ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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The Effect of Vitamin D on Disease Severity in Rheumatic Patients with COVID-19

COVID-19 Geçiren Romatizmal Hastalarda D Vitamini Düzeyinin Hastalık Şiddeti Üzerine Etkisi

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This study was presented as an oral presentation at 7th National Osteoporosis Congress, October 8-10, 2021, Online.

ABSTRACT Objective: To investigate the effect of vitamin D levels on rheumatic diseases after coronavirus disease-2019 (COVID-19). **Material and Methods:** In this retrospective study, age, gender, duration of rheumatic disease, medications used, COVID-19 symptoms, hospitalization, oxygen use, intensive care report, sedimentation, C-reactive protein, and vitamin D levels were obtained from patient files and electronic platforms. The data of patients with low vitamin D levels and without were compared using the t-test and Mann-Whitney U test. X^2 test was used for categorical data and binary logistic regression analysis was performed to identify risk factors affecting hospitalization. **Results**: A total of 121 (101 women) patients were included in this study. The mean age of the patients was 49.08±11.72 years, body mass index (BMI) (kg/m²) 30.27±6.52, and vitamin D 23.27±10.15. It was determined that 80.1% (97) of the patients were followed up outpatient, 19.9% (21) were hospitalized and 5% (6) were admitted to the intensive care unit. Vitamin D deficiency was detected in 35.5% (43) of the patients. Those with vitamin D deficiency had a significantly shorter rheumatic disease duration, younger age, and a diagnosis of asthma compared to those without (all $p<0.05$). In addition, diabetes mellitus, spondyloarthritis (SpA) diagnosis, and BMI were the most consistent risk factors affecting hospitalization. **Conclusion:** This study showed that patients with COVID-19 who had low vitamin D levels were younger and had a shorter rheumatic disease duration and asthma diagnosis. Most importantly, diabetes mellitus, SpA diagnosis, and BMI were the highest independent risk factors for hospitalization.

Keywords: Rheumatology; vitamin D; COVID-19

ÖZET Amaç: D vitamini düzeylerinin koronavirüs hastalığı-2019 (COVID-19) ile romatizmal hastalıklar üzerindeki etkisini araştırmak. **Gereç ve Yöntemler:** Bu retrospektif çalışmada, hasta dosyalarından ve elektronik platformlardan yaş, cinsiyet, romatizmal hastalık süresi, kullanılan ilaçlar, COVID-19 semptomları, hastaneye yatış, oksijen kullanımı, yoğun bakım takibi, sedimantasyon, C-reaktif protein ve D vitamini seviyeleri elde edildi. D vitamini düzeyi düşük olan ve olmayan hastaların verileri t-testi ve Mann-Whitney U testi kullanılarak karşılaştırıldı. Kategorik veriler için X^2 testi, hastaneye yatışı etkileyen risk faktörlerini belirlemek için ikili lojistik regresyon analizi yapıldı. **Bulgular:** Bu çalışmaya toplam 121 (101 kadın) hasta dâhil edildi. Hastaların yaş ortalaması 49,08±11,72, beden kitle indeksi (BKİ) (kg/m²) 30,27±6,52, D vitamini 23,27±10,15 idi. Hastaların %80,1'inin (97) ayaktan izlendiği, %19,9'unun (21) hastaneye yatırıldığı ve %5'inin (6) yoğun bakıma yattığı belirlendi. Hastaların %35,5'inde (43) D vitamini eksikliği saptandı. D vitamini eksikliği olanlarda, olmayanlara kıyasla önemli ölçüde daha kısa romatizmal hastalık süresi, daha genç yaş ve astım tanısı vardı (tümü $p<0,05$). Ayrıca diabetes mellitus, spondiloartrit (SpA) tanısı ve yüksek BKİ'ye sahip olmak hastaneye yatışı etkileyen en güçlü risk faktörleriydi. **Sonuç:** Bu çalışma, COVID-19'lu ve D vitamini düzeyi düşük olan hastaların daha genç olduğunu ve daha kısa romatizmal hastalık süresine ve astım tanısına sahip olduğunu gösterdi. En önemlisi, diabetes mellitus, SpA tanısı ve BKİ, hastaneye yatış için en yüksek bağımsız risk faktörleriydi.

