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Serum vitamin D levels and the severity and clinical course of COVID-19

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Abstract

Low vitamin D levels are associated with different pulmonary diseases, such as chronic obstructive pulmonary disease, bronchial asthma, and obstructive sleep apnea. In this study, we aimed to assess the relation between vitamin D levels and COVID-19 severity. Positive COVID-19 patients were subjected to clinical examination, computed tomography of the chest, and laboratory investigations. Serum vitamin D level was measured and correlated with the severity and the clinical course of the disease. The study included 72 patients, classified into four groups according to the severity of the disease. There was a statistically significant difference between the four groups regarding age, lymphocyte count, serum vitamin D, C-reactive protein, and lactate dehydrogenase levels. Serum vitamin D levels can be correlated with COVID-19 severity and clinical course.

Key words: COVID-19, vitamin D, C-reactive protein.

Introduction

Disease severity in COVID-19 is assessed by the occurrence of pneumonia, acute respiratory distress syndrome, vascular thrombosis, myocarditis and cytokine storm, with inflammation being the main pathogenic mechanism [1]. Vitamin D deficiency is associated with increased in inflammatory cytokines and vitamin D supplementation can increase the level of T regulatory lymphocytes (that protects against uncontrolled inflammation) which was found to be extremely low in severe cases of COVID-19 [2].

Vitamin D can protect against respiratory tract infections as it enhances T-lymphocytes chemotaxis, induces apoptosis and autophagy of infected epithelial cells facilitating removal of infecting organisms [3]. It poses antiviral activity as it can inhibit replication of the virus by stimulating monocytes and macrophages to release cathelicidin and defensin proteins [4]. The aim of our study was to assess the relation between serum level of vitamin D, severity and clinical course of COVID-19 infection.

Materials and Methods

This prospective study was conducted in the period from November 2022 to March 2023. The study was approved by research ethics committee of faculty of medicine, Cairo university (No: MD-236-2022). Written informed consent was obtained from each patient.

The study included 72 patients diagnosed with COVID-19 infection, classified according to the disease severity grades of World Health Organization definition into 4 groups [5]. Group-1: asymptomatic patients; group 2: patients with mild disease, group 3: patients with moderate disease and group 4: patients with severe disease.

Disease severity grades of World Health Organization

Mild disease: symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia.

Moderate disease: adult with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including SpO2 90% on room air. The diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.

Severe disease: adult with clinical signs of pneumonia (fever, cough, dyspnea) plus one of the following: respiratory rate > 30 breaths/min, severe respiratory distress, or SpO2 < 90% on room

air. The diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.

Inclusion and exclusion criteria

Adult patients with confirmed COVID-19 infection were included; confirmed case were defined as a positive result of real-time reverse-transcriptase–polymerase-chain-reaction assay of nasopharyngeal swab. Exclusion criteria included patients with liver disease, chronic renal disease, parathyroid disease and mal-absorption.

Methodology

History taking, with particular attention to: age, comorbidities, and symptoms of Covid-19, physical examination, including vital signs (temperature, heart rate, respiratory rate) and oxygen saturation. Computed tomography (CT) of the chest was done. Laboratory investigations: Complete blood count, inflammatory markers: C-reactive protein (CRP) and serum lactate dehydrogenase (LDH). Determination of serum vitamin D levels by enzyme linked immunosorbant assay (ELISA) kit (Biovantion inc, Beijing, China) according to manufacturer instructions.

Statistical methods

The data was statistically analyzed via Minitab program 17.1.0.0 for windows (Minitab Inc., 2013, Pennsylvania, USA). Continuous data were presented as mean and standard deviation (SD) and categorical data as number and percentage (%), the normality of data was examined using Shapiro-Wilk test. Comparison between mean of more than two groups was performed by one way ANOVA test with Turkey methods for intergroup comparison, independent t-test, and by Kruskal Wallis test for non-parametric data, while Chi square test was used for comparing between groups of categorical data. Pearson correlation coefficient was used for linear relationship evaluation, the sign before "r" denoting the direction of relation. All test was two sided, P 0.05 was considered significant.

