Research Article

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A notable key for estimating the severity of COVID-19: 25-hydroxyvitamin D status

COVID-19'un şiddetini tahmin etmek için dikkate değer bir anahtar: 25-hidroksivitamin D durumu

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Abstract

Background: Vitamin D is recognized to be an immune regulator. Also, it is known to have antiviral effects by several mechanisms, including reducing inflammatory cytokines.

Objectives: To examine the 25-hydroxyvitamin D (25(OH) D) status for assessing the severity of COVID-19.

Methods: This study consisted of 596 patients confirmed as SARS-CoV-2 infection and 59 healthy individuals. The cases separated into non-severe group, severe survival, and severe non-survival group. 25(OH)D and other laboratory parameters were evaluated retrospectively.

Results: In all COVID-19 groups 25(OH)D levels were low compared to controls ($p<0.05$). 25(OH)D concentrations were lowest in patients in severe non-survival groups than those in other SARS-CoV-2 infection groups ($p<0.05$). Multivariate regression analysis exhibited that decreasing 25(OH)D was associated with an increased likelihood of non-severe, severe survival and severe non-survival disease. There were significant associations between 25(OH)D and certain inflammatory and hemostatic parameters ($p<0.05$, for all).

Conclusions: 25(OH)D deficiency was observed among patients with COVID-19. Declined steadily 25(OH)D levels make a huge contribution to the scale of the progression of the disease. Correlations support that 25(OH)D may be a substantial tool for utilizing the severity of the disease and estimating the survival. Also, supplementation of 25(OH)D might slow down the course of the COVID-19.

Keywords: COVID-19; 25-hyrdroxyvitamin D; laboratory parameters; SARS-CoV-2; vitamin D.

Öz

Amaç: D vitamini bir bağışıklık düzenleyici olarak kabul edilir ve ayrıca inflamatuar sitokinlerin azaltılması da dahil olmak üzere çeşitli mekanizmalarla antiviral etkilere sahip olduğu bilinmektedir. Çalışmanın amacı COVID-19'un

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şiddetini değerlendirmek için 25-hidroksivitamin D (25 (OH) D) durumunu incelemekti.

Gereç ve yöntem: Bu çalışma, SARS-CoV-2 enfeksiyonu olarak doğrulanan 596 hasta ve 59 sağlıklı kişiden oluştu. Vakalar şiddetli olmayan grup, şiddetli sağ kalan ve şiddetli sağ olmayan grup olarak ayrıldı. 25 (OH) D ve diğer laboratuvar parametreleri geriye dönük olarak değerlendirildi.

Bulgular: Tüm COVID-19 gruplarında 25 (OH) D seviyeleri kontrollere kıyasla düşüktü ($p<0.05$). 25 (OH) D konsantrasyonları, şiddetli hayatta kalmayan gruptaki hastalarda, diğer SARS-CoV-2 enfeksiyon gruplarına göre en düşüktü ($p<0.05$). Çok değişkenli regresyon analizi, 25 (OH) D'nin azalmasının şiddetli olmayan, şiddetli sağ kalan ve şiddetli sağ kalmayan hastalık olasılığının artmasıyla ilişkili olduğunu gösterdi. 25 (OH) D ile belirli inflamatuar ve hemostatik parametreler arasında önemli ilişkiler vardı (tümü için $p<0.05$).

Sonuç: COVID-19'lu hastalarda 25 (OH) D eksikliği gözlendi. Kademeli olarak düşen 25 (OH) D seviyeleri, hastalığın ilerleme ölçeğine büyük katkı sağladı. Korelasyonlar, 25 (OH) D'nin hastalığın ciddiyetini değerlendirmek ve sağ kalımı tahmin etmek için önemli bir araç olabileceğini desteklemektedir. 25 (OH) D takviyesi, COVID-19'un seyrini yavaşlatabilir.

Anahtar kelimeler: 25-hidroksivitamin D; COVID-19; D vitamini; laboratuvar parametreleri; SARS-CoV-2.