Anahtar Kelimeler: Romatoloji; D vitamin; COVID-19

Coronavirus disease-2019 (COVID-19), which emerged from severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), quickly occurred a pandemic. As of the end of September 2021, more than 233 million people worldwide were infected and more than 4.7 million people died.[1]

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Vitamin D is synthesized as a fat-soluble prohormone in a secosteroid structure. Low-level vitamin D is a public health problem globally and can be easily treated. Although vitamin D has a main role in mineral homeostasis, it has many different roles. It is suggested that the immune-modulatory function is effective in cardiovascular diseases, autoimmune diseases, multiple sclerosis, and cancer.[2-6] An inadequate immune modulator effect due to vitamin D deficiency was thought to be associated with increased immune response in COVID-19 patients.[6] Some studies reported that the level of vitamin D in hospitalized COVID-19 patientswas not associated with mortality.[2] It is common in publications reporting that COVID-19- related mortality increases with heredity and vitamin D deficiency.[7]

Vitamin D demonstrates its immunomodulatory effects in many ways.[5] Evidence indicates interaction among acquired immune response cell macrophages, B and T lymphocytes, neutrophils, and dendritic cells.[7,8] 1,25(OH)2D3 regulates the increased immune response through T-helper-17 cells.[3] Another study revealed that vitamin D supplementation at appropriate levels could decrease the rate of respiratory infection and enhance the immune response in COVID-19 patients.[9-11] Similarly, a study reported that 25(OH)D concentrations below 75 nmol/L are likely to develop severe respiratory system disease.[12]

It is suggested that a more robust inflammatory response occurs in patients with COVID-19 who do not have a vitamin D shortage. This is possibly the antiviral effect of vitamin Dagainst enveloped viruses.[13-15] In addition to the immunomodulatory and antiviral action of supplementation of D vitamin, it increases the expression of the renin-angiotensin-aldosterone system and angiotensin-converting enzyme-2 (ACE2) receptor.[16-18]

Although there is some evidence for the beneficial effects of vitamin D in patients infected with SARS-CoV-2, the results in other studies are controversial.[17-19] Cerada et al. claimed that vitamin D supplementation could adversely affect the course of COVID-19 by triggering the development of macrophage response and cytokine storm.[19] However, in severe COVID-19 cases, 25(OH)D levels decrease by accelerating vitamin D metabolism and decreasing hepatic vitamin D-binding protein synthesis.[19,20]

It has been suggested that vitamin D deficiency is associated with the incidence and severityof autoimmune diseases, and it is recommended to correct the deficiency.[5] Inflammatory cytokines are secreted in those infected with COVID-19, as in autoimmune diseases. Rheumatic diseases carry an increased risk of severe infection due to immunosuppressive and biological treatments.[21] Hydroxychloroquine, one of the disease-modifying agents used in treating rheumatic diseases, has been used in treating COVID-19.[22] In addition, in case of apathological immune response such as a cytokine storm during COVID-19, biological treatments such as interleukin (IL)-6 blocker (tocilizumab, sarilumab) and IL-1 blocker (anakinra) are used.[23] Few publications are investigating the relationship.[24,25] Vitamin D may provide a balanced immune response via ACE2 receptors and inflammatory cells. Our aim in this study; To determine the effect on 25(OH)D_3 levels and disease severity in rheumatic patients with COVID-19.

MATERIAL AND METHODS

In this retrospectively designed study, data were collected by scanning the files of patientswho were followed by the rheumatology outpatient clinic of Erciyes University hospital between 01.07.2021 and 31.08.2021. Data from patients with at least three months of history of rheumatic disease and who had COVID-19 in the last month were included in the study. Since rheumatic patients were thought to be prone to infections due to both the disease andthe drugs used during the pandemic, the COVID-19 disease symptoms and findings of the patients were recorded manually and electronically at the first post-COVID-19 visit to the rheumatology outpatient clinic. COVID-19-associated symptoms, including hospitalization, need for oxygen, need for intensive care, and pneumonia status was obtained from files, some recorded electronically and some manually. The accuracy of COVID-19 positive test results was confirmed on the electronic platform.