Results

Table 1 shows demographics of study population. The mean age of asymptomatic and mild COVID-19 patients was significantly lower than those with moderate and severe disease (p value <0.001), and the number of female patients was significantly higher in mild disease group

in relation to other groups (p value: 0.02). Chronic pulmonary diseases included chronic obstructive pulmonary disease, bronchial asthma and fibrotic hypersensitivity pneumonitis. Neurological disorders included Parkinsonism and old stroke, and were reported frequently in severe cases (p value< 0.001).

Table 2 summarizes laboratory investigations results of the study population. Total leucocyte count, CRP and LDH were significantly elevated in moderate and severe COVID-19 disease, while lymphocytes % and hemoglobin were significantly decreased.

Table 3 showed serum level of vitamin D among studied groups and Table 4 showed serum level of vitamin D in relation to clinical course of patients

Figures 1 and 2 show the correlation between serum vitamin D level and CRP, LDH, total leucocyte count and lymphocytes %. There were significant negative linear correlation between CRP, LDH, total leucocyte count and the level of vitamin D in serum. While the correlation between serum vitamin D level and lymphocytes (%) was significantly positive.

Discussion

Vitamin D has an immune-regulatory function, through its receptors (located on multiple immune cells such as dendritic cells, monocytes and activated lymphocytes) it can affect activation and proliferation of immune cells, production of antibodies and cytokines [6]. There is conflicting data about the relationship between vitamin D deficiency and the increased risk of COVID-19, and the severity of the disease [7].

In this study, the severity of the disease increased with increasing the age. These results were in line with those of Jain et al. [8]; Vasheghani et al. [9]; Kalichuran et al. [10]; Yosef et al. [11]. While Campi et al. [12] did not observe any difference in the age between mild and severely-symptomatic COVID-19 cases.

As known in viral infections, elder patients have the greatest risk of severe disease and death. This can be attributed to many reasons. First, immunesenescence, where decreased production of T and B cells, impairment of innate immunity, and uncoordinated adaptive immune response occur. This results in ineffective viral clearance and deranged immune response and a cytokine storm [13]. Secondly, inflammaging (chronic subclinical systemic inflammation that occur in old age) predisposes to unfavorable outcome in old COVID-19 patients [14]. Thirdly, comorbidities associated with old age, increases the risk for severe COVID-19 [15].

In our study, serum level of vitamin D was significantly associated with the severity (p value: <0.001), and with the clinical course of the disease (p value: <0.0001). This agreed with

previous studies**:** Jain et al. [8]; Vasheghani et al. [9]; Kalichuran et al. [10]; Yosef et al. [11]; Campi et al. [12]; Demir et al. [16]; Davoudi et al.[17]; Nielsen et al.[18]; Qiu et al. [19]; Renieris et al. [20], while Abdel Ati and Shahin [21]; AlKhafaji et al. [22] did not find any association between serum level of vitamin D and severity and outcome of COVID-19.

Several explanations were proposed to demonstrate the relation between deficiency of vitamin D and COVID-19 risk and outcomes; as vitamin D: it enhances cellular immunity and can attenuate the levels of pro-inflammatory cytokines, such as TNF-α and IFN-γ (produced during the cytokine storm) while increasing the levels of anti-inflammatory cytokines [23]. It manipulates adaptive immune response by preventing T-helper 1 response, increasing production of T-helper 2 (Th2) cytokines, and inducing T-regulatory cells [24]. It induces cathelicidin, IL-37 and defensins (antimicrobial peptides) and decreases viral replication [25]. It augments the expression of some antioxidant genes, such as the glutathione reductase gene [23]. Also some studies have reported that vitamin D metabolites can have anticoagulant effects by altering the thrombomodulin and tissue factor expression in monocytes [26]. Absence of the previously mentioned roles of vitamin D may lead to the severe form of the disease.

This study revealed significant negative correlation between serum vitamin D level, CRP, LDH and total leucocyte count, while the relationship with lymphocytes % was significantly positive. Similar results were reported by Yosef et al. [11]; Renieris et al. [20]. While Qiu et al. [19] found a non-significant link between serum vitamin D, lymphocyte and LDH.