Introduction

The world is struggling with coronavirus infection which was nominated as coronavirus disease 2019 (COVID-19) [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) elicits the infection of COVID-19. It was initially identified in subjects in Wuhan province in China [2]. It has widely disseminated overrun the world and has pronounced a pandemic by the world Health Organization (WHO) [1]. As of 16 August 2020, there have been 21,260,760 confirmed cases of COVID-19, including 761.018 deaths, reported to WHO [3].

The pathophysiology of COVID-19 is not great brought into light, it constitutes a complicated interplay through SARS-CoV-2 and immune system. SARS-CoV-2 is recognized to lead an acute lung harm which ends in aggressive inflammation triggered by viral replication [4]. The inflammatory response displays a crucial part in the clinical presentations of COVID-19 [4].

Besides its traditional line, vitamin D [25-hydroxyvitamin D (25(OH)D)] is conceived to be a vigorous immune modulator [5]. The dynamics between viral infections and (25(OH)D) circumstance sustains challenging [6]. The antiviral impresses of 25(OH)D have been pointed in many researches [7, 8]. Initiation of generation of antimicrobial proteomics, reduction of pro-inflammatory cytokines, association with cellular and viral constituents, and promotion of apoptosis are the principal emphasized approaches that 25(OH)D insufficiency could involve in viral situations [6, 7]. The protective impacts of 25(OH)D have published in a good deal of cases, like pneumonia, excessive cytokine production, and ARDS [9]. 25(OH)D deficiency has been closely linked to enhanced jeopardy of respiratory infections just as tuberculosis and influenza [7].

Severe deficit of 25(OH)D is worldwide and 25(OH)D own a crucial act on various cellular responses [5]. In the light of above reasons, we investigated 25(OH)D status and its relationships with other laboratory parameters in COVID-19.

Materials and methods

Study design

A retrospective study was carried on patients suffering from COVID-19 from March to June 2020 in Ankara City Hospital which is one of the pandemic hospitals in Turkey. All patients were established a final diagnosis with regard to the World Health Organization guides for COVID-19. All subjects were in-patient and own a confirmed laboratory test data of COVID-19 infection. Patients were classified into three groups in terms of survival and severity of illness. Epidemiologic data including travel and contact history, underlying comorbidities, smoking habits, signs and symptoms and laboratory results were obtained from electronic medical records. Age and sex paired healthy participants set off the control group. The study procedure was approved by the local ethic committee.

25(OH)D levels, hematology tests [hemoglobin concentration (Hb), platelet (PLT), white blood cell (WBC), neutrophil (NEU) and, lymphocyte (LYM) counts], coagulation biomarkers [D-dimer and fibrinogen amounts, prothrombin time (PT) and activated partial thromboplastin time (APTT)], blood biochemistry variables [lactate dehydrogenase (LDH), albumin, aspartate aminotransferase (AST), creatinine and alanine aminotransferase (ALT),], ferritin and C-reactive protein (CRP) levels of all subjects were gained from laboratory information system.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) software program (v.22; IBM, Armonk, NY, USA) was executed for statistical utilizations. The Kolmogorov-Smirnov test was applied to assess distribution sort. If the data displays normal distribution, it is stated as mean and standard deviation; if it displays non-normal distribution it is stated as median (25th–75th percentile, interquartile range [IQR]). The categorical variables are described just as frequencies and percentages. The significance of difference through categorical parameters examined via the chi-square or Fisher's exact test (when proper). A one-way

ANOVA and post hoc Bonferroni correction was managed to compare the parameters among study groups. The correlations between 25(OH) D levels and other variables were investigated by the Pearson's correlation analysis. Multivariate logistic regression analysis was conducted to determine the independent risk factors for the severity of COVID-19. p<0.05 was focused statistically significant for all analyzes.

