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Research Article

Phosphate levels and pulmonary damage in COVID-19 patients based on CO-RADS scheme

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Abstract:

Background: Preliminary studies of COVID-19 have provided some evidence that electrolyte disturbances may also be present in patients. In this study, we aimed to evaluate the role of the arrival biochemical indices and symptoms in prediction of lung damage in CT scan based on the CO-RADS system.

Methods: This was a retrospective cross-sectional analytical study. We included patients with laboratory-confirmed COVID-19 infection, from June 15 to July 7, 2020. Patients were included in study if there was no previous history of kidney disease. Demographic, clinical characteristics, laboratory findings, and CO- RADS High-Resolution Computed Tomography (HRCT) of lung reports were collected. Univariate logistic regression was employed first to identify the effects and correlated items. All statistics were performed with SPSS version 18.0.

Results: Computed tomography assessment revealed CO-RADS 2 in 4 (11.1%) patients, CORADS 3 in 1 (2.8%), CO-RADS 4 in 20 (55.6%), and CO-RADS 5 in 11 (30.6%) patients. In the comparison with the study groups based on the HRCT status (CO-RADS II, III vs. CO-RADS IV, V), patients with severe HRCT damage had a significantly lower level of phosphate. Univariate logistic regression analysis showed that only one factor was associated with HRCT damage status (phosphate, P=0.040). Phosphate upper than 4.5 was associated with better HRCT results with OR ratio of 3.71 ($X^2(1)$=5.69; p=0.017).

Conclusion: Higher phosphate levels may be associated with better CT scan of lung outcomes in COVID- 19; while hypophosphatemia is associated with severe lung injuries. This could help clinicians to manage hospitalized patients and may link the COVID-19 and parathyroid gland.

Keywords: Hypophosphatemia, Phosphate, Lung damage, COVID-19, Parathyroid

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Introduction

A new infectious disease, caused by coronavirus 2 (SARS-CoV-2), was discovered in Wuhan, China in December 2019. The rapid emergence of COVID-19 in Wuhan, China, all around the world has resulted in thousands of deaths worldwide. However, many infected patients show mild symptoms such as the

common cold and recover quickly, there is extremely increasing number of deaths due to COVID-19. Preliminary case reports and cohort studies have described many clinical features of patients with coronavirus Disease 2019 (COVID-19). Research studies of COVID-19 have provided some evidence that disturbances in biochemical indices may also be present in patients, including sodium, potassium, chloride, and calcium abnormalities (1,2). No specific treatment is currently available, and current management includes supportive medical care (3). Electrolyte disturbances can have important implications not only for patient management (4) but also for the identification of potential pathophysiological mechanisms underlying COVID- 19, which in turn can lead to new treatment opportunities. However, limited and heterogeneous sample sizes can be seen in the report of electrolyte interpretation in studies to date. Therefore, in order to compare the analysis in this study, we evaluate the electrolyte properties in the initial trials of patients with confirmed COVID-19 (by PCR) infection in Jahrom city of Iran and the relationship with the involvement of patients in HRCT.

Methods:

This was a retrospective cross-sectional analytical study. We admitted patients with COVID- 19 infection who were transferred from clinics to designated hospitals for the treatment of specific infectious diseases (June 15 to July 7). The study design of this study was approved by the ethics committee of Jahrom University of Medical Sciences (code of IR.JUMS.REC.1398.130) and the written informed consent was obtained from the patients due to the retrospective nature of the study. Inclusion criteria of study were patients who were referred to the hospital with a positive PCR test for COVID-19, if there was no previous history of kidney disease (due to possible effect on electrolytes). Exclusion criteria were patient dissatisfaction to participate in the study. Data collection: At the patient's arrival at the emergency department of COVID-19 special ward, 5 cc of blood was taken for blood biochemical indices analysis, and blood sugar was assessed by a glucometer. Measurement of blood biochemical indices for calcium was performed by complexometric colorimetry with o-Cresolphthalein assay (Pars Azmoon, Iran), phosphate by complex complexometric colorimetric with phosphomolybdate (Pars Azmoon, Iran), and levels by Xylidyl blue MG assay kit (ParsAzmoon, Iran). History and physical examination taking was performed by physician. Demographic variables were also recorded. CO-RADS having 5 levels was the classification method used to address severity of lung injury in COVID-19 patients. Category I of CO-RADS indicates a relatively small level of suspicion of COVID-19 pulmonary involvement; category V of CO-RADS implies a very strong level of suspicion of COVID-19 pulmonary involvement based on standard CT findings like ground-glass opacities (5). CT scan was performed at the arrival of patients. Statistical analysis: Continuous variables are presented as the mean ± standard derivation (SD), and the student's t-test was used to determine whether there was a significant difference between the two groups based on the HRCT results (Table 1). Continuous variables of biochemical indices with significant differences were transformed into dummy variables. To examine the effect of demographic factors on the HRCT lung damage, univariate logistic regression was employed first to identify the effects, and correlated items. All statistics were performed with SPSS version 18.0, and the level of significance was set at $P < 0.05$.

