DOI: 10.4149/BLL_2023_069

Bratisl Med J 2023; 124 (6)
449 – 453

CLINICAL STUDY

Serum vitamin D levels and inflammatory status in COVID-19 patients

Desislava ARABADZHIYSKA[1], Tanya DENEVA[1,2], Oliana BOYKINOVA[3]

Department of Clinical Laboratory, Medical University of Plovdiv, University Hospital "St. George", Plovdiv, Bulgaria. **Desislava.Arabadzhiyska@mu-plovdiv.bg**

ABSTRACT

OBJECTIVES: The coronavirus 2019 disease (COVID-19) is characterized by a heterogeneous clinical presentation, a complex pathophysiology and a wide range of laboratory findings, depending on disease severity.

BACKGROUND: We studied some laboratory parameters in correlation with vitamin D status representing the inflammatory state in hospitalized COVID-19 patients on admission.

METHODS: The study included 100 COVID-19 patients with moderate (n=55) and severe (n=45) form of the disease. Complete blood count and differential blood count, routine biochemical parameters, C-reactive protein and serum procalcitonin, ferritin, human IL-6 and serum vitamin D (measured as 25-OH vitamin D) concentrations, were performed.

RESULTS: According to the severity of the disease, patients with severe form had significantly lower serum vitamin D (16.54±6.51 ng/ml vs 20.37±5.63 ng/ml, p=0.0012), higher serum interleukin-6 (41.24±28.46 pg/ml vs. 24.75±16.28 pg/ml, p=0.0003), C-reactive protein (101.49± 57.15 mg/l vs 74.43±42.99 mg/l, p=0.0044), ferritin (969.89±338.37 ng/ml vs 845.96±359.91 ng/ml, p=0.0423) and LDH (1050.53±369.11 U/l vs 905.31±335.57 U/l, p=0.0222) compared to those with moderate form of the disease.

CONCLUSION: The presented data provide a relationship between increased inflammatory laboratory markers, low vitamin D levels and disease severity in COVID-19 patients *(Tab. 2, Fig. 3, Ref. 32)*. Text in PDF *www.elis.sk*

KEY WORDS**:** COVID-19, 25-OH vitamin D, IL-6, C-reactive protein.

Introduction

COVID-19, caused by the new coronavirus SARS-Cov-2, very quickly became pandemic and spread all over the world. Although most of the patients with COVID-19 have a mild influenza-like illness or may be asymptomatic, there are others, who develop severe pneumonia, acute respiratory distress syndrome, multiple organ failure and can even die. It is still not well understood why some individuals become critically ill, while others do not. The pathophysiologic mechanisms are not completely elucidated, and the clinicians still need additional, easily accessible and affordable prognostic markers for differentiation of patients that might develop a more serious form of the disease and worse outcome. It is supposed that patients critically ill with COVID-19 reveal hyperinflammation and some laboratory biomarkers may be significant predictors for high risk and poor outcome. Clinical data on vitamin D (Vit D) status in conjunction with inflammatory parameters in patients infected with SARS-Cov-2 are still limited.

During the last decade, Vit D has attracted increased interest in biomedical and health researchers more than all other micronutrients. Firstly, Vit D deficiency is widely spread all around the world, and serum Vit D concentrations follow a well-known seasonal and geographical pattern. Bulgarian population has high prevalence of Vit D deficiency (1) and at the same time has reached very high rates of SARS-CoV-2 infection and lethality. Secondly, Vit D is responsible for the regulation of calcium and phosphate metabolism, bone mineralization and skeletal development (2), but it is also known as an immunomodulatory hormone (3–6). It is a steroid hormone involved in the modulation of the innate and acquired immune system and in the production of antimicrobial peptides, as well as in the expression of genes concerned with the intracellular destruction of pathogens – beta defensins that can directly cleave the membrane of a virus and cathelicidins that are involved in the activation of macrophages, dendritic cells, and neutrophils (7–9). Thirdly, low levels of Vit D can be associated with various chronic disorders, such as autoimmune diseases, cardiovascular diseases, diabetes mellitus, and

[1]Department of Clinical Laboratory, Medical University of Plovdiv, University Hospital "St. George", Plovdiv, Bulgaria, [2]Research Institute at Medical University of Plovdiv, Bulgaria, and [3]Department of Infectious Diseases, Parasitology and Tropical medicine, Medical University of Plovdiv, University Hospital "St. George", Plovdiv, Bulgaria

