mellitus		228 (33,9)	445 (66,1)
COPD-Asthma		607 (90,2)	66 (9,8)
CKD		631 (93,8)	42 (6,2)
CVD		516 (76,7)	157 (23,3)
CHF		626 (93,0)	47 (7,0)
Cancer		648 (96,3)	25 (3,7)
Chronic Liver Disease		670 (99,6)	3 (0,4)
Other		584 (86,8)	89 (13,2)

Table 2. Comparison of Various Variables According to Phosphorus Groups

	Phosphorus		
Gender, N(%)	**Normal-High N=311**	**Low N=362**	**p**
Female	119 (49,4)	122 (50,6)	0.218[a]
Male	192 (44,4)	240 (55,6)	
Age, Mean±SD	61,40±11,66	62,00±13,70	**0.545[b]**
Hospitilazition, Mean±SD	13,30±8,93	20,14±11,64	**<0.001[b]**
HT, N(%)			
Absent	134 (43,5)	174 (56,5)	0.196[a]
Present	177 (48,5)	188 (51,5)	
DM, N(%)			
Absent	63 (27,6)	165 (72,4)	**<0.001[a]**
Present	248 (55,7)	197 (44,3)	
COPD-Astım, N(%)			
Absent	281 (46,3)	326 (53,7)	0.897[a]
Present	30 (45,5)	36 (54,5)	
CKD, N(%)			
Absent	284 (45,0)	347 (55,0)	**0.015[a]**
Present	27 (64,3)	15 (35,7)	
CVD, N(%)			
Absent	229 (44,4)	287 (55,6)	0.084[a]
Present	82 (52,2)	75 (47,8)	
CHF, N(%)			
Absent	291 (46,5)	336 (53,6)	0.700[a]
Present	20 (43,5)	26 (56,5)	
Cancer, N(%)			
Absent	300 (46,3)	349 (53,8)	0.970[a]
Present	11 (45,8)	13 (54,2)	
Chronic Liver Disease, N(%)			
Absent	311 (46,4)	359 (53,6)	0.253[b]
Present	0 (0,0)	3 (100,0)	
Other, N(%)			
Absent	280 (47,9)	304 (52,1)	**0.021[a]**
Present	31 (34,8)	58 (65,2)	
SpO2	90,91±5,56	88,89±7,43	**<0.001**
HbA1c	8,72±2,33	8,71±2,15	0.971
HGB	12,7±1,9	13,02±1,92	**0.032**
HTC	38,17±5,09	38,73±5,21	0.160
WBC	8142,84±4406,23	8277,29±4577,1	0.699
Lymphocyte	1281,4±762,31	1106,75±902,95	**0.007**
Neutrophil	6343,06±4048,14	6634,59±4179,4	0.360
Eosinophil	48,44±106,21	27,42±82,48	**0.004**
PLT	232,05±97,41	204,32±95,59	**<0.001**
Glucose	224,01±114,24	198,33±97,58	**0.003**

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Table 2. Comparison of Various Variables According to Phosphorus Groups *(continued)*

AST	43,34±34,04	51,82±35,77	**0.002**
ALT	38,62±39,39	38,72±34,63	0.971
Urea	48,72±31,14	47,64±26,33	0.626
Creatinine	1,59±4,83	1,08±0,84	0.067
LDH	379,85±180,83	445,25±228	**<0.001**
Albumin	7,63±19,19	14,6±15,34	**<0.001**
Ferritin	381,34±455,57	323,34±654,02	0.204
Triglyceride	176,73±144,83	284,29±508,99	**<0.001**
CK	334,3±593,74	612,62±1045,74	**<0.001**
Procalcitonin	26,26±69	74,39±145,75	**<0.001**
CRP	84,6±77,45	56,42±84,63	**<0.001**
Fibrinogen	522,83±122,08	538,79±147,21	0.130
PTZ	14,54±5,82	15,19±7,42	0.226
APTT	38,03±26,47	36,24±9,58	0.233
D-Dimer	0,82±1,42	0,88±1,33	0.543

a=Chi Square test, b=Independent t test, p<0.05 is statistically significant

A statistically significant difference was found between phosphorus groups and mortality (p<0.001). While the mortality of the patients in the group without hypophosphatemia was 14.5%, it was found as 36.7% in the group with hypophosphatemia.