Results

A total of 596 patients with COVID-19 were included in this research. As regards to the survival and disease severity, 450 cases were categorized as non-severe (75.5%) and 146 cases (24.5%) were categorized as severe (120 as severe-survival and 26 as severe non-survival). Remarkably, severe non-survival patients were about two decade older than non-severe patients; the mean age of severe non-survival patients was 68.2 while the mean age of non-severe patients was 48.1 (p<0.05). Comorbidities were existed in 314 patients (52.7%). Comorbidity rate was highest in patients in severe non-survival group (80.7%) than those of other groups (p<0.05). hypertension and diabetes were observed as the most common comorbidities (47.8 and 38.5% of total comorbidities, respectively). Dyspnea is the third most common symptom after cough and fever (30.7%). Characteristics of patients with COVID-19 are presented in Table 1.

Laboratory parameters of study population are indicated in Table 2. Severe non-survival group had the lowest 25(OH)D levels than that of other groups (p<0.05). When compared based upon the hematologic tests WBC, NEU, LYM counts, neutrophil to lymphocyte ratio (NLR) and Hb concentrations were statistically different among study groups (p<0.05). WBC, NEU counts and NLR levels were significantly lower and LYM counts and Hb concentrations were significantly higher in non-severe group than severe survival and severe non-survival groups (p<0.05, for all). D-dimer and fibrinogen concentrations were significantly increased in patients in severe non-survival group than those of non-severe and severe survival group (p<0.001, for both). When biochemistry parameters were considered; LDH, AST and ALT levels were higher in severe non-survival group than other COVID-19 groups (p<0.001, p<0.001, p<0.05, respectively). Albumin concentrations were higher in non-severe group than the other groups. Also, albumin concentrations were similar in severe survival and severe non-survival group. Patients in severe non-survival group had the highest CRP and ferritin levels than those of patients in non-severe and severe survival group (p<0.001, for both).

Table 1: Demographic characteristics of patients with COVID-19.

	No., %		
	Non-severe cases (n=450)	**Severe-survival cases (n=120)**	**Severe-non-survival cases (n=26)**
Age, mean ± SD	48.1 ± 9.4	66.6 ± 7.2	68.2 ± 9.2*
Sex			
Male	258 (57.3)	72 (60)	18 (69.2)
Female	192 (42.7)	48 (40)	8 (30.8)
Comorbidities	210 (46.6)	83 (69.1)	21 (80.7) *
Coronary heart disease	30 (6,66)	24 (20)	7 (26.9)
Hypertension	102 (22.6)	39 (32.5)	9 (34.6)
Diabetes	78 (17.3)	33 (27.5)	10 (38.4)
Chronic lung disease	51 (11.3)	9 (7.5)	5 (19.2)
Chronic kidney disease	12 (2.6)	18 (15)	5 (19.2)
Cancer	24 (5.3)	18 (15)	6 (23)
Signs and symptoms			
Fever	312 (69.3)	87 (72.5)	20 (76.9)
Cough	330 (73.3)	96 (80)	22 (84.6)
Dyspnea	90 (20)	74 (61.6)	19 (73)*
Nausea and vomiting	23 (5.1)	13 (10.8)	3 (11.5)
Diarrhea	40 (8.88)	5 (4.1)	2 (7.6)
Myalgia	65 (14.4)	12 (10)	2 (7.6)
Fatigue	107 (23.7)	11 (9.2)	1 (3.8)*
Headache	46 (10.2)	4 (3.3)	1 (3.8)

Categorical variables were expressed as numbers (n) and percentages (%). Continuous variables were stated as mean ± standard deviation (SD). *p-value<0.05 considered statistically significant.

Relationships between the 25(OH)D test and other blood parameters were examined. 25 (OH)D levels were significantly correlated with LYM, Hb and PLT (r=0.38, p<0.001; r=0.18, p<0.05; r=0.16, p<0.05, respectively) Significant negative correlations were observed between 25(OH)D levels and NLR, LDH, ferritin, CRP, D-dimer an fibrinogen (r=0.34, p<0.001; r=0.33, p<0.001; r=0.43, p<0.001; r=0.25, p<0.05; r=0.27, p<0.001; r=0.25, p<0.05, respectively).