Address for correspondence: Desislava ARABADZHIYSKA, Bul. "Vasil Aprilov" 15 a, Plovdiv 4000, Bulgaria. Phone: +359889252142

Acknowledgements: This work was supported by Project COV-4/2021 "Laboratory monitoring of prognostic biomarkers in hospitalized patients with COVID-19", contract R-2375/ 02.08.2021, Medical University of Plovdiv, Bulgaria; Project "COVID-19 HUB – Information, innovations and implementation of integrative research activities", contract KP-06-DK1/6 from 29.03.2021, National Science Foundation, Ministry of Education and Science, Bulgaria.

malignancies (10), as well as increased morbidity and mortality from respiratory tract infections and a higher risk of developing acute respiratory distress syndrome (ARDS) (11). In COVID-19 patients the severity of the illness is frequently determined by the presence of pneumonia and ARDS, myocarditis, microvascular thrombosis and/or cytokine storm, all of which involve underlying inflammation (12–13). Through angiotensin converting enzyme-2 (ACE-2) receptors SARS-CoV-2 damages not only the pulmonary epithelial cells, but also infects macrophages and activates them. Macrophages, neutrophils, and T cells get activated through sustained elevation of cytokines including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α), which leads to pneumocyte apoptosis (14). The expressed proinflammatory cytokines can be the reason for endothelial dysfunction, causing damage to vital organs, especially the lungs. Vit D can inhibit proinflammatory cytokine production in human monocytes/macrophages (15), and chronic deficiency may induce renin-angiotensin system activation, leading to the production of fibrotic factors and, therefore, lung damage (16).

Currently, Vit D status has been identified as a potentially achievable supplement within the treatment or prevention of COVID-19 (17, 18). Some studies demonstrated a significant correlation between Vit D and COVID-19 cases and its related outcomes (19) while other studies failed to find the correlation when confounding variables are adjusted (20, 21). There's insufficient evidence on the association between COVID-19 severity or outcomes and Vit D levels (22).

The aim of this study is to assess the potential relationship between serum Vit D levels, inflammatory laboratory parameters and disease severity in hospitalized COVID-19 patients.

Material and methods

The study included 100 COVID-19 patients with moderate (n = 55) and severe (n = 45) form of the disease, admitted to the University Hospital "St. George", Plovdiv, Bulgaria between October 2021 and December 2021 and 40 healthy controls. Patients under the age of 18 and above 64 years old were excluded from this study. The diagnosis and classification of COVID-19 were based on the Living guidance for clinical management of COVID-19 issued by the WHO (23 November 2021) (23). All the participants gave their informed written consent. The study was conducted in accordance with the Declaration of Helsinki, as revised in 2013 and was approved by the Ethics committee of the Medical University of Plovdiv, Bulgaria with Protocol No. 1/25.01.2022. Demographic features, comorbidities, clinical and laboratory findings were obtained from the hospital database retrospectively. On admission to the clinic, hematological, biochemical and coagulation parameters, arterial blood gas parameters, liver and kidney function tests were observed. The patients were confirmed to have SARS-CoV-2 infection by real-time polymerase chain reaction assay (RT–PCR) from nasopharyngeal swab specimen. The control group was composed of volunteers who gave a negative result for COVID-19 by RT–PCR assay and haven't suffered from an infection in the last six months. Venous blood of the patients and healthy controls was taken in the morning between 6–8 AM from the antecubital vein after a requested 12-hour overnight fast. Complete blood count (CBC), differential blood count (DBC), neutrophil to lymphocyte ratio (NLR) were measured on Advia 2120i, Siemens. Routine biochemical parameters, C-reactive protein (CRP) and serum procalcitonin (PCT) were measured by standard automated methods on Olympus AU480, Beckman Coulter. Serum Vit D (measured as 25-OH vitamin D (25(OH)D) concentrations, ferritin and human IL-6 were performed on a fully automated system Access 2, Beckman Coulter by chemiluminescence enzyme immunoassay.

Statistical analysis

Collected data was analyzed using IBM SPSS Statistic software, version 24.0. Continuous variables were expressed as means and standard deviations (mean ± SD). Statistical differences were considered significant at $p < 0.05$. Pearson's chi-square test and Mann–Whitney U test were used for intergroup comparisons of parametric data and nonnormally distributed numerical data, respectively. Independent samples t-test was used to compare demographic data and laboratory parameters between the groups. Wilcoxon analysis was used for intragroup comparisons of laboratory values. Pearson correlation analysis was used to evaluate relationships between serum Vit D and IL-6 and CRP concentrations.