Patients were having spondyloarthritis (SpA), systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis (RA), Sjogren's syndrome, familialMediterranean fever, Behçet disease and adult Still's a disease with a diagnosis of COVID-19 are participated in this study. Demographic features (age, gender, height, weight) and clinical variables such as type of rheumatic disease, drugs used, COVID-19 symptoms, hospitalization, oxygen use, and intensive care follow-up were filled in. Body mass index (BMI) (kg/m^2) was calculated. The level of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and value of vitamin D was recorded. ESR and CRP are taken from the latest values in the electronic platform. Patients whose vitamin D levels were measured approximately 15 days before COVID-19 positivity was recorded. Vitamin D level wasmeasured by the chemiluminescence immunoassay method of $25(OH)D_3$. Patients were separated into Group 1 (0-19 ng/mL) and Group 2 (20-60 ng/mL), and clinical and demographic variables were compared between those groups.

Patients with non-COVID-19 infectious, malignant, neurological, renal, decompensated heart,liver, and pulmonary diseases and those who received vitamin D replacement therapy in the last three months were not included in the study.

Approval for this study was obtained from the Clinical Research Ethics Committee of the Faculty of Medicine of Erciyes University (date: September 22, 2021, no: 2021/616). In addition, permission was obtained from the Ministry of Health (2021-09). The study was executed by the Declaration of Helsinki.

STATISTICAL ANALYSIS

SPSS v23.0 (SPSS, Inc, Chicago, IL, USA) program was performed to calculate data. ShapiroWilks and Kolmogorov-Smirnov tests were performed for the normality of data distribution. Comparisons of values of the two groups were made via independent-samples t-test or its non-parametric equivalent. X^2, Yates correction, and Fisher's exact tests were used to compare categorical variables according to groups. Correlation analysis was performed by Spearman's correlation test. If a p value <0.05 was considered significant.

RESULTS

One hundred twenty-one patients (101 female, 16.6% male) were included in this study. The patient's mean age was 49.08±11.72 years, BMI was 30.27±6.52 kg/m^2. Most of the patients were women, and SpA and RA were the most common rheumatic disease diagnosis ofindividuals with COVID-19. It was determined that 12.4% (15) of the patients smoked.

The most frequent clinical symptoms associated with COVID-19 were sore throat 76.03% (92), followed by cough 74.38% (90), headache 70.24% (85), anorexia 69.42% (84), and loss of taste and smell 67.76% (82) (Table 1).

Comparison of patients' variables according to vitamin D levels are given in Table 2.

Vitamin D deficiency was determined in 35.5% (43) of the patients. In comparing the two groups, the value of D vitamin was relatively lower in those younger and had a short duration of rheumatic disease (all $p<0.05$). In terms of the level of D vitamin, the two groups are not different according to gender, hospitalizations, those receiving oxygen therapy, those treatedin the intensive care unit, pneumonia, COVID-19 symptoms, diagnosis of rheumatic disease, and drugs used. (All $p>0.05$) (Table 3). Positive and reasonable correlation was found between age and vitamin D ($r=0.301$, $p=0.01$) and between disease duration and vitamin D ($r=0.235$, $p=0.011$). These results are not given in tables.

PREDICTORS OF HOSPITALIZATION

All factors that may be effective for hospitalization were analyzed by binary logistic regression and given in Table 4. According to the univariate model hospitalization, significant risk factors were BMI [odds ratio (OR) 1.071], age (OR 1.092), rheumatic disease duration (OR 1.064), pneumonia (OR 17.25), hypertension (OR 3.404), diabetes mellitus (4.235). The significant risk factors for hospitalization identified in the univariate model were analyzed in the multivariate model. According to the multivariate analysis, pneumonia (OR 0.016), and biologic disease-modifying antirheumatic drugs (OR 0.003) were the most low-influencing factors for hospitalization.

TABLE 1: Demographic and clinical variables and clinical symptoms of the patients with COVID-19.