In this study hemoglobin was found to be decreased in severe disease, this was in line with Wang et al. [27] and can be explained by altered erythropoiesis due to the effect of systemic inflammation, which is the main pathogenetic mechanism in COVID-19 [28]

In severe cases leukocytosis with lymphopenia was observed that was in line with the findings of Chen et al. [29] and Yamadaa et al. [30]. Leucocytosis can be due to bacterial superinfection [31] and lymphopenia may be related to atrophy of lymphatic tissue, direct lymphocyte invasion, or lymphocyte apoptosis due to inflammation and cytokine release [32].

Conclusions

Given the above mentioned results, and findings of multiple studies that assessed the effect of vitamin D supplementation on the risk of infection, severity and outcomes of COVID-19, vitamin D supplementation may be an easy and inexpensive approach for decreasing the consequences of COVID- 19.

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Table 1. Demographics of study population.

	Group-1		Group-2		Group-3		Group-4		p-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age	41.67	12.18	46.67	12.05	65.67	14.74	67.78	14.24	<0.001
	N	%	N	%	N	%	N	%	
Sex									
Female	8	44.44	16	88.89	9	50	9	50	0.02
Male	10	55.56	2	11.11	9	50	9	50	
Comorbidities									
Diabetes mellitus	2	11.11	5	27.78	8	44.44	8	44.44	0.07
Systemic hypertension	4	22.22	9	50	11	61.11	9	50	0.09
Chronic pulmonary diseases	3	16.67	2	11.11	5	27.78	8	44.44	0.11
Neurological disorders	0	0	1	5.56	1	5.56	6	33.33	0.006

SD, standard deviation.

Table 2. Laboratory investigations results in study groups.

	Group-1		Group-2		Group-3		Group-4		p value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Total leucocyte count	8.29	3.24	7.26	3.04	7.74	3.39	14.66	9.18	0.001
Lymphocytes (%)	37.82	14.09	38.91	12.18	36.74	18.92	14.89	17.04	0.001
Hemoglobin	12.79	1.02	12.36	1.98	11.50	1.67	11.24	2.16	0.03
Platelets count	264.2	18.2	293.2	19.7	244	20.7	282.4	28.3	0.38
CRP	4.72	0.97	4.44	0.92	27.89	5.72	49.00	9.56	<0.001
LDH	242.1	44.3	251.4	56.5	425.5	102.2	441.7	147.4	<0.001

SD, standard deviation; CRP, C-reactive protein; LDH, serum lactate dehydrogenase.

Table 3. Serum vitamin D levels in study groups.

Serum vitamin D level	Group-1		Group-2		Group-3		Group-4		p-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
	17.18	4.92	14.165	2.074	12.923	2.467	10.083	2.082	<0.001

SD, standard deviation.

Table 4. Serum vitamin D level and course of the disease.

Outcome	N	%	Serum vitamin D		p value
			Mean	SD	
Deteriorated	12	16.67	9.633	2.192	<0.0001
Improved	42	58.33	13.178	2.408	

SD, standard deviation.

