Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1120563
J Health Sci Med 2022; 5(5): 1232-1237

Evaluation of the correlation of serum calcium, phosphorus levels and calcium phosphorus product with disease severity and ICU mortality in SARS-COV-2 pneumonia patients followed up in ICU

Derya Hoşgün, Semih Aydemir

Atatürk Sanatoryum Training and Research Hospital, Department of Intensive Care Unit, Ankara, Turkey

Cite this article as: Hoşgün D, Aydemir S.Evaluation of the correlation of serum calcium, phosphorus levels and calcium phosphorus product with disease severity and ICU mortality in SARS-COV-2 pneumonia patients followed up in ICU. J Health Sci Med 2022; 5(5): 1232-1237.

ABSTRACT

Background: Calcium and phosphorus are important elements in the body that have been shown to decrease in critical inflammatory diseases. The aim of this study was to evaluate serum levels of calcium and phosphorus and the calcium phosphate product (CPP) in patients followed up in intensive care unit (ICU) due to hypoxemic respiratory failure caused by coronavirus disease 2019 (COVID-19) pneumonia. The secondary endpoint of the study were respiratory support therapies used in the evaluation of independent mortality and disease severity in ICU that were divided into four groups depending on the time of administration: (i) first 24 hours, (ii) 48-72 hours, (iii) 72 hours, and (iv) 72 hours-28 days.

Material and Method: The retrospective study included patients with critical and severe COVID-19 pneumonia followed up in ICU.

Results: The study included 369 patients with a mean age of 64.3±14.8 years. ICU mortality was observed in 142 (38.5%) patients, among whom 17 (4.6%) patients died within 24 hours, 28 (7.6%) died between 48-72 hours, 50 (12.7%) died within 72 hours, and 47 (12.7%) died between 72 hours and 28 days. Serum calcium level established a significant relationship with ICU mortality at 28 days and 72 hours ($p<0.05$). Serum phosphorus and calcium levels were not found as significant predictors of CPP ($p>0.05$).

Conclusion: Serial assessment of serum calcium may be a new criterion in the prediction of independent mortality in critical and severe COVID-19 pneumonia, which has been recently identified and has numerous unknown features.

Keywords: Mortality, calcium, phosphorus

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was renamed as coronavirus disease 2019 (COVID-19) and was declared a pandemic by the World Health Organization (WHO) in 2020. This disease primarily affects the respiratory system and causes acute respiratory distress syndrome (ARDS). Clinical manifestations of COVID-19 comprise four categories: mild, moderate, severe and critical. In COVID-19 infection, laboratory abnormalities can be observed as a result of cytokine storm caused by exaggerated systemic inflammation, particularly in severe and critical cases (1-3).

Calcium and phosphorus are critical electrolytes found in the body. Calcium plays a role in neurotransmitter release, cardiac automaticity, skeletal, vascular, and smooth muscle function as well as blood coagulation, cell persistence, and functional activity of numerous enzymes (4). In a previous study conducted with COVID-19 patients, calcium alterations were associated with a poor prognosis in 70% of the patients (5). A study by Zhou et al. (6) evaluated 127 COVID-19 patients and found a significant relationship between calcium alterations and elevated inflammatory cytokines. The authors suggested that calcium alterations might be a novel and important indicator of mild, moderate, and severe COVID-19 (6). Phosphorusis an essential element playing an important role in intracellular oxygen delivery, immune system, acid-base balance, and coagulation cascade. Hypophosphatemia has been associated with respiratory failure as well as increased mortality and morbidity in

Corresponding Author: Derya Hoşgün, deryahosgun@gmail.com
Received: 24.05.2022 **Accepted:** 07.07.2022

critical diseases (7,8). In a previous study conducted with COVID-19, low calcium and phosphorus levels were found to be correlated with the disease severity (9).

Since COVID-19 is a recently identified disease, to our knowledge, there have been few studies on the relationship between serum calcium and phosphorus levels and CPP and the severity of COVID-19 and mortality. The aim of this study was to evaluate serum calcium and phosphorus levels and CPP in patients followed up in ICU due to hypoxemic respiratory failure caused by COVID-19 pneumonia. The secondary endpoint of the study were respiratory support therapies used in the evaluation of independent mortality and disease severity in ICU that were divided into four groups: (i) first 24 hours, (ii) 48-72 hours, (iii) 72 hours, and (iv) 72 hours-28 days.

