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Investigation of the Effect of Vitamin D in Severe COVID-19 Patients

Ciddi COVID-19 Hastalarında D Vitamininin Etkisinin Araştırılması

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ABSTRACT Objective: This study aimed to examine the effect of vitamin D on I interleukin (IL-6) and coagulation parameters in coronavirus disease-2019 (COVID-19) patients treated in the intensive care unit. **Material and Methods:** Two hundred and forty patients who were followed up in the intensive care unit due to severe COVID-19 infection between March 2020-April 2022 were analyzed retrospectively. The demographic characteristics of the patients and serum levels of vitamin D and interleukin (IL-6), complete blood count, troponin, pro-brain natriuretic peptide (pro-BNP), procalcitonin, D-dimer, ferritin, fibrinogen, activated partial thromboplastin time, prothrombin time, and international normalized ratio (INR) levels were analyzed. **Results:** Considering the groups, those with vitamin D deficiency were 79.2%, those with vitamin D insufficiency were 13.3% and those with normal vitamin D were 7.5%. There was a significant difference in age, vitamin D, cytokine measurement, prothrombin time, INR level, D-dimer, fibrinogen, platelet count, ferritin, pro-BNP, procalcitonin, and C-reactive protein (CRP) levels between the surviving and deceased patients ($p<0.001$). In the correlation analysis, a weak negative correlation was found between vitamin D and only cytokine and CRP levels. **Conclusion:** The fact that vitamin D levels are high in survivors after treatment for COVID-19 is proof that it affects mortality. However, there is no evidence that vitamin D reduces the prothrombotic effect of cytokines.

Keywords: Severe COVID-19; vitamin D; interleukin-6

ÖZET Amaç: Bu çalışmada, yoğun bakım ünitesinde tedavi gören koronavirüs hastalığı [coronavirus disease-2019 (COVID-19)] hastalarında D vitamininin interlökin (IL-6) ve pıhtılaşma parametreleri üzerindeki etkisinin incelenmesi amaçlanmıştır. **Gereç ve Yöntemler:** Mart 2020-Nisan 2022 tarihleri arasında şiddetli COVID-19 nedeniyle yoğun bakım ünitesinde takip edilen 240 hasta retrospektif olarak analiz edildi. Hastaların demografik özellikleri ve serum D vitamini ve interlökin-6 (IL-6) tam kan sayımı, troponin, pro-beyin natriüretik peptidi (pro-BNP), prokalsitonin, D-dimer, ferritin, fibrinojen, aktive parsiyel tromboplastin zamanı, protrombin zamanı ve uluslararası normalleştirilmiş oran [international normalized ratio (INR)] düzeyleri analiz edildi. **Bulgular:** D vitamini eksikliği olanların oranı %79,2, D vitamini yetersizliği olanlar %13,3 ve D vitamini normal olanlar %7,5 idi. Yaş, D vitamini, sitokin ölçümü, protrombin zamanı, INR seviyesi, D-dimer, fibrinojen, trombosit sayısı, ferritin, pro-BNP, prokalsitonin ve C-reaktif proteini (CRP) seviyeleri arasında hayatta kalan ve ölen hastalar arasında istatistiksel anlamlı farklılık vardı ($p<0,001$). Korelasyon analizinde, D vitamini ile yalnızca sitokin ve CRP seviyeleri arasında zayıf bir negatif korelasyon bulundu. **Sonuç:** COVID-19 tedavisinden sonra hayatta kalanlarda D vitamini seviyelerinin yüksek olması, bunun mortaliteyi etkilediğinin kanıtıdır. Ancak, D vitamininin sitokinlerin protrombotik etkisini azalttığına dair bir kanıt yoktur.