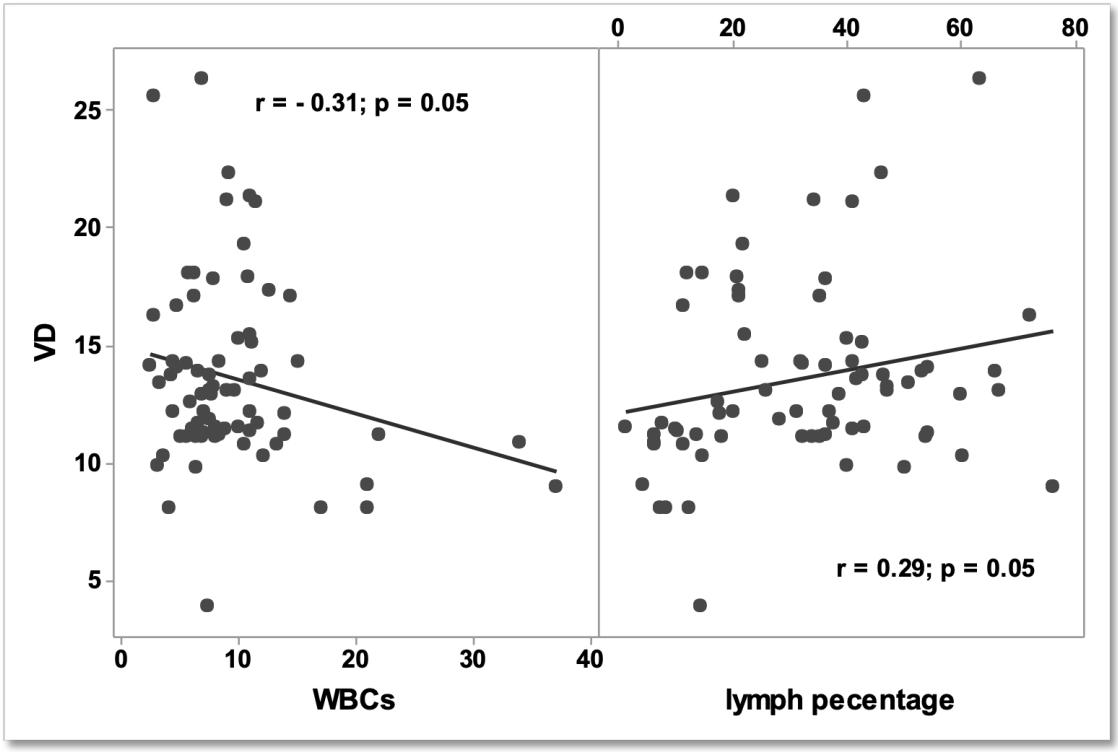

Figure 1. Correlation between serum vitamin D level with total leucocyte count and lymphocytes %.

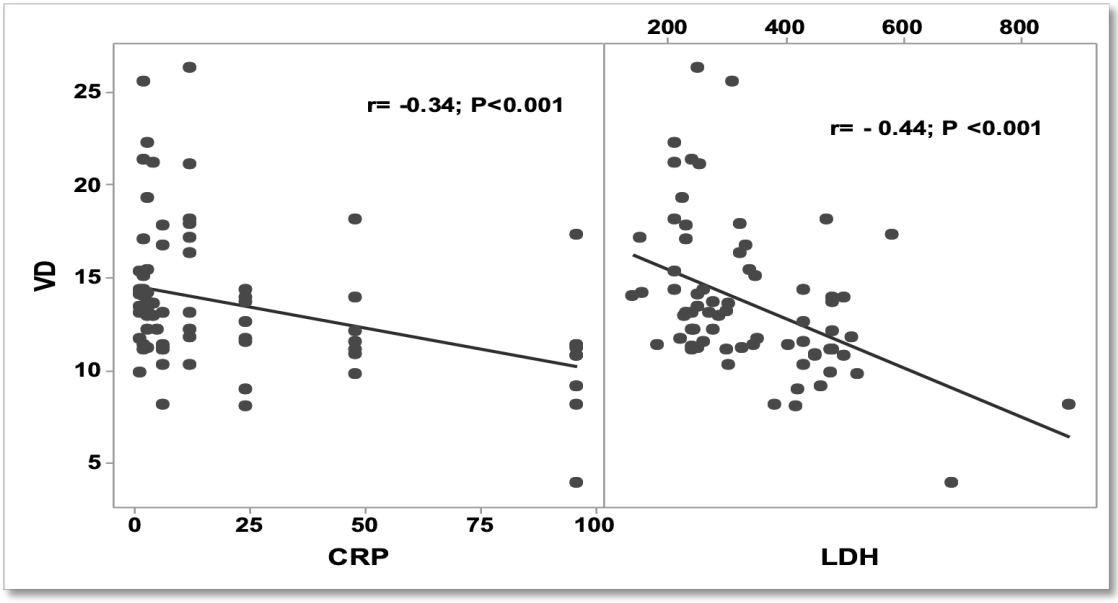

Figure 2. Correlation between serum vitamin D level and inflammatory markers. CRP, C-reactive protein; LDH, serum lactate dehydrogenase.