Variable	X̄±SD
Number of patients (n)	121
Female n (%)	101 (83.4)
Male n (%)	20 (16.6)
Age (years)	49.08±11.72
Body mass index (kg/m^2)	30.27±6.52
Rheumatic disease duration (years)	12.57±7.54
Vitamin D (ng/mL)	23.27±10.15
Vitamin D deficiency	43 (%35.5)
Disease diagnosis n (%)	
Spondyloarthropathy	53 (43.80)
Rheumatoid arthritis	30 (24.79)
Sjogren's syndrome	8 (6.61)
Systemic sclerosis	7 (5.78)
Behçet disease	7 (5.78)
Familial Mediterranean fever	7 (5.78)
Adult still's disease	2 (1.68)
Patients' treatment and follow-up n (%)	
Outpatients follow	97 (80.1)
Hospitalization	21 (19.9)
Intensive care	6 (5)
Oxygen treatment	21 (17.3)
Main symptoms n (%)	
Pneumonia	49 (40.5)
Fever	71 (58.67)
Sore throat	92 (76.03)
Dyspnea	65 (53.71)
Cough	90 (74.38)
Chest pain	72 (59.50)
Loss of taste and smell	82 (67.76)
Headache	85 (70.24)
Eye redness	58 (47.93)
Swelling of the nasal mucosa	74 (61.15)
Diarrhea	50 (41.32)
Stomachache	63 (52.06)
Anorexia	84 (69.42)
Nausea	68 (56.19)
Nausea-vomiting	54 (44.62)
Restless	62 (51.23)
Drug n (%)	
csDMARDs	29 (23.8)
bDMARDs	25 (20.5)
NSAIDs	28 (23.0)
HCQ	22 (18.0)
Other drugs	17 (13.9)

SD: Standard deviation; csDMARDs: Conventional synthetic disease-modifying antirheumatic drugs; bDMARDs: Biologic disease-modifying antirheumatic drugs; NSAIDs: Non-steroidal anti-inflammatory drugs; HCQ: Hydroxychloroquine.

At the same time, BMI (OR 1.37), diabetes mellitus (OR 46.732), and SpA (OR 25.31) were the most robust risk factors. Analysis of risk factors affecting hospitalization is given in Table 4.

DISCUSSION

This study showed that younger age, shorter duration of rheumatic disease and asthmadisease were significantly higher in those with vitamin D deficiency than in those without deficiency. In addition, among the factors affecting hospitalization, BMI, diabetes mellitus, and rheumatic disease, SpA was the most potent independent risk factor. Pneumonia and biological agents were low-level risk factors for hospitalization. In addition, we did not find any connection between vitamin D and COVID-19-related hospitalization, outpatient follow-up, intensive care unit admission, and oxygen therapy in rheumatic patients.

Vitamin D deficiency was detected in 35.3% and no relationship was reported between serum vitamin D metabolites and 30-day hospitalization outcomes of COVID-19 patients. In addition, 25(OH)D, 24,25(OH)2D3,25,26(OH)2D3, and vitamin D metabolites were not associated with mortality and ventilatory support.[2] The results of our study were consistent with the results of this study. On the other hand, Ma et al. claimed that habitual vitamin D supplementation reduces the risk of COVID-19 infection in their prospective study.[26] However, it has been reported that vitamin D values are lower in an individual with COVID-19 than without it.[27,28] Al-Daghri et al. reported that the meager value of the D vitamin does not increase the risk of SARS-CoV-2 infection.[29] Similarly, Hernández et al. reported that vitamin D levels were not associated with the severity of COVID-19.[30] In a meta- analysis, Akbar et al. reported that decreased D vitamin levels were associated with the severity and mortality of COVID-19.[31] In our study, we could not find a relationship between COVID-19 and vitamin D in terms of hospitalization and intensive care unit admission.

It is well known that vitamin D has essential roles in regulating the natural and acquired immune system, as well as its effects on bone mineralization.[25] Vitamin D, which has a lipophilic structure, can be detected in adipose tissue for two months. Vitamin D

TABLE 2: Comparison of patients' variables according to vitamin D levels.