Results:

Thirty-six patients were evaluated in this study. There were 20 male and 16 female patients with a mean age of 54.7±17.5 years old. The most common symptom at the arrival was fever (52.8%), followed by fatigue (18%), and dyspnea (44.4%).

Table 1. Blood biochemical indices comparison between CO-RADS II, III vs. IV, V

	CO-RADS Category				
	II & III		IV & V		P
	Mean	STD	Mean	STD	
Mg, mg/dL	1.8	0.07	1.89	0.21	0.35
Phosphate, mg/dl	5.36	1.63	3.43	1.15	0.002
BUN, mg/dL	16.6	11.76	18.42	10.29	0.72
Creatinine*, mg/dL	2.1	2.03	1.28	0.5	0.05
Potassium, mmol/L	3.92	0.36	4.13	0.59	0.45
Na, mEq/L	136.2	1.64	144.9	50.1	0.70
Albumin, g/dL	3.16	0.5	3.39	0.37	0.23
Blood sugar, mg/dL	129.8	46.62	116.03	37.26	0.46
***non-parametric (Mann-Whitney test)**					

Computed tomography Assessment Scheme revealed CO-RADS 2 in 4 (11.1%) patients, CO-RADS 3 in 1 (2.8%),CO-RADS 4 in 20 (55.6%), and CO-RADS 5 in 11 (30.6%) patients. In comparison with the study groups based on the HRCT status (mild, severe), patients with severe HRCT damage had a significantly lower level of Phosphate ($P < 0.01$, Table 1). Phosphate was then transformed into a dummy variable (Table 2) based on the cut-off level of 2.5-4.5mg/dl, as proposed by kit developer, and was used in the univariate logistic regression analysis. To carry out a univariate logistic regression analysis, HRCT damage status was set as the dependent variable, and the independent variables consisted of 13 factors including age, gender, cough, dyspnea, fatigue, body pain, headache, fever, chills, abdominal pain, gastroenteritis, eye redness, phosphate. Univariate logistic regression analysis showed that only one factor was associated with HRCT damage status (Phosphate, P=0.040). So, no further multivariate analysis was conducted (table 2). Phosphate upper than 4.5 mg/dl was associated with better HRCT results with OR of 3.71 ($X2(1)=5.69$; $p=0.017$). As shown in figure 1, there were significant differences in serum level of phosphate in patients with CORADS IV and V versus patients with CO-RADSII ($P<0.05$).

Discussion:

Our study revealed that higher phosphate levels may be associated with better CT scan of lung outcomes in COVID-19; while hypophosphatemia is associated with severe lung injuries. There are some previous studies showing possible role of the hypophosphatemia in severity of the disease. Kormann et al. (6) study evaluated 42 laboratory-confirmed COVID-19 patients, and compared phosphate serum levels of patients admitted to ICU versus other patients admitted to medical department wards. Their result didn't reveal any significant difference between the baseline serum phosphate of these groups of patients. Higher than4.5 mg/dL phosphate level was just seen in 2 (5%) patients who were admitted to ICU while no patient in the medical department had hypophosphatemia. But in our study, there were4patients with higher than 4.5 mg/dL phosphate levels among severely damaged lungs and 5 subjects among the mild HRCT lung damage group. On the other hand, 7 patients had hypophosphatemia in our study and all were experiencing severe lung injury.

Arenas et al. (7) study showed hypophosphatemia in renal patients with confirmed COVID-19 in comparison to renal patients who were negative for the COVID-19 PCR test. Our study is in contrast with Arenas et al. as we observed a wide range of

Table 2. Univariate logistic regression analysis for HRCT damage status

Variable	n(%)	B*	SE	Wald	p	OR	95% CI	
							Lower limit	Upper limit
Age		0.06	0.09	0.72	0.47			
Under 30 y	2(5.6)	0.43	0.26	1.69	0.10	-0.09	0.97	0.08
30-60 y	18(50)	0.10	0.12	0.88	0.39	-0.14	0.35	0.02
60 and higher	16(44.4)	-	-	-	-	1.00	-	-
Gender								
Male	20(55.6)	0.73	0.98	0.98	0.46	2.08	0.30	14.25
female	16(44.4)	-	-	-	-	1.00	-	-
Symptoms								
cough	1(2.8)	-2.03	1.47	1.92	0.17	0.13	0.01	2.32
dyspnea	16(44.4)	-0.00	1.5	0.00	0.99	0.99	0.047	20.90
fatigue	18(50)	NE	NE	NE	NE	NE	NE	NE
body pain	2(5.6)	NE	NE	NE	NE	NE	NE	NE
headache	4(11.1)	NE	NE	NE	NE	NE	NE	NE
fever	19(52.8)	2.28	1.46	2.42	0.11	9.80	0.55	173.01
chills	2(5.6)	NE	NE	NE	NE	NE	NE	NE
abdominal pain	2(2.8)	NE	NE	NE	NE	NE	NE	NE
gastroenteritis	2(5.5)	NE	NE	NE	NE	NE	NE	NE
eye redness	1(2.78)	NE	NE	NE	NE	NE	NE	NE
Phosphate		-	-	-	-	-	-	-
under 4.5 mg/dL	24(66.7)	2.44	1.19	4.20	0.04	11.50	1.11	118.70
higher than 4.5 mg/dL	12(33.3)	-	-	-	-	1	-	-