Anahtar Kelimeler: Ciddi COVID-19; D vitamini; interlökin-6

Coronavirus disease-2019 (COVID-19) is caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), which uniquely resembles the SARS-CoV-2 that was an epidemic in the early 2000s.[1] SARS-CoV-2 enters human cells primarily by binding to the highly expressed angiotensin converting enzyme 2 receptor.[2] The disease, which starts with various symptoms, can progress to serious illness such as systemic inflammatory response syndrome, acute respiratory distress syndrome, multi-organ involvement, disseminated intravascular coagulation (DIC), and shock. In COVID-19, thrombosis in the arterial and venous system is caused by the activation of the coagulation system by several

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risk factors such as increased inflammation, platelet activation, endothelial dysfunction, and stasis in the blood flow due to immobilization.[3] Thromboembolic events in a COVID-19 case showed signs of worsening clinical condition, sudden hypoxia, and hemodynamic instability.[4] Lympopenia, liver function tests, D-dimer, inflammation markers [C-reactive protein (CRP), ferritin], fibrinogen degradation products, abnormally activated partial thromboplastin time, and high levels of interleukin (IL-6) and cardiac troponin were found to be associated with the severity of the disease in patients with COVID-19.[5] It has been determined that the increase in D-dimer may be due to the increased systemic pro-inflammatory activation triggering the prothrombotic process and that high D-dimer levels are a strong marker of mortality in cases with COVID-19.[5,6]

Along with D-dimer levels, increased IL-6 levels may also reflect disease severity and procoagulant profile. In a study, increased circulating IL-6 was correlated with increased fibrinogen levels.[7] In studies conducted on COVID-19, it has been reported that the prolongation of international normalized ratio (INR) initially showed increased thrombin time and reduction of the Activated Partial Thromboplastin Clotting Time (APTT). Furthermore, the development of DIC in the advanced period of the critically ill patient also showed prolongation.[4] Tang et al. also found a significant correlation between some hemostasis tests, such as increased D-dimer level, fibrin degradation products, and prolonged prothrombin time (PT), and disease severity and mortality risk, and found a significant difference between the laboratory results of deceased and surviving patients.[8]

Some of the risk factors for COVID-19 severity are advanced age, black ethnicity, immunodeficiency, chronic kidney disease, chronic metabolic diseases (including diabetes), and obesity.[9,10] Many of these factors have also been associated with an increased risk of vitamin D deficiency.[11] Vitamin D plays a role in the optimal function of the immune system, and its deficiency has also been associated with susceptibility to respiratory tract infections.[12]

In a recent experimental study, vitamin D was shown to inhibit the proatherothrombotic effect of IL-6 in human umbilical vein endothelial cells. It has been reported that IL-6 is one of the main mediators responsible for the cytokine storm in COVID-19 infection. In addition, IL-6 has been shown to convert these mediators into a prothrombotic phenotype by inducing functionally active tissue factors and gene expression. Interestingly, vitamin D has been shown to modulate the transcriptional activity of factor Nuclear Factor kappa B (NF-κB) and STAT3 to counteract all the detrimental effects of IL-6. The data from this study highlighted the partially unresolved questions about IL-6-related inflammation and the beneficial effects of vitamin D in COVID-19 infection.[13] Based on these findings, we aimed to retrospectively examine the relationship between vitamin D, IL-6, and coagulation parameters in patients with COVID-19 treated in the intensive care unit for COVID-19 infection.

MATERIAL AND METHODS

The demographic characteristics of 240 patients who were hospitalized in the intensive care unit due to COVID-19 in Elazığ Fethi Sekin City Hospital between March 2020-April 2022 were obtained. All procedures performed involving human participants were conducted in accordance with the Declaration of Helsinki. Once enrolled for the study, vitamin D, cytokine measurement, complete blood count, troponin, pro-brain natriuretic peptide (pro-BNP), procalcitonin, D-dimer, ferritin, fibrinogen, APTT, PT/sec, and international normalized ratio (INR) were examined. Patients were divided into 3 groups based on serum 25(OH) vitamin D levels: Group 1, sufficient vitamin D levels greater than 20 ng/mL; Group 2, vitamin D insufficiency in case of 10-20 ng/mL; and Group 3, vitamin D deficiency in case of <10 ng/mL.[14] The patients were further sub-divided into 2 groups as those who died and those who were discharged. Parameters between the groups were compared. The study was approved by the Fırat University Local Ethics Committee (date: May 26, 2022; no: 8765), and written informed consent forms were obtained from all the participants.