A statistically significant difference was found between the phosphorus level and mortality among the patients who were discharged (p<0.001). The mean phosphorus level was higher in the discharged group compared to the group with mortality (Table 3).

To differentiate the presence of mortality, the estimation of the Phosphorus parameter was statistically significant (p<0.001). The AUC in the ROC analysis designed to differentiate the phosphorus values from mortality was 0.703 (95%[CI], 0.654-0.751) (Figure 1). Phosphorus values at a cut-off value of ≤2.31 have a sensitivity of 66.3% and a specificity of 66.1% in the diagnosis of one-month mortality.

A statistically significant difference was found between the length of stay and the phosphorus groups (p<0.001). The length of stay was found to be longer in the hypophosphatemia group than in the other group. (Table 2)

In the hypophosphatemia group, compared to the non-hypophosphatemia group; lymphocyte (p=0.007), eosinophil (p=0.004), platelet (p<0.001) counts were found to be significantly lower, while AST (p=0.002), LDH (p<0.001), triglyceride (p<0.001), CK (p<0.001) levels were found to be significantly higher. Glucose (p=0.003) and CRP (p<0.001) measurements; It was found to be lower in the group with hypophosphatemia. (Table 2)

No statistically significant difference was found between mortality and gender (p=0.219). Patient age (p<0.001) and length of stay (p=0.002) showed a statistically significant difference between mortality and discharged groups. Age and length of hospital stay were higher in the group with mortality compared to the discharged group (Table 3).

At first admission, lymphocyte (p=0.004), neutrophil (p=0.013), eosinophil (p=0.001), PLT (p=0.003), AST (p=0.031), urea (p<0.001), creatinine (p=0.003) 0.036), LDH (p<0.001), albumin (p<0.001), CK (p<0.001), procalcitonin (p<0.001), CRP (p<0.001), fibrinogen (p=0.003) and D-Dimer (p =0.042) levels showed a statistically significant difference between mortality groups. Neutrophil, AST, urea, creatinine, LDH, CK, procalcitonin, CRP, fibrinogen and D-Dimer measurements were higher in the group with mortality compared to those who were discharged. Lymphocyte, eosinophil and PLT measurements were found to be higher in the discharged group compared to the mortality group. (Table 3)

As a result of univariate analysis; a statistically significant difference was found between the groups in terms of age, length of stay, CRF, lymphocyte, neutrophil, eosinophil, PLT, AST, urea, creatinine, LDH, CK, procalcitonin, CRP, fibrinogen, D-Dimer values according to mortality status (p< 0.05). These variables, which were found to be significant as a result of univariate analysis, were included in the Multivariate logistic regression model. According to the results of the multivariate logistic regression model, the increase in age (OR: 1.05% 95% CI: 1.03-1.08), the increase in urea values (OR: 1.01% 95% CI: 1.01-1.01), the increase in LDH values (OR: 1.00 95% CI: 1.00-1.01) 1.01), an increase