Multivariate logistic regression analysis was applied to identify the independent risk predictors for the severity of COVID-19 from 25(OH)D, ferritin levels, LYM and NEU counts with the odd ratios presented in Table 3. It has been found that the levels of 25(OH)D and ferritin were associated with each stage of the disease. However, LYM and NEU were only associated with severe survival and severe non-survival stages. Other variables were not found to be related to disease severity.

Table 2: Laboratory findings of patients with COVID-19.

	Non-severe cases (n=450)	Severe-survival cases (n=120)	Severe-non-survival cases (n=26)	Healthy subjects (n=59)	p-Value
25(OH)D, ng/mL	21.17 ± 5.13$^{a,c,\ d}$	14.61 ± 3.72^{a,b}	10.5 ± 3.44^{a,b}	36.26 ± 4.91^{b,c,d}	<0.001
WBC, $\times10^9$/L	6.62 ± 1.56^{d}	7.35 ± 1.76	9.28 ± 2.64^{a,b,c}	6.51 ± 1.67^{d}	<0.05
NEU, $\times10^9$/L	4.38 ± 0.96^{d}	5.71 ± 1.27^{a,d}	7.72 ± 1.03^{a,b,c}	3.49 ± 0.93^{c,d}	<0.001
LYM, $\times10^9$/L	1.68 ± 0.43^{a,c,d}	0.97 ± 0.39^{a,b}	0.78 ± 0.37^{a,b}	2 ± 0.45^{b,c,d}	<0.001
NLR	3.53 ± 0.82^{c,d}	6.75 ± 1.56^{a,b,d}	13.8 ± 3.17^{a,b,c}	1.85 ± 0.37^{c,d}	<0.001
Hb, g/dL	13.5 ± 1.79^{a,c,d}	12.4 ± 1.98^{a,b,d}	11 ± 1.74^{a,b,c}	14.43 ± 1.6^{b,c,d}	<0.001
PLT, $\times10^9$/L	242.37 ± 25.63	235 ± 37.22	211.35 ± 24.94	248.45 ± 39.1	> 0.05
PT, s	13.06 ± 2.11	14.73 ± 1.75	13.8 ± 1.63	14.06 ± 1.57	>0.05
APTT, s	25.41 ± 3.17	25.75 ± 2.94	26.44 ± 4.02	36.26 ± 4.91	> 0.05
D-dimer, mg/L	0.65 ± 0.09^{a,c,d}	1.76 ± 0.42^{a,b,d}	2.66 ± 0.54^{a,b,c}	0.19 ± 0.03^{b,c,d}	<0.001
Fibrinogen, g/L	3.63 ± 0.77^{a,c,d}	4.59 ± 0.51^{a,b}	4.96 ± 0.63^{a,b}	2.6 ± 0.45^{b,c,d}	<0.001
LDH, U/L	236.86 ± 33.5^{c,d}	340.47 ± 39.05^{a,b,d}	437.13 ± 49.66 ^{a,b,c}	176.7 ± 23.43^{c,d}	<0.001
Ferritin, µg/L	155.06 ± 10.38 ^{a,c,d}	350.1 ± 30.2^{a,b,d}	513.4 ± 42.84^{a,b,c}	49.7 ± 9.83^{b,c,d}	<0.001
ALT, U/L	29.8 ± 2.81^{d}	39.67 ± 4.29	44.92 ± 5.82^{a,b}	28 ± 4.67^{d}	<0.05
AST, U/L	26.27 ± 2.93^{c,d}	43.5 ± 5.09^{a,b,d}	60.86 ± 7.52^{a,b,c}	22.5 ± 3.49^{c,d}	<0.001
Albumin, g/L	42.98 ± 4.74^{c,d}	37.40 ± 4.5^{b}	37.97 ± 4.88^{b}	40 ± 5.05	<0.001
Creatinine, mg/dl	0.77 ± 0.17^{c,d}	0.65 ± 0.10^{a,b}	1.07 ± 0.22^{a,b}	1.23 ± 0.35^{c,d}	<0.001
CRP, g/L	0.044 ± 0.01^{c,d}	0.097 ± 0.08^{a,b}	0.141 ± 0.09^{a,b}	0.0019 ± 0.0003^{c,d}	<0.001