Results

The studied patient group included 52 female (52 %) and 48 male (48 %) COVID-19 patients. The control group included 20 female (50 %) and 20 male (50 %) healthy individuals. The mean age of the patients was 53.72 ± 8.00 years and the mean age of the control group was 52.00 ± 5.13 years. No statistically significant difference in gender and age was observed between the groups ($p > 0.05$). The laboratory findings of COVID-19 patients on admission and healthy controls are presented on Table 1.

Serum Vit D levels were significantly lower in the COVID-19 patients group compared with the values in the control group

Tab. 1. Comparison of laboratory parameters of COVID-19 patients on admission and healthy controls.

Variables	Patients (n=100) (mean±SD)	Controls (n=40) (mean±SD)	Mann-Whitney Test
WBC (x10^9/l)	8.13±2.08	6.69±1.17	p=0.0010
Neutrophils (%)	82.39±4.36	57.98±2.53	p<0.0001
Lymphocytes (%)	10.28±3.13	31.38±9.74	p<0.0001
NLR	9.33±5.49	1.87±0.26	p<0.0001
Eosinophils (%)	0.059±0.056	2.36±0.87	p<0.0001
Total protein (g/l)	58.28±2.91	69.2±5.47	p<0.0001
Albumin (g/l)	30.09±1.84	44.72±3.53	p<0.0001
CRP (mg/l)	86.61±51.65	2.94±1.12	p<0.0001
LDH (U/l)	970.66±358.41	321.8±64.60	p<0.0001
Ferritin (ng/ml)	901.73±355.76	37.11±9.46	p<0.0001
IL-6 (pg/ml)	32.17±24.03	2.93±1.14	p<0.0001
PCT (ng/ml)	0.86±0.73	0.22±0.05	p=0.0321
Vit D (ng/ml)	18.65±6.34	31.00±4.22	p<0.0001
paO2 (%)	90.86±3.08	98.5±0.5	p<0.0001

WBC – white blood cells, NLR - neutrophil to lymphocyte ratio, CRP – C reactive protein, LDH-lactate dehydrogenase, IL-6 – interleukin-6, PCT – procalcitonin, Vit D – vitamin D

Tab. 2. Comparison of laboratory parameters of COVID-19 patients with moderate disease and severe disease on admission.

Variables	Moderate disease (n=55) (mean±SD)	Severe disease (n=45) (mean±SD)	Mann-Whitney Test
WBC (x10⁹/l)	8.02±2.06	8.28±2.10	p>0.05
Neutrophils (%)	81.67±4.34	83.28±4.20	p=0.0336
Lymphocytes (%)	10.57±3.17	9.93±3.03	p>0.05
NLR	8.80±3.93	9.97±6.88	p>0.05
Eosinophils (%)	0.05±0.05	0.07±0.06	p>0.05
Total protein (g/l)	58.23±2.56	58.33±3.29	p>0.05
Albumin (g/l)	30.12±1.72	30.06±1.99	p>0.05
CRP (mg/l)	74.43±42.99	101.49±57.15	p=0.0044
LDH (U/l)	905.31±335.57	1050.53±369.11	p=0.0222
Ferritin (ng/ml)	845.96±359.91	969.89±338.37	p=0.0423
IL-6 (pg/ml)	24.75±16.28	41.24±28.46	p=0.0003
PCT (ng/ml)	0.75±0.78	0.98±2.07	p>0.05
Vit D (ng/ml)	20.37±5.63	16.54±6.51	p=0.0012
– Vit D deficient	15.46±2.80	12.47±3.93	p=0.0011
– Vit D insufficient	25.10±3.02	23.92±2.62	p=0.1031
paO2 (%)	93.29±1.50	87.69±1.26	p<0.0001

($p < 0.0001$). On admission COVID-19 patients exhibited significantly higher neutrophils, lower lymphocytes, higher NLR, lower eosinophils, lower serum total protein and albumin, higher serum CRP, LDH, Ferritin, IL-6, PCT and lower PaO_2 than the healthy controls ($p < 0.0001$).