Table 3. Comparison of Various Variables According to Mortality Groups

	Mortality		
Gender, N(%)	**Discharged N=495**	**Ex N=178**	**p**
Female	184 (76,3)	57 (23,7)	0.219[a]
Male	311 (72,0)	121 (28,0)	
Age, Mean±SD	60,45±13,20	65,25±10,87	**<0.001[b]**
Hospitilazition, Mean±SD	16,21±11,21	19,12±10,16	**0.002[b]**
Phosphorus			
Normal-High	266 (85,5)	45 (14,5)	**<0.001[a]**
Low	229 (63,3)	133 (36,7)	
Phosphorus, Mean±SD	2,58±0,65	2,16±1,01	**<0.001[b]**
HGB	12,90±1,85	12,80±2,08	0.583
WBC	8053,54±4470,26	8664,61±4549,75	0.120
Lymphocyte	1244,3±857,07	1029,37±790,67	**0.004**
Neutrophil	6262,98±4022,93	7158,65±4317,97	**0.013**
Eosinophil	42,94±102,35	21,00±66,77	**0.001**
PLT	223,76±95,65	198,69±99,91	**0.003**
AST	46,14±33,76	52,77±38,64	**0.031**
ALT	39,52±38,71	36,32±31,2	0.321
Urea	44,2±24,11	59,08±36,43	**<0.001**
Creatinine	1,05±0,83	2,05±6,31	**0.036**
LDH	387,12±176,44	492,38±268,56	**<0.001**
Albumin	8,89±17,42	18,28±16,04	**<0.001**
Ferritin	365,04±588,67	310,33±501,02	0.297
CK	375,55±704,06	787,2±1190,52	**<0.001**
Procalcitonin	32,05±71,06	107,57±187,81	**<0.001**
CRP	77,82±78,79	46,44±88,32	**<0.001**
Fibrinogen	520,36±123,97	561,23±161,72	**0.003**
D-Dimer	0,78±1,34	1,04±1,43	**0.042**

a=Chi Square test, b=Independent t test, p<0.05 is statistically significant

in procalcitonin values (OR:1.01, 95% CI:1.01-1.02) is risky for the presence of mortality, an increase in phosphorus values (OR: 0.49, 95% CI: 0.35-0.70) for the presence of mortality. It has been determined that it reduces the risk.

Discussion

Although Hypophosphatemia is defined as a serum phosphorus level below 2.5 mg/dL in adults, distinct symptoms of hypophosphatemia rarely occur unless the serum phosphorus level is less than 2 mg/dL in different studies. In our study, we accepted values below 2.5 mg/dl as hypophosphatemia [10].

In present study; male patients constituted 64.2% of the total patients. This situation was considered to be because of the higher immunological response in male patients and the protective effect of female sex hormones. In other studies in the literature, it has been associated with the severe course of Covid 19 disease and the higher hospitalization rates in male patients than female patients. [11-12].

Malinowska et al. stated in their study that hyperphosphatemia may contribute to the development of severe COVID-19. However, in many other studies; it has been shown that hypophosphatemia is associated with increased mortality in patients with Covid 19, especially in critical diseases such as sepsis. In our study, similar to previous studies, mortality was significantly higher in patients with hypophosphatemia than in patients with low serum phosphorus levels [1,14,15].

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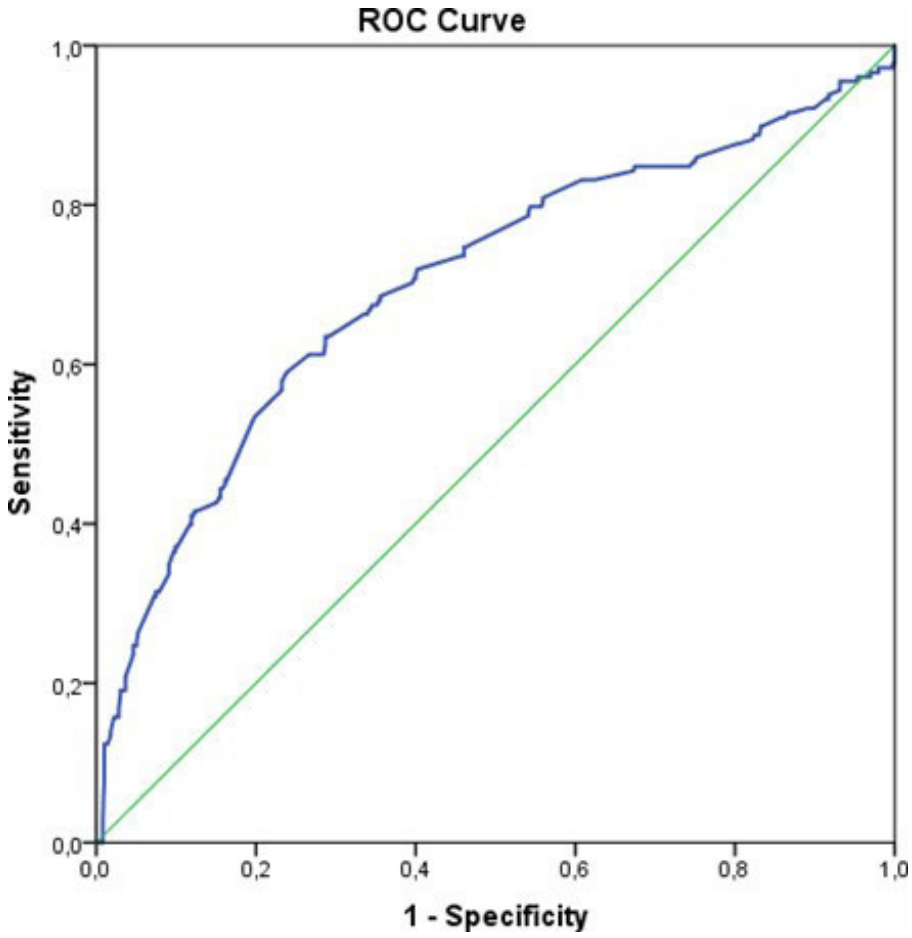