STATISTIC

Data were analyzed with SPSS version 21 software (IBM Corp. Released 2012. IBM SPSS Statistics for

Windows, Version 21.0. Armonk, NY: IBM Corp.). The conformity to the normal distribution was evaluated by the Shapiro-Wilk test and Kolmogorov-Smirnov test. The independent samples t-test was used to compare the normally distributed parameters and the Mann-Whitney U-test was used to compare the non-normally distributed parameters according to the outcome variable. The Kruskal-Wallis test was used to compare the parameters that were not normally distributed according to the groups, and multiple comparisons were made with the Dunn test. The Pearson chi-square test was used to compare categorical data. The analysis results were presented as the frequency (percentage) for categorical variables, and mean±standard deviation and median (minimum-maximum) for the quantitative variables. The significance level was taken as $p<0.050$.

RESULTS

Of the 240 patients examined, 46.7% were female and 53.3% were male. Interestingly, 56.3% of the patients died and 43.8% were discharged. Considering the groups, those classified into Group 3 were 79.2%, Group 2 were 13.3%, and Group 1 were 7.5%. The average age of the participants was 64.96 years. While 51.1% of those who lost their lives were women, 48.9% were men. Interestingly, 41% of the survivors were female, while 59% were male. There was no statistically significant difference between the distributions of the genders (p=0.118). Table 1 summarizes the frequency distributions and descriptive statistics of the variables.

There was a significant difference in age, vitamin D, cytokine measurement, prothrombin time, INR level, D-dimer, fibrinogen, platelet count, ferritin, pro-BNP, procalcitonin, and CRP levels between the survivors and deceased patients ($p<0.001$). Table 2 summarizes the mean values of the parameters measured in both groups.

The patients were examined in 3 groups according to their vitamin D levels. There was no statistically significant difference between the gender distribution of the participants according to the groups (p=0.910). In Group 3, 46.3% of those with vitamin D deficiency were female and 53.7% were male. In Group 2, 50% of those with vitamin D insufficiency were female, and 50% were male. In Group 1, 44.4% of those with normal vitamin D were women and 55.6% were men. No significant difference was observed in terms of the parameters examined in each of the 3 groups. In Table 3, the mean values of the parameters in each of the 3 groups are

TABLE 1: Frequency distributions and descriptive statistics of the variables

	Frequency/ $\bar{X}$±SD	%/$\bar{X}$ (minimum-maximum)
Gender		
Female	112	46.7
Male	128	53.3
Result		
Death	135	56.3
Discharge	105	43.8
Groups		
Vitamin D deficiency (ng/mL)	190	79.2/6.2 (0-10)
Vitamin D insufficiency (ng/mL)	32	13.3/14.8 (10-20)
Normal vitamin D (ng/mL)	18	7.5/56.7 (20-150)
Age (years)	64.96±15.46	66 (21-97)

SD: Standard deviation

TABLE 2: Comparison of parameters according to outcome variable

	Result		
	Death $\bar{X}$±SD	Discharge $\bar{X}$±SD	p value
Age (years)	69.2±13.8	59.4±15	**<0.001***
Vitamin D (ng/mL)	12.2±14.2	16.4±12	**<0.001***
Cytokine (IL-6)	206±332	63.2±115	**<0.001***
APTT	24.9±7.26	23.1±4.3	0.131*
Pt/sec	14.63±4.2	12.9±1.8	**0.001***
Pt/INR	1.24±0.42	1±0.1	**<0.001***
D-Dimer	4.81±7.76	2.3±2.71	**<0.001***
Fibrinogen	5.34±2.01	5.4±1.7	0.812**
Troponin	179.8±473	48.±110.6	**<0.001***
WBC	14.7±18.41	11.5±5.5	0.172*
PLT	224±120.7	284±119	**<0.001***
Ferritin	726.2±492.2	467.6±433.8	**<0.001***
Pro-BNP	5946±9610	2016±3936.7	**<0.001***
Procalcitonin	118.2±1241	1.12±3.69	**<0.001***
CRP	153.27±111.41	103.52±82.64	**<0.001***

