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Original Article

Is low level of serum phosphorus within normal range a predictive parameter for disease severity in hospitalized COVID-19 patients?

Normal aralıktaki düşük serum fosfor seviyesi, hastanede yatan COVID-19 hastalarında hastalık şiddeti için öngörücü bir parametre midir?

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Abstract

Aim: Patients with COVID-19 may develop several electrolyte imbalances that can cause multiple clinical complications. Low serum phosphorous level usually leads to a decreased muscle ATP synthesis which may cause diaphragmatic or other kinds of respiratory muscle weakness. We investigated the predictive power of serum phosphorus levels in patients with hospitalized COVID-19.

Material and Methods: This is a retrospective and observational study of 957 patients with SARS-CoV-2, who were diagnosed with COVID-19 by real-time PCR testing and hospitalized due to moderate and severe COVID-19 pneumonia.

Results: Among 957 patients with COVID-19 pneumonia, 387 (40,4%) were moderate and 570 (59,6%) were severe. Phosphorus was significantly lower in severe patients, within the reference range. Our final analysis showed that age, respiratory rate, d-dimer, and phosphorus level were independent risk factors for disease severity. Phosphorus was found to be negative correlated with respiratory rate (r: 0,091, p=0,005) and was positive correlated with SPO2 (r: 0,069, p=0,03).

Conclusion: Our results suggest prognostic significance of phosphorus level, which has correlation with the respiratory rate and has considered to be independent risk factor for disease status, especially in severe patients. It is concluded that phosphorus monitoring, at least in severe patients, may prevent serious clinical consequences such as respiratory insufficiency.

Keyword; COVID-19, pneumonia, phosphorus, respiratory muscle, disease status, predictive value

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Öz

Amaç: COVID-19'lu hastalarda, çoklu klinik komplikasyonlara neden olabilecek birkaç elektrolit dengesizlikleri görülebilir. Düşük serum fosfor seviyesi genellikle, diyafram veya diğer solunum kas güçsüzlüğüne neden olabilen kas ATP sentezinin azalmasına yol açar. Bu çalışmada hastanede yatan COVID-19 hastalarında serum fosfor düzeylerinin tahmin gücünü araştırdık.

Gereç ve Yöntemler: Polimeraz zincir reaksiyonu (PZR) ile COVID-19 tanısı konan ve orta ve şiddetli COVID-19 zatürresi nedeniyle hastaneye yatırılan 957 SARS-CoV-2 hastasının gözlemsel bir çalışması olarak incelendi.

Bulgular: COVID-19 pnömonisi olan 957 hastanın 387'si (%40,4) orta ve 570'i (%59,6) şiddetli idi. Fosfor, ciddi hastalarda referans aralığında önemli ölçüde daha düşüktü. Son analizimiz, yaş, solunum hızı, d-dimer ve fosfor seviyesinin hastalık şiddeti için bağımsız risk faktörleri olduğunu gösterdi. Fosfor solunum sayısı ile negatif (r: 0,091, p=0,005), parmak ucu oksijen satürasyonu (r: 0,069, p=0,03) ile pozitif korelasyon gösterdi.

Sonuç: Sonuçlarımız, solunum hızı ile korelasyon gösteren ve hastalık durumu için bağımsız risk faktörü olarak kabul edilen fosfor düzeyinin özellikle ağır hastalarda prognostik önemini göstermektedir. En azından şiddetli hastalarda fosfor düzeylerinin izlenmesinin solunum yetmezliği gibi ciddi klinik sonuçları önleyebileceği sonucuna varılmıştır.

