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Association between vitamin D levels and frequency of disease exacerbations and hospitalizations in patients with COPD

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) is a debilitating disorder that restricts the physical activity of patients who are deprived of sunlight, which is a source of vitamin D. The purpose of this study was to assess the relationship between vitamin D and the frequency of exacerbation and hospitalization among patients with COPD.

Material and Method: In the main analysis, 303 patients with COPD (stage GOLD A to D) were included in a retrospective cohort study in Turkey. Serum levels of vitamin D (25-hydroxyvitamin D) were measured in 303 patients with COPD and were associated with pulmonary function, AECOPD frequency and hospitalization in the previous year. Results: For COPD patients, the mean reference level of 25 hydroxyvitamin D in serum was 12.5 ng/dL. In comparison to patients with a serious 25-hydroxyvitamin D deficiency (< 10 ng/dL, n=119 [39,3%]), patients with a moderate deficiency (10-19.99 ng/dL, n=100 [33%]), inadequate levels (20-29.99 ng/dL, n=49 [16,2%]) presented a different risk of exacerbation (incidence rate ratio, 2.3 [95% CI, 1.9-2.6], 1.6 [95% CI, 1.2-2.0], and 0.8 [95% CI, 0.3-1.2] respectively). In patients with desirable levels (> 30 ng/dL, n=34 [11,2%]), the risk was lower but not significant (incidence ratio, 0.7 [95% CI, 0.2-1.2]. In COPD patients, 25-hydroxyvitamin D rates are low correlated with 1-s forced expiratory volume (FEV1) (r=0.187, p=0.0013).

Conclusion: 25-hydroxyvitamin D deficiency is a frequent occurrence in COPD and is correlated with the frequency of exacerbation and hospitalization in COPD patients.

Keywords: 25-hydroxyvitamin D, COPD, COPD exacerbation

INTRODUCTION

COPD is a big public health threat and the fourth cause of mortality worldwide (1). COPD progression varies greatly among affected individuals, both in terms of lung function decrease (2) and exacerbation frequency (3). COPD is a chronic and progressive illness characterized by periods of exacerbation associated with reduced health-related quality of life, increased use of health resources, and increased mortality (4). Acute exacerbations of COPD requiring hospitalization are especially important because they cause an economic burden and threaten the life of the affected patients (5).

Cross-sectional studies have shown that 25-hydroxyvitamin D deficiency is widespread in patients with COPD, and that it is associated with lower lung function in patients with COPD (6-8). Some investigators found a link between 25-hydroxyvitamin D levels and the risk of COPD and the severity of the disease in patients with COPD (9). While this is true, it can be explained by systemic and pulmonary immunomodulatory effects of 25-hydroxyvitamin D (10,11). Laboratory studies have revealed an extensive range of immunomodulatory effects of 25-hydroxyvitamin D in the lungs. that maintain immune system activity to fight microbial pathogens and inflammation (12,13). As a result, 25-hydroxyvitamin D deficiency can increase chronic and systemic inflammation of the respiratory tract, decrease bacterial clearance and increase the risk of infectious exacerbations (14). However, these results are not conclusive. There have been few studies of 25-hydroxyvitamin D function in COPD patients, and one of them did not show any association between 25-hydroxyvitamin D and impaired lung function or exacerbation (15). The relationship between 25-hydroxyvitamin D deficiency and the frequency of exacerbation in observational studies remains controversial; however, a meta-analysis

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(including some of the available studies which did not find any association) showed a negative association between serum 25-hydroxyvitamin D and exacerbation frequency (9).

It is not clear whether 25-hydroxyvitamin D deficiency is more widespread among COPD patients than among the general population of Turkey. Whether patients with COPD with diverse 25-hydroxyvitamin D levels experience different exacerbation frequencies is unknown. In addition, 25-hydroxyvitamin D levels at different COPD stages have not been studied. The aim of this retrospective study was to evaluate the possible role of serum 25-hydroxyvitamin D as a predictor of airway obstruction (FEV1), frequency of exacerbation, hospitalization, and results of MCRC scores in patients with COPD.

MATERIAL AND METHOD

The study was initiated with the approval of the Keçiören Training and Research Hospital Ethics Committee (Date: 23.11.2021, Decision No: 15-2409). All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration.