MATERIAL AND METHOD

The study was carried out with the permission of Atatürk Sanatoryum Training and Research Hospital Clinical Researches Ethics Committee (Date: 12.04.2022, Decision No: 2012-KAEK-15/2502). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The retrospective study reviewed medical records of patients that were hospitalized due to pneumonia and had a positive SARS-CoV-2 result on polymerase chain reaction (PCR) between March 2020 and May 2021. Patients that were hospitalized in ICU according to the Infectious Disease Society of America (IDSA) and American Thoracic Society (ATS) guidelines and had radiological infiltrations of >50%, tachypnea (respiratory rate >30/min), and a ratio of arterial oxygen partial pressure (PaO_2) to fractional inspired oxygen (FiO_2) (PaO_2/FiO_2) of <300 mmHg were included in the study (10). Laboratory parameters that were assessed within the first hour of ICU admission, including calcium, phosphorus, magnesium, vitamin D, albumin, ferritin, neutrophil count (NE), lymphocyte count (LYM), white blood cell count (WBC), D-dimer, C-reactive protein (CRP), and procalcitonin (PCT) were analyzed for each patient. The albumin-adjusted calcium level was calculated retrospectively, using the following formula: Albumin-adjusted calcium=total calcium + [0.9x(4-albumin)] (11). The albumin-adjusted calcium level was multiplied by the simultaneous phosphorus level (calcium x phosphorus). Respiratory support therapies administered within the first hour of ICU admission were classified as invasive mechanical ventilation (IMV), noninvasive mechanical ventilation (NIMV), high-flow nasal oxygenation (HFNO), and non-rebreather mask (NRB) therapy. Twenty-eight-day ICU mortality was divided into four groups depending on the time of death: (i) first 24 hours, (ii) 48-72 hours, (iii) 72 hours, and (iv) 72 hours-28 days. The Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Sequential Organ Failure Assessment (SOFA) scores were used to predict mortality and prognosis within the first 24 hours of ICU admission (12). Pregnant women, individuals under 18 years of age, and patients with thyroid dysfunction, history of thyroid and parathyroid surgery, drug use within the last month that might affect serum levels of calcium, phosphorus, and vitamin D, history of collagen tissue and, an active infection other than SARS-CoV-2, and a history of dialysis were excluded from the study. Moreover, patients that had a creatinine value of >1.44 mg/dL due to a 0.3 mg/dL increase of creatinine within 48 hours prior to ICU admission due to SARS-CoV-2 pneumonia according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines were also excluded from the study. Electrolyte replacement therapy was administered within the first hour of ICU admission accordance to laboratory parameters.

Normal reference ranges for calcium, phosphorus, albumin, magnesium, vitamin D, ferritin, NE, LYM, WBC, D-dimer, CRP, and creatinine were accepted as 8.8-10.6 mg/dL, 2.5-4.5 mg/dL, 3.5-5 mg/L, 1.9-2.5 mg/dL, 30-100 ng/ml, 22-275 ng/ml, 2-6.9×10^3 µL, 0.6-3.4×10^3 µL, 4.6-10.2×10^3 µL, 0-0.44 mg/L, 0-5 mg/L, and 0.81-1.44 mg/dL, respectively. A PCT level of <0.5 ng/ml was considered to indicate a low risk and a level of >2 ng/ml was considered to indicate a high risk. WBC, NE, and LYM were measured using a photometric analyzer (Mindary BC-6800 device), vitamin D level was measured using an ADVIA Chemistry XPT analyzer (Siemens, München, Germany), PCT immunoassay and the assessment of ferritin level were performed using an ADVIA Centaur XPT analyzer (Siemens, München, Germany), CRP, albumin, calcium, phosphorus, magnesium, and creatinine levels were measured using a Beckman Coulter hematology autoanalyzer (Beckman Coulter, USA), and D-dimer level was measured using a Sysmex autoanalyzer (Sysmex, Kobe, Japan) with the turbidimetric method.

Statistical Analysis

Data were analyzed using SPSS for Windows version 23.0 (Armonk, NY: IBM Corp.).Categorical variables were expressed as frequencies (n) and percentages (%) and continuous variables were expressed as mean, standard deviation (SD), and minimum-maximum. The conformity of variables to normal distribution was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. inary variables that did not conform to normal distribution were compared using Mann-Whitney U test. Correlations between continuous variables were assessed using Spearman's Correlation Coefficient. Logistic regression analysis was performed to determine the independent variables affecting mortality. A p value of <0.05 was considered significant.