SD: Standard deviation; IL: Interleukin; APTT: Activated Partial Thromboplastin Clotting Time; PT/sec; prothrombin time/second Pt/INR; prothrombin time/international normalized ratio; WBC: White blood cell; PLT: Platelet; BNP: Brain natriuretic peptide; CRP: C-reactive protein

TABLE 3: Comparison of parameters according to groups

	Groups			
	Vitamin D deficiency (0-10ng/mL) X̄±SD	Vitamin D insufficiency (10-20ng/mL) X̄±SD	Vitamin D normal (20-150ng/mL) X̄±SD	p value*
Age (years)	65.8±16.12	61.38±12.78	62.33±11.54	0.132
Cytokine (IL-6)	161.2±293.5	67.74±83.79	97.1±186.4	0.051
APTT	24.66±6.6	22.62±3.7	21.36±3.99	0.051
Pt/sec	14.15±3.75	13.15±1.9	12.77±1.5	0.051
Pt/INR	1.19±0.34	1.08±0.16	1.16±0.47	0.071
Troponin	99.9±246.4	274.9±797.7	88.6±118.7	0.182
WBC	13.2±14.8	14.7±14.3	11.5±7.07	0.596
PLT	251.8±124	265.3±108.1	216 ±136.4	0.247
Ferritin	609±489	648.59±457.35	584±490	0.756
Pro-BNP	4270±7947	4600±7676.1	3105 ±8081	0.255
Procalcitonin	84±1046	1.5±4.88	0.9±1.27	0.709
CRP	137±104.1	110±100.3	105.2±85.98	0.084

Kruskal-Wallis test; There is no difference between groups with the same letter; SD: Standard deviation; IL: Interleukin; APTT: Activated Partial Thromboplastin Clotting Time; PT/sec; prothrombin time/second Pt/INR; prothrombin time/international normalized ratio; WBC: White blood cell; PLT: Platelet; BNP: Brain natriuretic peptide; CRP: C-reactive protein

TABLE 4: Correlation analysis between parameters

	Vitamin D	
Parameters	p value	r value
Age (years)	**0.003**	0.191
IL-6 (pg/L)	0.029	0.141
APTT	0.327	0.064
Pt/sec	0.11	0.106
INR	0.483	0.046
D-dimer (ng/mL)	0.401	0.054
Fibrinogen (g/L)	0.900	0.08
Troponin (ng/l)	0.238	0.074
Platelet (10^9/L)	0.546	0.039
Ferritin (mg/dL)	0.450	0.049
Pro-BNP (pg/mL)	0.333	0.063
Procalcitonin (µg/l)	0.183	0.084
CRP (mg/dL)	**0.026**	0.144

IL: Interleukin; APTT: Activated Partial Thromboplastin Clotting Time; PT/sec; prothrombin time/second; INR: International normalized ratio; BNP: Brain natriuretic peptide; CRP: C-reactive protein

summarized.

When the death and survival rates were compared according to the groups, no significant difference was observed in all 3 groups. The mortality rate was 56.8% in Group 3, 59.4% in Group 2, and 44.4% in Group 1.

In the correlation analysis, we found a weak negative correlation between vitamin D and only cytokine and CRP levels. The correlation analysis results are summarized in Table 4.

DISCUSSION

Several studies have demonstrated that vitamin D deficiency is associated with an increased risk of acute respiratory tract infections, whereas sufficient levels correlate with improved clinical outcomes in COVID-19 patients.[15] The immunomodulatory, anti-inflammatory, and antiviral properties of vitamin D may provide a protective effect by suppressing cytokine storms and reducing the risk of multi-organ failure in severe infections.[16,17] Moreover, numerous studies have reported that COVID-19 patients with low vitamin D levels are more likely to experience severe disease progression and higher mortality rates.[18-21] Furthermore, supplementation with vitamin D has been associated with reduced disease severity, decreased need for intensive care, and shorter duration of hospitalization.[22]