Anahtar kelime; COVID-19, zatürre, fosfor, solunum kası, hastalık durumu, prediktif değer

Introduction

Pneumonia and acute respiratory distress syndrome (ARDS) are observed major complications of COVID-19. Patients with COVID-19 may also develop several electrolyte imbalances that can cause multiple clinical complications. Phosphorus is essential to many vital physiological processes which makes its homeostatic balance crucial for survival. Phosphorus is one of the most abundant anions in the intracellular space (1). As an essential component in the adenosine 5'-triphosphate (ATP) molecule which is the energy currency of the cell in phosphorylation of the proteins, it plays a central role in the energy production. Phosphorus is also present in nucleic acids and acts as an important intracellular tampon (2). Hence, depleted phosphorus storage may lead to reduced ATP production which may afterwards impair several vital systemic functions, such as immune system and the capability of the lungs to clear edema (3). Intracellular phosphorus is more crucial for some tissues like muscles due to ATP. Previous papers described that low serum phosphorus levels may lead to diaphragmatic or other kind of respiratory muscle weakness as a result of low muscle ATP synthesis. And reduced muscle contraction in respiratory system may cause mortal circumstances like acute heart or respiratory failure, cardiac arrhythmias or cardiac arrest (4,5,6,7,8,9). In addition to that, hypophosphatemia causes diminished intraerythrocytic 2,3-bisphosphoglycerate levels which promotes hemoglobin attraction to oxygen with reducing peripheral oxygen supply and producing left shift in the oxygen dissociation curve. This may seriously reduce the oxygen transfer from erythrocytes to tissues resulting in tissue hypoxia (10,11).

Serum phosphorus level disturbances in patients with pneumonia have been reported (12,13,14,15).

As known, the main clinical manifestations of COVID-19 are related to respiratory. But it may be varying from a mild presence to ARDS or even to cardiac or embolic complications which are potentially fatal. We believe that the clinical link between the phosphorus level and the COVID-19 pneumonia has not been adequately studied so far. The disturbance in electrolyte levels have important implications for patient management, even if they are within their allowed range. During at-risk situations, a systematic search for electrolyte imbalances whose treatment may limit the occurrence of serious consequences seems especially true for phosphorus.

Study Design and Cohort

We performed a retrospective observational study of 1509 patients with SARS-CoV-2, who were diagnosed with COVID-19 by real-time PCR testing, by radiologic involvement for CT scan and hospitalized due to COVID-19 pneumonia at our hospital, level-3 pandemic, from September 01, 2020 to December 31, 2020. Written informed consent forms were obtained for study participation. The hospital electronic database was screened and those patients without clinical or laboratory data or those having pneumonia arising from other causes were excluded from the study. Other criteria for exclusion were the existence

of endocrinological disease, end-stage renal failure, chronic dialysis, chronic use of corticosteroids, immunosuppressive conditions, chronic alcoholism, terminal conditions due to cancer and/or feeding with enteral nutrition supplements, diabetes mellitus, pregnancy or breast feeding. After the exclusion, 957 patients were eligible for the study. All the patients were over 18 years old and were not admitted to the intensive care unit (ICU). Demographic data and comorbidities were recorded. On the basis of COVID-19 related examinations, respiratory rate, oxygen saturation by pulse oximetry (SpO2), and mean oxygen requirement at hospitalization duration were recorded. Our hospital has accredited laboratories standardized for internal and external quality assurance measures to monitor the precision and accuracy of the tests performed. In all cases, blood samples were obtained from peripheral vein within 24 hours of hospitalization. Data were categorized as moderate or severe in accordance with the severity classification based on the Chinese Guidelines for Diagnosis and Treatment of Novel Coronavirus Pneumonia (Trial Version 7) (16). Patients with moderate COVID-19 had fever (>37.3 0C) and respiratory symptoms identified with radiological findings of pneumonia. COVID-19 cases were considered severe if they met any of the following criteria: (1) respiratory distress (≥30 breaths/min), (2) oxygen saturation ≤93% at rest, (3) arterial partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) ≤300 mmHg (l mmHg =0.133 kPa). All patients were scanned with spiral computerized tomography (CT) on admission. Radiologist-evaluated CT results were classified into three categories, mild, moderate and severe involvement (17). All of the cases enrolled in the study were managed in accordance with the COVID 19 treatment protocol of Turkish Health Ministry(18). The research was first registered in the data of Turkish Health Ministry Scientific Research Committee and then reviewed and approved by the Local Ethics Committee (University of Health Sciences, Bakirkoy Dr. Said Konuk Training and Research Hospital, Approval number: 2021/125–15/03/2021). We are committed to protecting the privacy of patients and to comply with the Declaration of Helsinki.