RESULTS

Table 1 presents demographic and clinical characteristics of the patients. A total of 369 patients with a mean age of 64.3±14.8 years (223 men [60.4%] and 146 women [39.6%]) were included in the study. ICU mortality occurred in 142 (38.5%) patients, among whom 17 (4.6%) patients died within 24 hours, 28 (7.6%) died between 48-72 hours, 50 (12.7%) died within 72 hours, and 47 (12.7%) died between 72 hours and 28 days. In ICU, IMV was administered in 242 (65.6%), NIMV was administered in 82 (22.0%), HFNO was administered in 192 (52.0%), and NRB was administered in 86 (23.3%) patients. **Table 2** shows the mean values of laboratory parameters measured within the first hour of ICU admission. A positive correlation was found between calcium level and LYM, between phosphorus and magnesium, and between albumin and LYM (p<0.05 for all).

Table 1. Demographic and clinical characteristics

Variables	Frequency (N)	Percent (%)
Gender		
Male	223	60.4
Female	146	39.6
ICU mortality	142	38.5
24 hours ICU mortality	17	4.6
48-72 hours ICU mortality	28	7.6
72-hour ICU mortality	50	13.6
72 hours - 28 Days ICU mortality	47	12.7
PaO_2/FiO_2		
<100 mmHg	19	5.1
<150 mmHg	21	5.7
<200 mmHg	40	10.8
<250 mmHg	47	12.7
<300 mmHg	242	65.6
Comorbidities	213	57.7
HT	139	37.7
CAD	68	18.4
CHF	20	5.4
DM	82	22.2
Neurological	6	1.6
COPD	49	13.3
Bronchial asthma	10	2.7
Malignancy	16	4.3
CKF	2	0.5
Variables	**Mean±SD**	**Median (Min-Max)**
Age (years)	64.3±14.8	66(19-94)
APACHE II	21.2±6.2	20(11-38)
SOFA	6.2±3.45	5(2-30)

ICU: Intensive care unit, PaO_2/FiO_2: Ratio of the partial pressure of oxygen in arterial blood (PaO_2) to fractional inspired oxygen (FiO_2) HT: Hypertension, CAD: Coronary artery disease, CHF: Congestive heart failure, DM: Diabetes mellitus, CKF: Chronic kidney failure, APACHE II: Acute Physiology and Chronic Health Evaluation II score, SOFA: Sequential Organ Failure Assessment Score

Although there was a significant relationship between ICU mortality and calcium level(p=0.015),no significant relationship was found between serum phosphorus level and CPP (p=0.401 and p=0.144, respectively). Mortality within the first 24 hours, 48-72 hours, and 72 hours-28 days established no significant relationship with serum phosphorus and calcium levels and CPP (p=0.531, p=0.822, p=0.728, p=0.362, p=0.418, p=0.157, p=0.383, p=0.626, and p=0.321, respectively). In contrast, a significant relationship was found between 72-hour mortality and calcium level(p=0.012) and no significant relationship was found between phosphorus level and CPP (p=0.456 and p=0.841, respectively). Similarly, no significant relationship was found between serum calcium and phosphorus level and CPP and the administration of IMV, NIMV, HFNO, and NRB in ICU (p>0.05 for all) (**Table 3**). When factors affecting mortality were evaluated in multiple regression analysis, the risk of mortality was 1.23-fold greater in patients with a higher APACHE II score (OR:1.230;95% CI, 1.083-1.396, p=0.001) and was 1.001-fold greater in patients with a higher ferritin level (OR:1.001;95%CI,1.00-1.001, p=0.017).

Table 2. Laboratory parameters

Variables	Mean±SD	Med (Min-Max)
Phosphorus (mg/dL)	2.9±1.19	2.7 (0.8-11.6)
Magnesium (mg/dL)	2.15±0.53	2.1 (1.3-8.9)
Albumin (mg/L)	3.09±0.67	3 (1-4.9)
Calcium (mg/dL)	9.44±4.3	9.2 (6.49-90.8)
CPP	12.3±4.4	11.9 (9.4-92.4)
Vitamin D (ng/ml)	17.89±12.91	14.35 (1.73-79.36)
Ferritin (ng/ml)	655.9±551.6	482.7 (7.3-1650)
Neutrophil ($\times10^3\mu L$)	8.8±5.46	8.03 (1.13-34.87)
Lymphocyte ($\times10^3\mu L$)	1.05±1.14	0.81 (0.05-16.49)
C-Reactive protein(mg/L)	118.3±98.6	104.1 (0.37-562.9)
Procalcitonin (ng/ml)	1.43±4.53	0.12 (0.01-41.4)
D-Dimer (mg/L)	8.47±72.01	1.11 (0.19-1366)
White blood cell (WBC) count ($\times10^3$ µL)	10.3±5.6	9.43 (2.3-35.93)