On the other hand, some studies contradict these findings, reporting no significant benefit of vitamin D supplementation in COVID-19 outcomes.[23,24] Certain experts argue that routine vitamin D screening and supplementation may be unnecessary in the absence of a clear deficiency.[25,26] In addition, observational studies have failed to show a consistent link between vitamin D deficiency and adverse clinical outcomes.[27,28] For instance, a randomized trial in Brazil found that a single high dose of vitamin D did not im-

prove clinical parameters such as hospital stay duration or mortality.[29]

Recent studies, including the present one, have reported statistically significant but weak inverse correlations between serum vitamin D levels and inflammatory biomarkers. In a study from India, a significant negative correlation was observed between vitamin D and IL-6 levels (p=0.002), although the correlation coefficient remained weak.[30] Similarly, Saporano et al. documented inverse associations between vitamin D and CRP, D-dimer, and IL6 levels; however, these associations were modest in magnitude.[31] The present study also revealed weak but statistically significant correlations between vitamin D levels and IL-6 (r=0.141, p=0.029) and CRP (r=0.144, p=0.026). In alignment with our findings, Jain et al. reported inverse correlations between vitamin D and inflammatory markers such as IL6, tumor necrosis factor-α (TNF-α), ferritin, and CRP in a prospective cohort of 154 COVID-19 patients, noting similar weak correlation coefficients despite statistical significance.[32]

Furthermore, a systematic review by Halim et al. involving 8,802 patients observed statistically significant but modest inverse associations between vitamin D levels and pro-inflammatory cytokines (IL-6, TNF-α).[33] These consistent results across larger cohorts reinforce our conclusion that while the relationship between vitamin D and systemic inflammation in COVID-19 is present, its clinical relevance may be limited and warrants cautious interpretation. These findings suggest that while some associations exist, their clinical relevance remains uncertain and must be interpreted with caution. The weak correlations may be attributed to confounding factors such as age-related differences, comorbid conditions, or heterogeneity in nutritional status and immune response.

Interestingly, in this cohort, a difference in vitamin D levels was observed between patients who survived and those who died, implying a possible link to mortality. However, this association was not supported by significant differences in cytokine or inflammatory marker levels among the vitamin D subgroups. In addition, correlation analyses did not reveal robust relationships with coagulopathy parameters such as D-dimer, platelet count, or fibrinogen.

Emerging evidence indicates that vitamin D can modulate inflammatory cascades through NF-κB and STAT3 signaling, particularly in endothelial cells exposed to IL6. One study demonstrated a reduction in tissue factor gene expression and procoagulant activity in vitamin D-enriched cells stimulated with IL6, supporting its potential anti-thrombotic role in COVID-19-related endothelial dysfunction.[13] Nonetheless, this study could not confirm a direct effect of vitamin D on coagulation abnormalities.

Although the current study does not primarily focus on the musculoskeletal system, the role of vitamin D in modulating systemic inflammation and immune response has indirect but important implications for physical medicine and rehabilitation. Vitamin D deficiency has been associated with muscle weakness, fatigue, delayed recovery, and impaired neuromuscular function-all of which are highly relevant to rehabilitation strategies, particularly in post-viral or post-COVID-19 patients.

This study has several limitations. First, its retrospective design limits the ability to establish causal relationships. Second, the relatively small sample size may limit the statistical power and generalizability. Third, we did not control for key confounding factors such as body mass index, nutritional status, comorbidities, or baseline inflammatory status-all of which can influence both vitamin D levels and immune responses.

CONCLUSION

Severe inflammatory response secondary to COVID-19 causes consumptive coagulopathy characterized by decreased platelet count, increased fibrin degradation products such as D-dimer, and decreased fibrinogen level. In the present study, decreased platelet count, increased D-dimer, prolonged prothrombin time and increased ferritin, CRP, and procalcitonin levels were found to be consistent with the literature. However, we could not determine whether vitamin D had any effect on the coagulopathy. There is a need for studies involving many more patients on this subject. The limitations of this study are the small number of patients and the absence of additional disease questioning.

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