Statistical analysis

Descriptive statistics were expressed as mean ± standard deviation. Median and percentage distributions have been used to determine the deviation from normality. Continuous variables having normal distribution were evaluated by the Student's t-test. Categorical data were evaluated by Chi-square test. Mann-Whitney U test was used to evaluate the continuous variables having abnormal distribution. A $p< 0,05$ was accepted as statistically significant. All statistical analyses were performed in commercially available SPSS software v.21 (Statistical Package for the Social Sciences Inc., Chicago, IL, USA). Receiver operating characteristic (ROC) curves were used to obtain the best parameters for predicting the mortality from phosphorus levels which were later incorporated into the cox regression model. Possible factors identified with multivariate analyses were further entered into the Cox regression model, with backward selection, to determine independent predictors of disease severity and death. The univariate effects of type of age, respiratory rate, d-dimer and phosphorus on disease severity of patients were investigated using the log rank test. The proportional hazards assumption and model fit was assessed by means of residual (Schoenfeld and Martingale) analysis.

Results

Among 957 patients with COVID-19 pneumonia, 387 (40,4%) were moderate and 570 (59,6%) were severe. No significant difference in sex was found between moderate and severe patients. Severe patients were significantly older than the moderate group. Severe patients exhibited a significantly higher incidence of hypertension (OR:1,45, 95% CI:1,10-1,90) and atrial fibrillation (OR:3,10, 95% CI:1,42-6,76) than the moderate. No significant difference was found between two groups for other comorbid diseases, such as prior coronary artery disease, prior stroke, chronic obstructive pulmonary disease, asthma bronchial and prior stroke. Body temperature, systolic and diastolic blood pressure and heart rate were not significantly different between groups. SpO2 under oxygen support was significantly lower in severe patients, and respiratory rate was significantly higher than in the moderate, with a mean demand of 7,9 liters/per minute oxygen supplement (Table 1). Lymphopenia was significantly lower whereas neutrophil counts were significantly higher in the severe group than in the moderate. Blood glucose, urea, creatinine, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, C- reactive protein, troponin I, d-dimer, fibrinogen and ferritin level were also significantly higher in severe patients than in the moderate. No significant difference in procalcitonin was found between groups although albumin was significantly lower in the severe patients. Sodium, potassium, magnesium and calcium values

were significantly higher in severe patients than in moderate patients, within the reference range. Also, phosphorus was significantly lower in severe patients, within reference range. Regarding their CT results, the moderate group had (35,9%) mild, (54,3%) moderate and (9,8%) more than severe involvement. The severe group had (10,4%) mild, (44%) more than moderate and (45,6%) severe involvement. CT results revealed a statistically significant involvement of severity in the severe group than in the moderate (Table 2).

Table 1. Evaluation of baseline characteristics and comorbidities for moderate and severe patients.

	Moderate (n=387)	Severe (n=570)	P values
Age, years	55,2±16,32	61,3±14,97	<0,001
Female, n (%)		209(36,6%)	NS
Respiratory rate, per minute	16,47±2,5	23,61±4,48	<0,001
SpO2¶	95,12±1,47	93,82±2,09	<0,001
Body temperature, oC	36,91±0,67	36,99±0,72	NS
Heart rate, per minute	82,79±13,7	83,08±15,97	NS
Systolic blood pressure, mmHg	124,30±17,69	124,72±17,36	NS
Diastolic blood pressure, mmHg	70,34±10,14	70,10±10,61	NS
Arterial hypertension on treatment	119(30,7%)	223(39,1%)	0,008
Prior coronary artery disease	35(9%)	70(12,3%)	NS
Chronic atrial fibrillation	8(2%)	35(6,1%)	0,003
Heart Failure	10(2,5%)	27(4,7%)	NS
COPD¶¶	14(3,6%)	27(4,7%)	NS
Asthma bronchiale	34(8,8%)	51(8,9%)	NS
Prior stroke	7(1,8%)	21(3,7%)	NS