Data are mean ± SD. One-way analysis of variance [ANOVA]. 25(OH)D, 25 hydroxy vitamin D; WBC, white blood cell; NEU, neutrophils count; LYM, lymphocyte count; NLR, neutrophil to lymphocyte ratio; Hb, hemoglobin; APTT, activated partial thromboplastin time, PT, prothrombin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; LDH, lactate dehydrogenase; PLT, platelet. *p-value<0.05, p-value<0.05 considered significant. [a]Statistically significant difference between healthy individuals vs. the other groups; [b]Statistically significant difference between the non-severe COVID-19 group vs. the other groups; [c]Statistically significant difference between the severe survival COVID-19 group vs. the other groups. [d]Statistically significant difference between the severe non-survival COVID-19 group vs. the other groups.

Table 3: Multivariate logistic regression analysis.

	Non-severe		Severe survival		Severe non-survival	
Parameters	**OR (95% CI)**	**p-Value**	**OR (95% CI)**	**p-Value**	**OR (95% CI)**	**p-Value**
25(OH)D, ng/mL	0.857 (0.780–0.941)	=0.001*	0.783 (0.690–0.888)	<0.001*	0.648 (0.507–0.829)	=0.001*
Ferritin, µg/L	1.036 (1,012–1.061)	=0.004*	1.044 (1.019–1.070)	<0.001*	1.046 (1.021–1.072)	<0.001*
LYM, 10^9/L	0.554 (0.127–2.409)	NS	0.030 (0.003–0.285)	=0.002*	0.002 (0.0003–0.068)	<0.001*
NEU, 10^9/L	1.783 (0.875–3.633)	NS	2.437 (1.160–5.121)	=0.019*	3.093 (1.423–6.720)	=0.004*

OR, odds ratio; CI, confidence interval; NS, not significant; 25(OH)D, 25 hydroxyvitamin D; LYM, lymphocyte count; NEU, neutrophils count. *p<0.05.

Discussion

The present COVID-19 pandemic is obviously an international public health difficulty [1]. COVID-19 ensues from the infection originated by acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. The number the individuals diagnosed with the SARS-CoV-2 disease holds to increase [10]. COVID-19 is recognized to provoke an acute lung damage which results in extreme inflammation [11]. Cytokine storm exists in patients with severe COVID-19 [10]. Uncontrolled release of inflammatory cytokines is closely related to acute respiratory syndrome which is one of the main occasions of mortality in COVID-19 [10, 11]. 25(OH)D presents a regulatory act in immunity and inflammation [12]. Moreover, 25(OH)D modifies the immunity of T-cells and reduces inflammatory cytokines particularly in the lung [7]. In vitro studies have pointed that 25(OH)D has a notable part in respiratory circumstance via having direct influence on reproduction of respiratory viruses and triggering the expression of antimicrobial proteomics [8, 7].

As seen in Table 2, 25(OH)D concentrations were significantly lower in patients with COVID-19 when compared to healthy subjects. The mean 25(OH)D levels in severe non-survival group were significantly lower than the severe survival group and non-severe group. Regression analysis presented that increasing 25(OH)D was associated

with a decreased likelihood of exhibiting non-severe, severe survival and severe non-survival disease. Hence it can be considered that 25(OH)D concentrations decrease as COVID-19 progresses. 25(OH)D may present a crucial position in the development and progression of SARS-CoV-2 disease.