CPP: Calcium phosphate product, SD: Standard deviation, The normal reference rangesof calcium, phosphorus, albumin, magnesium, vitamin D, ferritin, NE, LYM, WBC, D-dimer, CRP, and creatinine were accepted as 8.8-10.6 mg/dL, 2.5-4.5 mg/dL, 3.5-5 mg/L,1.9-2.5 mg/dL, 30-100 ng/ml, 22-275 ng/ml, 2-6.9×10^3 µL, 0.6-3.4×10^3 µL, 4.6-10.2×10^3 µL, 0-0.44 mg/L, 0-5 mg/L, and 0.81-1.44 mg/dL, respectively. PCT <0.5 ng/ml was considered to indicate a low risk, and >2 ng/ml was considered to indicatea high risk.

DISCUSSION

Clinical manifestations of COVID-19 comprise four categories: mild, moderate, severe and critical. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters the target cell by binding to the angiotensin-converting enzyme 2 (ACE2) molecule via the S protein. The ACE2 protein is released in large amounts in intestinal epithelial, renal tubular, alveolar, cardiac, and smooth muscle cells. It is also known that macrophage activation

Table 3. Relationship between calcium and phosphorus levels and CPPand ICU mortality

	Phosphorus		Calcium		CPP	
Variables	**Med (Min-Max)**	**p**	**Med (Min-Max)**	**p**	**Med (Min-Max)**	**p**
ICU Mortality						
No	2.7 (0.9-6.3)	0.401	9.24 (6.49-90.8)	0.015	11.96 (10.06-92.4)	0.144
Yes	2.6 (0.8-11.6)		9.12 (6.8-12.46)		11.71 (9.4-20.5)	
24-hr ICU Mortality						
No	2.7 (0.8-11.6)	0.531	9.2 (6.49-90.8)	0.822	11.9 (9.4-92.4)	0.728
Yes	2.5 (1.4-7.1)		9.1 (6.8-12.46)		11.7 (9.8-19.56)	
48-72 hour ICU Mortality						
No	2.7 (0.8-11.6)	0.362	9.2 (6.49-90.8)	0.418	11.92 (9.4-92.4)	0.157
Yes	2.3 (1.4-7.1)		9.15 (8.18-11.64)		11.27 (9.72-17.54)	
72-hour ICU Mortality						
No	2.7 (0.9-11.6)	0.456	9.23 (6.49-90.8)	0.012	11.9 (9.72-92.4)	0.841
Yes	2.8 (0.8-6.5)		9.1 (7.46-11.28)		11.96 (9.4-15.82)	
72 hours-28 days ICU Mortality						
No	2.7 (0.8-7.1)	0.383	9.2 (6.49-90.8)	0.626	11.92 (9.4-92.4)	0.321
Yes	2.7 (1.3-11.6)		9.18 (7.52-10.44)		11.74 (10.24-20.5)	

* p<0.05, Mann-Whitney U test, ICU: Intensive Care Unit, CPP: Calcium phosphate product

syndrome (MAS), which is characterized by cytokine storm due to exaggerated hyperinflammatory response, occurs particularly during severe COVID-19 infection. Additionally, MAS may also lead to cytokine storm due to systemic inflammation and involve multiple organs and systems. In such patients, laboratory abnormalities such as elevated D-dimer, CRP, ferritin and liver enzymes as well as lymphopenia, thrombocytopenia, and hypofibrinogenemia can be observed (2,13). In several studies, 28-day mortality rate in patients with COVID-19 pneumonia was reported as 40% (14). In our study, 28-day ICU mortality rate was 38.5%, which was consistent with the literature.