Patients with moderate disease were adults with clinical signs of pneumonia, but no signs of severe pneumonia, including $SpO_2 \geq 90$ % on room air. Severe cases additionally met at least one of the following conditions: $SpO_2 < 90$ % on room air, respiratory rate > 30 breaths/minute or presence of severe respiratory distress. The laboratory findings are shown in Table 2. Considering the disease severity, we found out significantly lower serum Vit D levels in the COVID-19 patients with severe disease than in those with moderate disease ($p < 0.05$).

According to the international recommendations for serum Vit D levels we divided the patients into two subgroups with Vit D deficient (< 20 ng/ml) and Vit D insufficient (20–30 ng/ml) (24, 25). Vit D deficiency was expressed in 64 % of the patients with

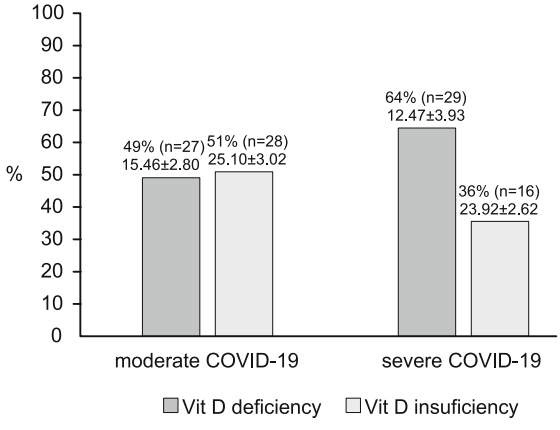

Fig. 1. Vitamin D deficient and Vitamin D insufficient COVID-19 patients according to disease severity.

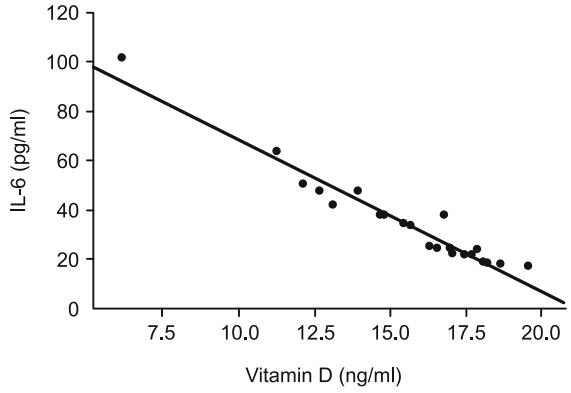

Fig. 2. Linear correlations between serum Vitamin D and IL-6 in patients with moderate COVID-19.

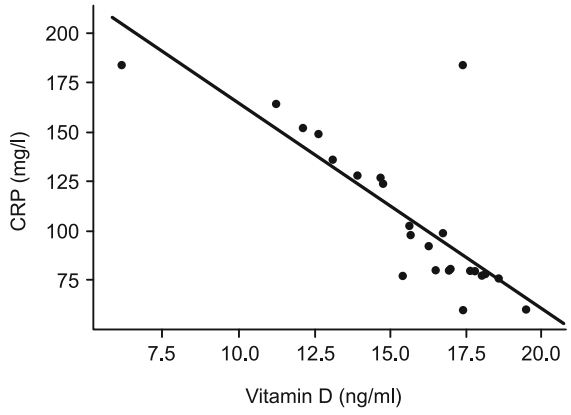

Fig. 3. Linear correlations between serum Vitamin D and CRP in patients with moderate COVID-19.

severe disease and 49 % of the patients with moderate disease. In the groups of Vit D deficiency and Vit D insufficiency the statistically significant difference between the concentrations of Vit D of the patients with moderate disease ($p < 0.05$) and the severe ones ($p < 0.05$) follows the same tendency of the whole patient group (Fig. 1). Serum CRP, LDH, Ferritin, IL-6 and Neutrophils in blood in COVID-19 patients with severe disease were significantly higher ($p < 0.05$) than in the group with moderate disease.

To assess the potential association between Vit D deficiency and disease severity in COVID-19 patients we analyzed the correlations between serum Vit D concentrations and selected laboratory parameters (CRP, IL-6 and ferritin) with statistically significant differences between the two groups. A negative correlation with statistical significance was observed between Vit D and IL-6 ($r = –0.88$, $p < 0.001$), Vit D and CRP ($r = –0.93$, $p < 0.001$), whereas the correlation between Vit D and ferritin was found to be not statistically significant ($r = –0.11$, $p > 0.05$) (Figs 2 and 3).