	Group 1 (Vitamin D 0-19 ng/mL) n=43	Median (Minimum-maximum)	Group 2 (Vitamin D 20-60 ng/mL) n=78	Median (Minimum-maximum)	p value
BMI (kg/m^2)	30.95±6.53	31.18 (18.73-46.06)	29.90±6.53	28.97 (15.62-54.53)	0.399*
Age (years)	45.04±11.95	45.00 (21.00-72.00)	51.31±11.05	52.00 (29.00-71.00)	**0.004***
RDD (years)	9.37±5.08	10.00 (1.00-20.00)	14.33±8.12	11.50 (1.00-40.00)	**0.001****
ESR, mm/h	15.42±12.14	11.00 (2.00-62.00)	16.21±13.85	12.00 (2.00-59.00)	0.981**
CRP	5.79±6.99	2.69 (0.11-28.51)	7.10±8.56	4.56 (0.16-47.49)	0.365**

*Independent t-test; **Mann-Whitney U test; BMI: Body mass index; RDD: Rheumatic disease duration; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein

makes its effect through the vitamin D receptor.[32] It has been reported that the half-life of $1,25(OH)_2D_3$ is approximately 15 hours, while the half-life of $25(OH)2D3$ is approximately 15 days.[33] Therefore, patients who have vitamin D levels 15 days before viral infection were included in the study.

The COVID-19 pandemic affects six continents and more than 140 countries, and it emerged from an enveloped RNA virus and exerts its effect with spike proteins on its surface.[34] ACE-2 receptors, commonly found in the lung, are thought to be a target for SARS-CoV-2.[35] While 80% of COVID-19 patients show flu-like symptoms, 20% require hospitalization and 5% require intensive care.[34]

Pulmonary edema, diffuse alveolar hemorrhage, type II pneumocyte hyperplasia, proteinous aggregates, fibrinous exudate, monocyte and macrophage activation in alveolar spaces, and interstitial mononuclear cell infiltration occur in the lung involvement of COVID-19. While SARS-CoV-2 could be detected by electron microscopy in bronchial and alveolar Type II pneumocytes, it could not be detected in other tissues.[33-36]

Excessive secretion of cytokines and pulmonary infiltration may cause acute respiratory distress syndrome. A weak interferon response provokes an excessive inflammatory response. Proinflammatory responsesof pathogenic T helper 1 (Th1) cells are regulated by CD14+ and CD16+ monocyte- dependent receptors. This situation causes lung damage bypassing the membrane of neutrophils and macrophages, and cytokine storms develop. SARS-CoV-2 rapidly stimulates Th1 cells, causing the release of cytokines such as granulocyte monocyte stimulating factor, IL-6, and tumor necrosis factor-alpha.[37]

Also, in the critical COVID-19 situation, genetic factors have been investigated. It has been reported that severe COVID-19 is associated with decreased expression of the interferon receptor gene and some chemotactic factors.[7] Symptoms such as fatigue, dyspnea, cough, arthralgia, and cognitive decline have been reported after COVID-19, and it has been published that fatigue is associated with vitamin D deficiency in the post-COVID-19 period.[38] In this study, patients were not followed up for post-COVID-19.

Rheumatic diseases and COVID-19 are clinical conditions that produce a similar hyper- inflammatory response. Many studies have shown that vitamin D deficiency is associated withthese hyper-inflammatory clinical conditions.[25] It has been suggested that hydroxychloroquine, one of the drugs used in the treatment of rheumatic diseases, may be beneficial for COVID-19.[23] However, in the case of the hyper-inflammatory immune response during COVID-19, biological treatments such as IL-6 blocker (tocilizumab, sarilumab) and IL-1 blocker (anakinra) are used.[24] However, our study did not find a relationship between vitamin D and COVID-19. In addition, this study detected vitamin D deficiency at a lower rate than in the general population. The increase in thehospital admission rate due to the conventional and biological treatment of rheumatic patients may have affected the results.

TABLE 3: Comparison of categorical variables of patients according to vitamin D levels.