Cytokine storm in SARS-CoV-2 is known to decrease adenosine triphosphate (ATP) pools, thereby leading to an increased need for electrolytes, particularly including phosphate and magnesium, for ATP production. Studies have shown that low serum phosphorus and magnesium levels are associated with the severity of SARS-CoV-2. In turn, these low levels decrease the ATP production as well as the production of 2,3-bisphosphoglycerate that is required for oxygen release from hemoglobin as a result of hypophosphatemia, ultimately resulting in tissue hypoxemia. In addition, the clinical and laboratory findings in hypophosphatemia are characterized by thrombocytopenia, liver and kidney dysfunction, neurological impairment, rhabdomyolysis, respiratory and immune failure, and multiple organ failure, as in MAS (13). There are several studies recommending the monitoring of phosphorus, magnesium and vitamin D serum levels in the early stages of COVID-19 infection in the risky population and their replacement when necessary (13). Magnesium is known to improve vitamin D function in addition to its antihypertensive, antithrombotic, and bronchodilator effects (15). A previous study conducted with COVID-19 patients found that serum concentrations of sodium, potassium, and calcium decreased in the presence of severe infection. The exact mechanism of calcium dysregulation in COVID-19 infection remains unclear. Experimental studies have shown that the SARS-CoV-2 E gene encodes the protein for extracellular calcium ions to enter the cell and that serum calcium plays a vital role in a series of critical physiological functions, including calcium phosphate deposition, manipulation, neuron electrical signal transmission, hormonal regulation, and blood coagulation (16).

In our study, elevated CRP, PCT, and ferritin levels suggestive of MAS were detected in our patients, which could be due to the inclusion of severe and critical COVID-19 pneumonia patients in the study. However, the adjusted serum calcium, magnesium, phosphorus, and albumin levels measured on ICU admission were found to be within the normal range. In addition, in line with the literature, our patients were found to have vitamin deficiency (<20 ng/ml) (17). In our patients, serum samples were collected at the time of ICU admission, as performed in studies conducted with COVID-19 patients. Nevertheless, contrary to several studies in the literature, serum calcium, phosphorus, and magnesium values in our study were found to be within the normal range in our patients with pneumonia due to COVID-19 (9,17). On the other hand, simultaneous arterial blood gas levels, which could affect serum phosphorus and calcium levels, and ionized calcium and parathormone (PTH) levels, which are more determinant in the assessment of calcium level, could not be measured due to the retrospective nature of the study (18). Accordingly, we consider that the measurements of our calcium and phosphorus levels were affected.

To our knowledge, there are very few studies evaluating the relationship between serum calcium and phosphorus levels and the severity of the disease and mortality in patients with COVID-19, which is a recently identified disease with numerous unknown features. A study by Zhou et al. (6) evaluated 127 COVID-19 patients and found that low calcium levels were observed in the early stage of viral infection and that this decrease was more prominent in the early stage of the disease in severe/critical patients. The authors also found a significant relationship between interleukin 6 (IL-6), a proinflammatory cytokine, and calcium alterations in mild, moderate, and severe patients and suggested that the calcium level in the early stage of viral infection could be a biomarker of the severity of COVID-19 (16). In a retrospective study of 316 hospitalized COVID-19 patients by Torres et al. (19), hypocalcemia was associated with poor clinical outcomes such as NIMV and IMV requirement. In that study, the authors assessed serum calcium level within the first 72 hours. In another study, hypocalcemia was associated with higher rates of hospitalization, ICU admission, ventilation, and mortality (6). Similarly, a retrospective study conducted with patients hospitalized in ICU due to sepsis found that calcium replacement therapy reduced the 28- and 90-day mortality rates (20). In our study, serum calcium and phosphorus levels were evaluated together with CPP. It is known that an increase in CPP (70 mg/dL) causes an increase in the mortality rate in dialysis patients with chronic kidney failure (21). In our study, however, no significant relationship was found between phosphorus and CPP levels and mortality. Additionally, no comparison could be made with regard to the relationship between CPP and mortality since,to our knowledge, there is no study in the literature evaluating CPP in COVID-19 patients. On the other hand, the calcium levels in our study established a significant relationship with 28-day and 72-hour ICU mortality. These findings of our study were consistent with the findings of several studies in the literature, whereas our findings that were related to phosphorus level were inconsistent with the findings in the literature (6,19). This inconsistency could be attributed to the inclusion of patients who received medical treatment due to low calcium and phosphorus levels and to the non-administration of serial laboratory measurements in our study (20).