NE, not estimated; *, unstandardized beta.

serum phosphate levels in our patients with a reasonable association with HRCT results. They suggested hypophosphatemia as a potential risk factor for COVID-19; while it could be a reflection of malnutrition. But in our study phosphate levels were assessed in the association with COVID-19 severity and a comparison of our results would not be possible as also their study sample were renal patients. As we know renal patients may show severe alternations in phosphate levels due to renal diseases and hemodialysis processes. On the other hand hyperphosphatemia due to kidney inability of phosphate excretion is frequent in renal patients (8) and the hypothesis of Arenas et al. for hypophosphatemia association with COVID-19 makes sense, as we expect up to 90%of chronic kidney disease patients to experience hyperphosphatemia (9), but further shreds of evidence are needed. Another study showed normal ranges of phosphate in 14,712 COVID-19patients, with no differences among male and female cases (10). While their data was collected from multiple centers' medical recorders through the TriNetX network- and no information was addressed about the time of the laboratory analysis, their results may be biased by the different timepoints of laboratory results recording based on the patient course of the disease. But we assessed laboratory results upon the arrival of the patient in the emergency department. phosphate is one of the most important ions inside and outside the cell due to its role in physiological processes, especially muscle contraction and adenosine triphosphate production (11). Therefore, hypophosphatemia is one of the most important

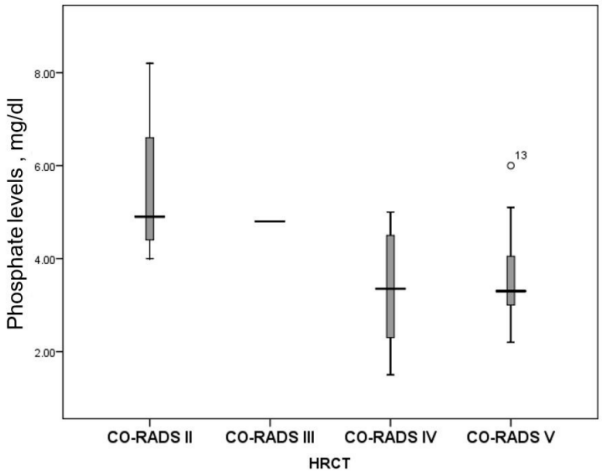

Figure 1. Phosphate levels in each group of CO-RADS schemes box-and-whisker plot of serum phosphate levels showing median (horizontal line in the box), upper, and lower quartiles (two ends of the box)

electrolyte disorders in special wards (12). The main causes of hypophosphatemia are diffuse infection, trauma, receiving volumetric agents, malnutrition syndrome, acid-base disorders, and some drugs, as well as conditions such as major surgery, hypoglycemia, osmotic diuresis, parathyroidectomy and thyroidectomy, and malnutrition. (13). This complication is very important in patients under mechanical ventilation due to the effect of hypophosphatemia on muscle contraction (14); Weak muscle contraction leads to increased duration of mechanical ventilation and difficulty separating (15). van Kempen and Deixler study recommend supplementation of phosphate in case of inadequacy during the beginning stages of COVID-19 or as a preventive measure (16), which is in line with our study findings. On the other hand, the findings of this study may be in line with researches looking for vitamin D benefits for COVID-19 patients. Calcitriol is the biologically active form of vitamin D, which is the main hormone that regulates calcium and phosphate metabolism, and its blood concentration is strongly regulated by parathyroid hormone, calcium, and phosphate.

Conclusion:

Our study showed that higher phosphate levels may be associated with better CT scan of lung outcomes in COVID-19; while hypophosphatemia is associated with severe lung injuries. This study had various limitations as well as no follow-up for the final treatment outcome and a low number of samples. The strength of this study is suggesting possible benefits of higher levels of serum phosphate for COVID-19 patients. But these results may have been biased by other confounding factors that weren't assessed in our study as well as malnutrition. So further studies are needed in this area of research.

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Conflict of interest:

The authors declare that there is no conflict of interest.

Author contribution:

FR, SP, NK, and NH conceptualized the study objectives and design. HS, RR, and AAareinfectious disease specialists who contributed to data collection from patients along with PK. and AS drafted the study design protocols to be submitted to research centers. Data were analyzed by NH and SP. The manuscript was drafted by FR, SP, and NK. All authors contributed to revisions.

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