¶SPO2; median; under oxygen support
¶¶ COPD; Chronic obstructive pulmonary disease

73 patients who had died from respiratory failure were all in the severe group. Mortality rate was 12,8 % in severe patients. The duration of hospitalization was found to be significantly higher in severe patients (12,89±7) compared with the moderate. Our final multivariate regression analysis showed that these were independent risk factors for disease severity (Table 3). Phosphorus and respiratory rate was negatively correlated (r:-0,091, p=0,005) as shown Figure 1. Phosphorus and SPO2 was positively correlated (r:0,069, p=0,03) shown in Figure 2.

Our findings show that serum phosphorus level serves as a powerful indicator in patients with hospitalized COVID-19 with regard to the clinical consequences awaiting them.

Table 2. Evaluation of laboratory, CT results and mortality for moderate and severe patients.

Characteristics Count	Moderate (n=387)	Severe (n=570)	P values
Neutrophil, cells/mL	4,28±2,28	6,12±3,13	<0,001
Lymphocytes, cells/mL	1,35±0,6	1,07±0,53	<0,001
Monocytes, cells/mL	0,56±0,27	0,52±0,31	0,05
Platelets, cells/mL	237,73±97,73	249,69±110,26	NS
Hematocrit, %	38±4,51	38,13±4,31	NS
Glucose, mg/dL	122,34±35,61	137,17±51,04	<0,001
Urea, mg/dL	30,92±14,63	40,90±23,13	<0,001
Creatinine, mg/dL	0,80±0,27	0,86±0,53	0,03
ALT, U/L	39,36±32,21	50,17±45,7	<0,001
AST, U/L	39,26±23,89	49,29±34,67	<0,001
Lactate dehydrogenase, U/L	298,44±99,96	409,81±175,69	<0,001
Potassium, mEq/L	4,13±0,44	4,22±0,52	0,009
Sodium, mEq/L	137,86±3,69	137,19±3,81	0,007
Magnesium, mg/dL	2,05±0,25	2,08±0,28	0,05
Calcium, mg/dL	8,85±0,57	8,58±0,55	<0,001
Phosphour, mg/dL	3,21±0,67	3,03±0,71	<0,001
C-reactive protein, mg/L	72,89±64,73	122,28±80,7	<0,001
Procalcitonin, ng/mL	0,2±0,77	0,43±2,93	NS
Ferritin, mcg/L	378,86±420,06	644,77±635,19	<0,001
D-dimer, mcg FEU/mL	0,63±1	0,97±1,35	<0,001
Fibrinogen, mg/dL	479,28±122,1	533,18±137,63	<0,001
INR	1,05±0,2	1,08±0,21	NS
Troponin I, ng/mL	7,74±19,38	28,46±74,78	0,02
Albumin, g/dL	37,97±5,41	34,42±4,78	<0,001
CT results (n,%)			<0,001
Mild involvement	139(35,9%)	59(10,4%)	
Moderate involvement	210(54,3%)	251(44%)	
Severe involvement	38(9,8%)	260(45,6%)	
Duration of hospitalization, day	8,1±3,6	12,89±7	<0,001

Table 3. Multivariate cox regression analysis on the risk factors associated with disease severity in patients with COVID-19.

Variable	Univariate			Multivariate		
	HR	95%	p	HR	95%CI	p
Age, (years)	0.97	0.96-0.98	<0,001	1.25	1.13-1.36	0.005
Respiratory rate, per minute	0.42	0.38-0.47	<0,001	0.26	0.16-0.35	0.05
SpO2¶	1.47	1.36-1.59	<0,001			
D-dimer, mcg FEU/mL	0.73	0.63-0.85	<0,001	1.55	1.51-1.59	0.005
Lactate dehydrogenase, U/L	0.99	0.99-0.99	<0,001			
Troponin I, ng/mL	0.97	0.96-0.98	0,02			
Fibrinogen, mg/dL	0.99	0.96-0.99	<0,001			
Ferritin, mcg/L	0.99	0.99-0.99	<0,001			
Phosphour, mg/dL	1.42	1.18-1.72	<0,001	1.8	1.71-1.99	0.015
Calcium, mg/dL	2.43	1.88-3.14	<0,001			
Duration of hospitalization, day	0.82	0.79-0.85	<0,001			