	Group 1 (Vitamin D 0-19 ng/mL) n=43	Group 2 (Vitamin D 20-60 ng/mL) n=78)	Total	p value
Sex				
Female	38 (88.4)	62 (79.5)	100 (82.6)	0.325**
Male	5 (11.6)	16 (20.5)	21 (17.4)	
Hospitalization				
No	38 (88.4)	59 (75.6)	97 (80.2)	0.149**
Yes	5 (11.6)	19 (24.4)	24 (19.8)	
Oxygen				
No	39 (90.7)	61 (78.2)	100 (82.6)	0.137**
Yes	4 (9.3)	17 (21.8)	21 (17.4)	
Intensive care				
No	43 (100)	72 (92.3)	115 (95)	0.088
Yes	0 (0)	6 (7.7)	6 (5)	
Pneumonia				
No	27 (62.8)	45 (57.7)	72 (59.5)	0.724
Yes	16 (37.2)	33 (42.3)	49 (40.5)	
DMARD	9 (20.9)	20 (25.6)	29 (24)	0.582*
Biological treatment	10 (23.3)	20 (25.6)	29 (24)	
NSAID	13 (30.2)	15 (19.2)	28 (23.1)	
Other drugs	5 (11.6)	12 (15.4)	28 (23.1)	
Hydroxychloroquine	6 (14)	16 (20.5)	22 (18.2	
Smoking				
No	37 (86)	69 (88.5)	106 (87.6)	0.922**
Yes	6 (14)	9 (11.5)	15 (12.4)	
Alcohol No	43 (100)	78 (100)	121 (100)	
Fever	25 (59.5)	46 (59.7)	71 (59.7)	
Stomachache	19 (45.2)	44 (57.1)	63 (52.9)	
Diarrhea	16 (38.1)	34 (44.2)	50 (42)	
Anorexia	27 (64.3)	57 (74)	84 (70.6)	
Nausea-vomiting	14 (33.3)	38 (49.4)	52 (43.7)	
Restlessness	21 (50)	41 (53.2)	62 (52.1)	
Sore throat	32 (76.2)	60 (77.9)	92 (77.3)	
Dyspnea	21 (50)	44 (57.1)	65 (54.6)	
Cough	32 (76.2)	58 (75.3)	90 (75.6)	
Chest pain	23 (54.8)	49 (63.6)	72 (60.5)	0.468
Loss of taste and smell	26 (61.9)	56 (72.7)	82 (68.9)	
Headache	31 (73.8)	54 (70.1)	85 (71.4)	
Eye redness	17 (40.5)	41 (53.2)	58 (48.7)	
Swelling of the nasal mucosa	22 (52.4)	52 (67.5)	74 (62.2)	
Hypertension	12 (75)	26 (76.5)	38 (76)	**0.036***
Diabetes mellitus	5 (31.3)	19 (55.9)	24 (48)	
Asthma	4 (25)	1 (2.9)	5 (10)	
Rheumatic disease*** Ankylosing spondylitis	17 (48.6)	22 (34.4)	39 (39.4)	0.718*
Familial Mediterranean fever	4 (11.4)	7 (10.9)	11 (11.1)	
Rheumatoid arthritis	8 (22.9)	22 (34.4)	30 (30.3)	
Behçet disease	4 (11.4)	4 (6.3)	8 (8.1)	
Sjogren syndrome	4 (11.4)	8 (12.5)	12 (12.1)	
Systemic sclerosis	2 (5.7)	5 (7.8)	7 (7.1)	
Connective tissue disease	1 (2.9)	1 (1.6)	2 (2)	
Marital status				
Single	8 (18.6)	14 (17.9)	22 (18.2)	1.000**
Married	35 (81.4)	64 (82.1)	99 (81.8)	

*Chi-square test; **Yates correction; ***Fisher's exact test; Frequency (percentile); DMARD: Disease-modifying anti-rheumatic drugs; NSAID: Non-steroid anti-inflammatory drugs.

TABLE 4: Analysis of risk factors affecting hospitalization by univariate model and multivariate model of logistic regression analysis.