Discussion

The findings of our study indicate that serum Vit D levels are significantly lower in hospitalized COVID-19 patients than

in population-based controls of similar age and sex. These levels were especially lower in the group of patients with severe disease compared to the moderate group of patients when admitted to the hospital. Severe COVID-19 patients have also significantly higher inflammatory biomarkers compared to the moderate group of patients when admitted to the hospital. Our COVID-19 patients had a high prevalence of Vit D deficiency, and serum 25(OH)D levels significantly and negatively correlated with IL-6 and CRP values, indicating that Vit D might have a special role on the systemic inflammatory state of this viral disease.

An association of Vit D deficiency with inflammation in patients with COVID-19 has been reported in several other clinical studies. In a prospective study of 154 COVID-19 patients, serum 25(OH)D concentrations were significantly lower in patients requiring Intensive care unit admission than in asymptomatic patients. Serum IL-6, TNF-α, and ferritin levels, were increased in COVID-19 patients with serum 25(OH)D < 20 ng/ml (26). Balzanelli et al found out in their study that Vit D deficiency, high level of IL-6 and low level of eGFR were highly indicative in the group of COVID-19 patients. They present a positive correlation between IL-6 and the grade of infection and suppose that IL-6 level could be a significant predictor of the non-survivor group, when compared to other inflammatory markers such as CRP or D-dimer (27). The plasma cytokine IL-6 plays a very important role in mediating inflammation and could be a central stimulus for the acute-phase response. When inflammation is triggered, IL-6 is released into circulation (by neutrophils and macrophages, likewise as resident cells at the place of infection or damage), partly induced by IL-1β and TNF-α. One major effect of IL-6 is to stimulate the production of CRP and other acute phase proteins (serum amyloid P component, serum amyloid A, fibrinogen, ferritin) within the liver and their release into the bloodstream. As IL-6 rises during acute inflammation, the concentration of CRP in serum increases dramatically too (28). According to Daneshkhah et al, patients with severe COVID-19 have higher CRP levels than those with a mild form of the disease and there is a possible link between Vit D deficiency and increased fatality rates of COVID-19 (29). Vit D deficiency leads to the production of cytokines such TNF-α and IL-6 which may cause inflammation and elevates CRP. This may explain the simultaneous elevation of both CRP and cytokines in severe COVID-19 patients (30). Another study had shown that Vit D can alter the bioactivity of IL-6 to induce more anti-inflammatory cytokines, such as interleukin-10 (IL-10), instead of pro-inflammatory cytokines such as interleukin-17 (IL-17), which is expected to lead to the reduction of CRP (31). Although serum CRP is a nonspecific marker, it becomes more specific to bioactivity of IL-6 and formation of a cytokine storm in patients with severe COVID-19. However, we don't know whether these patients had low Vit D levels before the disease and therefore had suffered severely, or whether the severe course of the disease led to decreased serum Vit D values. In another study, Dror A. et all also studied the association between serum Vit D deficiency and disease severity and supposed that patients with severe or critical COVID-19 disease were more likely to have pre-infection vitamin D deficiency of the level less than 20 ng/ml (32).

The results of this study however can be interpreted with some limitations.

First, the study excluded mild cases of the infection without evidence of viral pneumonia or hypoxia. All the patients were with moderate and severe forms of the COVID-19 infection because they are admitted in the University hospital with clinical signs of pneumonia, hypoxia, and other complications. Second, patients' Vit D supplementation history was not obtained or analyzed as part of this research. Further, well-designed studies are required to determine whether Vit D supplementation provides protective effects against worse COVID-19 outcomes. Third, the current study doesn't take comorbidities in account while estimating proinflammatory markers (as comorbidities like diabetes and hypertension enhance the severity of COVID-19). Therefore, future prospective research should be planned with standardization of the patients according to their nutritional status, supplemental therapy, exposure to sunlight and comorbidities in order to improve clarifying the association between Vit D and inflammatory parameters in COVID-19.

Conclusions

Our results show that serum Vit D levels were inversely associated with some inflammatory parameters, such as serum IL-6 and CRP and could assess the severity of the disease. They could be useful markers of risk stratification in COVID-19 considered in combination with clinical details and other laboratory tests while designing the patient treatment.

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Received November 11, 2022.
Accepted January 7, 2023.