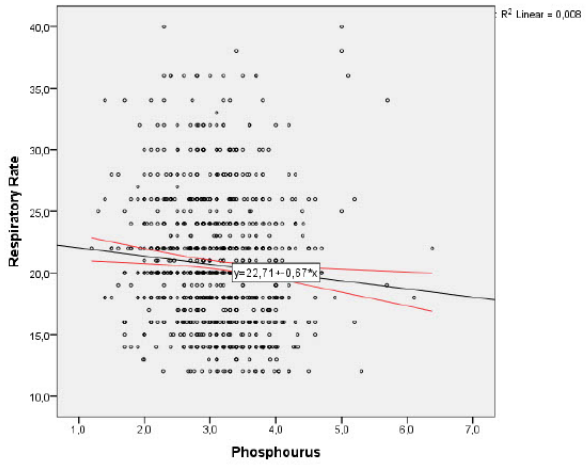

Figure 1: Correlation between phosphorus level and respiratory rate.

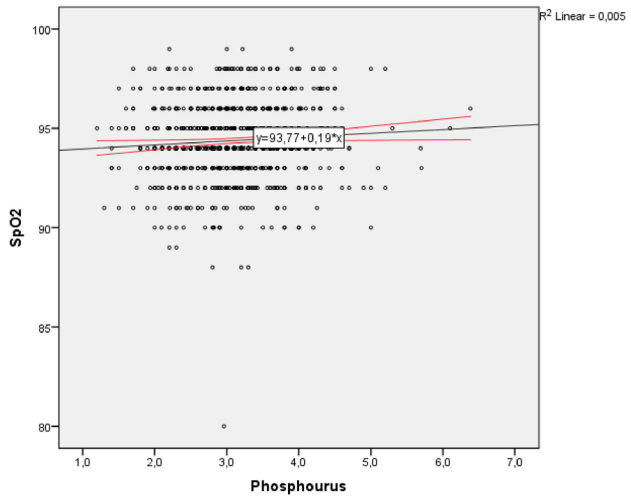

Figure 2: Correlation between phosphorus level and SPO2.

Discussion

Hospitalized patients were frequently observed to suffer from serum phosphorus derangement. It was encountered in 2-3 % of the patients hospitalized with medical illnesses, rising even up to 28% in intensive care unit patients.(7,19,20,21). Although a great deal of attention is paid to other electrolyte disturbances, abnormalities in phosphorus homeostasis is usually ignored in part due to its asymptomatic nature (22).

The essential role of hypophosphatemia is known in impaired chemotaxis, phagocytosis, and bactericidal activity of macrophages (23). Studies have previously revealed that overt hypophosphatemia was followed by serious clinical consequences (24). A longer stay in ICU and hospital, a prolonged duration of mechanical ventilation, an increased risk of arrhythmia, a higher rate of respiratory muscle dysfunction and a higher mortality due to respiratory illnesses were observed among patients with hypophosphatemia (22,25). Severe hypophosphatemia could even lead to rhabdomyolysis, metabolic encephalopathy and respiratory failure (26). Some studies show that hypophosphatemia can cause a decrease in cardiac contractility which may end up with acute cardiac/cardiorespiratory insufficiency, arrhythmia and/or even cardiorespiratory arrest (27,28,29,30). There are several studies showing an improvement in cardiac functions and a reduction in the incidence of arrhythmia after phosphorus replacement in severe and/or critically ill patients (27,31,32,33,34,35). It has been demonstrated that oral supplementation with a neutral phosphate salt in patients with hypophosphatemia after renal transplantation enhances the composition of phosphate in muscle tissue (36). However, we could not find any published investigation in the literature about phosphate replacement in the respiratory weakness.