Our study was limited since it was a single-center and retrospective study. Moreover, only the data of severe and critical COVID-19 pneumonia patients followed up in ICU were evaluated and no data was available regarding the patients hospitalized in the general ward.

CONCLUSION

Our findings indicated that serial assessment of serum calcium levels could be a new criterion for the prediction of independent mortality in critical and severe patients with COVID-19 pneumonia, which is a recently identified disease with numerous unknown features. Multicenter, randomized and controlled studies are needed to substantiate our findings.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Atatürk Sanatoryum Training and Research Hospital Clinical Researches Ethics Committee (Date: 12.04.2022, Decision No: 2012-KAEK-15/2502).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Chu KH, Tsang WK, Tang CS, et al. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. Kidney Int 2005; 67: 698-5.
2. Pan XW, Xu D, Zhang H, Zhou W, Wang LH, Cui XG. Identification of potential mechanism of acute kidney injury during the COVİD-19 outbreak: a study based on single-cell transcriptome analysis.Intensive Care Med 2020; 46: 1114-6.
3. Lim AYH, Goh JL, Chua MCW, Heng BH, Abisheganaden JA, George PP. Temporal changes of haematological and radiological findings of the COVID-19 infection-a review of literature. BMC Pulm Med 2021; 21: 37.
4. Aguilera IM, Vaughan RS. Calcium and the anaesthetist. Anaesthesia 2000; 55: 779-90.
5. Cappellini F, Brivio R, Casati M, Cavallero A, Contro E, Brambilla P. Low levels of total and ionized calcium in blood of COVID-19 patients. Clin Chem Lab Med 2020; 58: e171-3.
6. Zhou X, Chen D, Wang L, et al. Low serum calcium: a new, important indicator of COVID-19 patients from mild/moderate to severe/critical. Biosci Rep 2020; 40: BSR20202690.
7. Bugg NC, Jones JA. Hypophosphataemia: pathophysiologyd, effects and management on the intensive care unit. Anaesthesia 1998; 53: 895-2.
8. Shor R, Halabe A, Rishver S, et al. Severe hypophosphatemia in sepsis as a mortality predictor. Ann Clin Lab Sci 2006; 36: 67-2.
9. Yang C, Ma X, Wu J, et al. Low serum calcium and phosphorus and their clinical performance in detecting COVID-19 patients. J Med Virol 2021; 93: 1639-51.

10. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007; 44: S27-72.
11. James MT, Zhang J, Lyon AW, Hemmelgarn BR. Derivation and internal validation of an equation for albumin-adjusted calcium. BMC Clin Pathol 2008; 8: 12.
12. Keegan MT, Gajic O, Afessa B. Severity of illness scoring systems in the intensive care unit. Crit Care Med 2011; 39: 163-9.
13. van Kempen TATG, Deixler E. SARS-CoV-2: influence of phosphate and magnesium, moderated by vitamin D, on energy (ATP) metabolism and on severity of COVID-19. Am J Physiol Endocrinol Metab 2021; 320: E2-6.
14. Sun JK, Zhang WH, Zou L, et al. Serum calcium as a biomarker of clinical severity and prognosis in patients with coronavirus disease 2019. Aging (Albany NY) 2020; 12: 11287-95.
15. Dai Q, Zhu X, Manson J.E, Song Y, Li X, Franke AA. Magnesium status and supplementation influence vitamin D status and metabolism: results from a randomized trial. Am J Clin Nutr 2018; 108: 1258–69.
16. Lippi G, South AM, Henry BM. Electrolyte imbalances in patients with severe coronavirus disease 2019 (COVID-19). Ann Clin Biochem 2020; 57: 262-5.
17. Quraishi SA, Bittner EA, Christopher KB, Camargo CA. Vitamin D status and community-acguired pneumonia: results from the third national health and nutrition examination survey. PLoS One 2013; 8: e81120.
18. Kelly A, Levine MA. Hypocalcemia in the critically ill patient. J Intensive Care Med 2013; 28: 16677.
19. Torres B, Alcubilla P, Cordon-Gonzalez A, et al. Impact of low serum calcium at hospital admission on SARS-CoV-2 infection outcome. Int J Infect Diseases 2021; 164-8.
20. Zhang Z, Chen K, Ni H. Calcium supplementation improves clinical outcome in intensive care unit patients: a propensity score matched analysis of a large clinical database MIMIC-II. Springerplus 2015; 4: 594.
21. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphorus product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis 1998; 31: 607-17.