	Univariate OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Body mass index (kg/m²)	1.071 (1.001-1.146)	0.047	1.37 (1.099-1.709)	0.005
Age (years)	1.092 (1.039-1.148)	0.001	1.026 (0.899-1.17)	0.707
Sex	0.627 (0.169-2.332)	0.486	2.18 (0.024-194.567)	0.734
RDD (years)	1.064 (1.005-1.126)	0.034	1.01 (0.879-1.159)	0.893
Vitamin D level	1.033 (0.989-1.079)	0.141		
Vitamin D deficiency	0.409 (0.141-1.187)	0.100	0.23 (0.03-1.746)	0.155
Pneumonia	17.25 (4.763-62.476)	<0.001	0.016 (0.001-0.181)	0.001
csDMARD	0.273 (0.051-1.461)	0.129	0.317 (0.018-5.479)	0.430
bDMARD	0.857 (0.248-2.963)	0.808	0.003 (0-0.597)	0.031
NSAID	0.419 (0.076-2.301)	0.317	1.61 (0.052-49.713)	0.785
Other drugs	1.467 (0.426-5.049)	0.544	1.383 (0.013-146.63)	0.891
Sedimentation	1.014 (0.982-1.047)	0.392	0.94 (0.869-1.018)	0.129
C-reactive protein	1.032 (0.981-1.085)	0.219	0.971 (0.87-1.082)	0.590
Smoking	0.258 (0.032-2.065)	0.202	0.075 (0.002-2.662)	0.155
Hypertension	3.404 (1.352-8.565)	0.009	1.112 (0.112-11.028)	0.928
Diabetes mellitus	4.235 (1.574-11.391)	0.004	46.732 (1.343-1626.187)	0.034
Asthma	1.011 (0.108-9.48)	0.992	7.749 (0.219-274.744)	0.261
Marital status	1.139 (0.347-3.742)	0.830	7.111 (0.335-150.817)	0.208
Ankloysing spondylitis	1.065 (0.412-2.752)	0.897	25.31 (1.559-410.88)	0.023
Familial Mediterranean fever	0.889 (0.179-4.411)	0.885	21.313 (0.273-1665.161)	0.169
Rheumatoid arthritis	2.171 (0.834-5.656)	0.112	14.491 (0.6-349.879)	0.100
Behçet	0.559 (0.065-4.774)	0.595	0.098 (0-30.138)	0.427
Sjogren syndrome	3.383 (0.97-11.807)	0.056	3.975 (0.392-40.302)	0.243
Systemic sclerosis	0.659 (0.076-5.752)	0.706	0.084 (0-14.116)	0.343

OR: Odds ratio; IC: Intraclass correlation; RDD: Rheumatic disease duration; csDMARD: Conventional synthetic disease-modifying anti-rheumatic drugs; bDMARD: Biological disease-modifying anti-rheumatic drugs; NSAIDs: Non-steroid anti-inflammatory drugs.

A meta-analysis on vitamin D deficiency in Türkiye emphasized that age, gender, seasonal conditions, living geography, exposure to sunlight, clothing, socioeconomic status, and religious beliefs have a crucial role in the level of vitamin D in the body. In addition, this article mentions that newborns, women, and especially the elderly have a higher risk of vitamin D deficiency.[32] Another article published that vitamin D and K deficiency in the early period of acute COVID-19 is associated with the severity of the disease course of COVID-19.[39] When we consider the vital functions of vitamin D during the COVID-19 disease, we can mention that vitamin D has an important role in this process.

It has been published in a study that the sociodemographic factors associated with hospitalization and/or disease severity included older age, non-Hispanic Black or Hispanic race/ethnicity, and smoking. Also, many diseases that affect the immune system can affect hospitalization and mortality.[40] In our study BMI, diabetes mellitus, and SpA were strongly associated with hospitalization. These results of our study are compatible with the current literature.

Limitations: in our study, the retrospective nature of the study can be listed as not measuring $25(OH)D_3$ levels during COVID-19 and not following up with replacements for patients withvitamin D deficiency. Furthermore, the study group is heterogeneous regarding age and sex. Moreover, categorical variables such as age and sex of the groups according to vitamin D level are heterogeneous. In addition, the duration of exposure to the sun and the duration of the patient's social isolation were unknown, and this study was conducted on rheumatological patients with various diagnoses.

CONCLUSION

In this study, it was shown that in rheumatic patients with COVID-19, those with vitamin D deficiency were younger, their disease duration was shorter, and asthma comorbidity was higher than those without vitamin D deficiency. Diabetes mellitus, BMI, and spondylarthritis were effective independent risk factors for hospitalization. However, considering bone health, vitamin D deficiency should be eliminated in rheumatic diseases, even in the case of COVID-19.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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