Some previous studies have shown contradictory data regarding the mortality risk in hospitalized patients with hypophosphatemia. For example, Fisher et al. found hypophosphatemia to be associated with longer hospital stay, but not with higher mortality in patients with respiratory illness (13). On the other hand, hypophosphatemic patients with pneumonia or any other critical conditions were reported to have a longer hospital stay and/or a higher mortality when compared with normophosphatemic patients (12,31,37,38,39,40).

There are a few studies that associate the mortality and hospitalization rate to lower phosphorus levels, within the normal range, in the literature. Barash et al. showed that lower phosphorus levels, within the normal range were related to a higher rate of mortality in 30-day hospitalization at emergency department admission which reached to a total mortality in 90-day patients (41). The largest retrospective study of 42336 hospitalized patients demonstrated a higher in-hospital mortality rate associated with normal-range serum phosphorus abnormalities at admission. Their findings implied that low serum phosphorus level patients had higher all-cause mortality compared with patients with similar demographic and clinical characteristics, yet with a serum phosphorus level high, within normal range (42). However, there is no such data in COVID-19 pneumonia for phosphorus yet. Our results may not indicate

higher mortality rate or longer duration of hospital stay in low serum phosphorus (within reference range) patients with COVID-19 pneumonia, but it is associated with disease status.

Prior to any medical intervention, abnormalities in serum electrolyte levels are commonly observed in many viral diseases. A significantly low serum phosphorus and calcium within reference range in children with COVID-19 were observed (43). In our study, low-normal phosphorus levels were found to correlate with respiratory rate and SpO2, under oxygen support. These results suggest that a lower level of phosphorus is a factor that causes weakness in respiratory muscle contractility, a situation which contributes to the development of hypoxia related fatal complications and increases the severity in COVID-19 pneumonia.

COVID-19 pneumonia disreputably causes death after a rapidly progressing respiratory failure. Age and d-dimer levels are currently accepted markers of disease severity and mortality in COVID-19. Increased respiratory rate is also among the negative prognostic factors. The fact that, low phosphorus level within reference range is an independent risk factor in predicting disease severity in COVID-19 pneumonia.

Due to the lack of knowledge, identifying low-normal phosphorus levels as hypophosphatemia shows diversity in clinical practice. Bearing that in mind it may have dire clinical consequences even if it is within the reference range, characterization of its pathological effects may lead to a better treatment of the patients. A more in-depth investigation of the role of phosphorus in COVID-19 patients may seriously help prevent its progression during treatment. Our results affirm that more precise treatment recommendations are needed for the phosphorus which calls for more research to be focused on phosphorus-related studies in the future.

Limitations

There are several limitations in our study, first of which is its retrospective design. Secondly, there are other factors that may affect the phosphorus level arising from different etiologies (44,45). The balance of phosphorus is maintained by hormonal control of transport in the intestine, bone, and kidney. In our study, although many conditions were excluded such as endocrinological disease, end-stage renal disease, chronic dialysis patients, chronic corticosteroid intake and diabetes mellitus, there may be some patients who are using drugs such as antiacids which may interact with phosphorus metabolism. And serum calcium levels were not be measured simultaneously, this was another limitation of our study because of calcium and phosphorus shown negative correlation.

It will be more enlightening to examine the predictive power of serum phosphorus levels in patients with COVID-19 prospectively, along with vitamin D levels, parathyroid hormone, fibroblast growth factor-2,3 levels and the urinary phosphorus excretion.

Conclusions

Phosphorus abnormalities are common among the infected patients whose clinical consequences are not well known. In cases where COVID-19 infection causes death from respiratory failure the phosphorus mechanism seems to have a role to play. Our data suggests prognostic significance is presented for the prognostic significance of phosphorus levels to be checked, especially in severe patients, because phosphorus level shows a strong correlation with the respiratory rate which is considered to be an independent risk factor for the disease status. Its monitoring in severe patients may prevent serious clinical consequences such as respiratory insufficiency.

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Conflicts of interest

All authors declare that they do not have any conflict of interest.

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