In a cohort study, D'Avolio et al. [13] have retrospectively examined the 25(OH)D concentrations in patients with COVID-19. They have found significantly lower 25(OH)D levels in PCR-positive SARS-CoV-2 patients compared with negative patients [13]. Furthermore Merzon et al. [14] represented that patients who tested positive for COVID-19 had significantly lower 25(OH)D concentrations than negative for COVID-19. Also, they have revealed a relationship between low plasma 25(OH)D and enhanced probability of COVID-19 and hospitalization [14]. However, in UK biobank study, there was no relationship between the 25(OH)D levels and likelihood of COVID-19 [15]. In a recent study, the 25(OH)D concentrations for 20 countries and cases and deaths caused by SARS-CoV-2 disease were evaluated [16]. Negative associations between mean levels of 25(OH)D and the number of cases and mortality originated from COVID-19 were observed [16].

WBC and NEU counts were significantly higher in severe groups when compared to non-severe group and healthy control group (Table 2). Despite the increase in terms of WBC and NEU counts, the values were within the reference range (3.6–10.5; 1.5–7.7, respectively). In the literature researchers have gained normal, increased or decreased WBC and NEU counts in COVID-19 which vary in regard to the severity of the disease [17]. It has been observed that as the severity of the disease rises, the number of lymphocytes diminishes. This result is in line with the results of other studies about SARS-CoV-2 disease [18]. Diminished LYM counts were observed in severe groups than non-severe and healthy control group (Table 2). This outcome indicates that SARS-CoV-2 may essentially have an impact on lymphocytes. NLR is considered to be an indicator for inflammatory response [19]. NLR of severe non-survival patients were almost two fold of severe survival patients and four fold of non-severe patients (Table 2). It can be speculated that enhanced NLR is significantly related with the disease severity. Yang et al. used NLR to distinguish patients with non-severe and severe COVID-19 [19]. They have set the threshold for NLR 3.3 for the prognostic likelihood of symptoms from non-severe into severe [19]. Additionally, CRP, ferritin and LDH were found higher in severe groups when compared to non-severe groups. Virus triggers a cytokine storm and produces a wide range of immune responses [10]. Also, acute phase reactants like CRP play along with intensity of inflammation.

As COVID-19 exhibits a broad range of clinical presentation, it can lead hypercoagulable situation [20]. Increased cytokine release that occurs as a result of an extreme inflammatory response may augment the coagulopathy [21]. In this study D-dimer and fibrinogen levels were elevated in severe groups than non-severe study group (Table 2). Zhang et al. suggested that patients with D-dimer test results greater than 2 μg/ml had a higher incidence of mortality than those with D-dimer test results below 2 μg/ml [22].

25(OH)D acts as an immunomodulatory molecule nearby calcium phosphate metabolism [23]. 25(OH)D receptors are expressed by several immune cells involving lymphocytes and macrophages [23]. Also, 25(OH)D regulates endothelial function and brings down the producing of inflammatory cytokines [23, 24]. In addition, 25(OH)D have an impact on a number of pathways implicated in thrombosis like hemostatic and inflammatory process [25]. Strong significant associations between 25(OH)D and inflammatory and hemostatic parameters were obtained in this research. These results showed that 25(OH)D was closely related to the severity of the COVID-19.

In conclusion this study displays that 25(OH)D levels were lower in COVID-19. Also, 25(OH)D levels decrease as the severity of the disease progresses. Intense relationships among 25(OH)D levels and other blood inflammatory and hemostatic parameters support this outcome. 25(OH)D concentrations may be dynamic indicator for predicting the severity of COVID-19. 25(OH)D supplementation have a grand potential to slow or stop disease progress in SARS-coV-2.

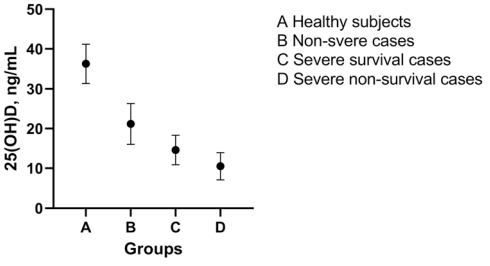

Figure 1: 25(OH)D status among study groups ($\bar{x} \pm \sigma_{\bar{x}}$).

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