Figure 1. ROC Curve Related to Phosphate Levels According to Mortality A statistically significant correlation has been discerned between mortality rates and a threshold phosphate level of 2.26 (p=0.001; p<0.01). It could be deduced that instances with phosphate levels at or exceeding 2.26 demonstrate a mortality risk that is elevated by a factor of 4.363. For phosphate, the calculated odds ratio stands at 4.363 (95% Confidence Interval: 3.028-6.286).

It has been shown that some biomarkers may be associated with severe disease in patients with Covid 19 who have severe systemic disease [16-17]. In our study, similar to previous studies, neutrophil count, Ast, urea, Ldh, Ck, Crp, fibrinogen and D-Dimer measurements were found to be higher in the mortality group compared to the patients who were discharged. Lymphocyte, eosinophil and platelet count measurements were higher in the discharged group compared to the mortality group. The presence of biomarkers such as clinical and inflammatory markers in predicting severe disease is undoubtedly of great importance for the clinical management of the disease. In addition to these biomarkers, blood phosphorus level can be added, but more comprehensive studies are needed for this.

Three basic mechanisms are held responsible for the formation of hypophosphatemia. First, inadequate intake caused by malnutrition, malabsorption, etc. reasons; the second one is an excess of excretion in the form of loss from the gastrointestinal tract and kidneys [18-19]. The third is transition from the extracellular space to the intracellular space. This situation mostly occurs during the treatment of diabetic ketoacidosis, refeeding after prolonged fasting, and acute respiratory alkalosis [20-22]. In Covid 19 patients, especially in the severe course of the disease, hypophosphatemia may be observed due to the transition from extracellular to intracellular due to inadequate intake, malabsorption, gastrointestinal damage, renal damage and respiratory alkalosis [13].

In our study, diabetes mellitus was found to be the highest comorbid condition with 66%. The reason for this is -similar to the literature- the probability of severe disease and hospital admission in diabetic patients was higher than in non-diabetic patients [23]. However; it should not be ignored that in patients with diabetes mellitus, insulin therapy, which is administered differently from other patients, increases the transfer of extracellular phosphate into the cell, in other words, hypophosphatemia can be observed with transcellular shift [20].

As a result, hypophosphatemia is an electrolyte disorder that has been shown to be associated with mortality in

patients with Covid 19, as in many studies including ours, and it can be a biomarker in predicting severe disease. However, it is not yet known whether correction of hypophosphatemia reduces mortality. More comprehensive observational studies are needed to learn all of these. Our study has some limitations as it is a retrospective observational study and was conducted in a single center.

Conflict of Interest: The authors declare no conflict of interest related to this article.

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Ethics Committee Approval: Bakirkoy Dr. Sadi Konuk Training and Research Hospital Medical Research Ethics Committee approved the study. Work was done to protect patient privacy and in accordance with the Declaration of Helsinki. (Ethical approval date:30/04/2020, Approval number: 2020-09-15).

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