Study Design and Population

We retrospectively collected electronic medical records at the Ataturk Chest Disease Hospital in Ankara (Turkey) from January 2018 to December 2019. Participants will be enrolled if they present with COPD exacerbation to the outpatient clinic or emergency department. We included patients suspected of having COPD based on their clinical history and meeting the GOLD criteria for COPD 16 as cases in the study. The inclusion criteria were the following: 1) Spirometry results displaying a forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) < 0.7 after bronchodilator therapy; and 2), smoking history of ≥ 10 pack-year; absence of vitamin D oral supplementation, and an increased frequency of Acute Exacerbation Chronic Obstructive Lung Disease (AECOPD) in the subsequent year. All records were retrospectively screened.

We described COPD exacerbations as a sustained aggravation of respiratory symptoms over a 48-hour period, requiring an oral corticosteroid, an antibiotic, or a combination of treatments initiated by a doctor. Respiratory symptoms included one or more of the Anthonisen criteria (increase in dyspnea, volume of sputum, or purulence of sputum) with or without minor symptoms (such as fever, coughing, wheezing, common cold symptoms, or sore throat). We assessed the severity of the patients' dyspnea according to the results of a modified Medical Research Council (mMRC) scale questionnaire applied in the outpatient clinic.

The exclusion criteria included a diagnosis of asthma or some other disease such as tuberculosis, bronchial carcinoma, sarcoidosis, kidney or liver failure (creatinine, > 1.5 mg/dl and estimated creatinine clearance, 20 ml/min) or bronchiectasis, or the use of active metabolites.

Measurement of 25-Hydroxyvitamin D

Serum screening concentration 25-hydroxyvitamin D will be measured within the exacerbation period. We classified 25-hydroxyvitamin D levels as normal (≥ 30 ng/ml), mild to moderately deficient (≥ 10, but < 30 ng/ml), or severely deficient (< 10 ng/ml) (17).

Covariates included characteristics potentially associated with 25-hydroxyvitamin D state and AECOPD risk (such as age, sex, percentage of expected FEV1, season [winter ¼, Jan-Mar; spring ¼, Apr-Jun; summer ¼, Jul-Sept; winter ¼, Oct-Dec) clinical center. .

Study design

In the original study, we allocated 303 patients into either a low (< 30 ng/dl, n=270) or the high (≥ 30 ng/dl, n=33) 25-hydroxyvitamin D level group according to their 25-hydroxyvitamin D level measured at the emergency/hospital admission. In the course of the analysis, the following parameters were compared between the two groups over one year after initial hospital care: number of exacerbations per patient-year; number of hospital days per patient-year.

STATISTICAL ANALYSIS

The Pearson chi-square test was used for comparing the prevalence of categorical variables between groups (two or more groups). Once we have determined the distribution of continuous variables, we present normally distributed variables as means±SD and non-normally distributed variables as medians (IQR).

We applied a t-test or Mann-Whitney-test to compare differences in the differences in continuous variable levels between the two groups (e.g., men vs. women or individuals with or without severe 25-hydroxyvitamin D deficiency). We assessed how the level-25-OH-VitD3 reference plasma affected exacerbations using the Chi-Square test considering that the variable (exacerbation frequency) is dichromatic.

Linear regression analyses were conducted to analyze the association between 25-hydroxyvitamin D (log-transformed) levels and rates of exacerbation. These associations have been tested in multiple linear regression models with adjustments to take into account possible confounding factors. We considered a two-tailed $p < 0.05$ as statistically significant.

RESULTS

We enrolled 303 cases in this study. Their mean±SD age was 66,1±8,3 years (median, 66 years; range, 44–88 years); their FEV1 median, 39% (ICQ 26–54%); and their level of dyspnea median (modified Medical Research Council scale level) 2 (ICQ 2-3; range, 0–4). According to the GOLD stages, 40 (13,2%), 96 (31,7%) and 167 (55,1%) patients were categorized into GOLD class A, B, and D, respectively.

The mean concentration for 25-hydroxyvitamin D was 12.5 ng/dL (IQR, 8.08–20,9 ng/dL), and 270 patients (88.4%) were 25-hydroxyvitamin D deficient (< 30 ng/dL). In total, 16.2% were deficient in 25-hydroxyvitamin D (definition > 20 ng/ml but < 30 ng/ml according to widely used criteria)17); 72.6% were deficient in 25-hydroxyvitamin D (< 20 ng/ml); and 39.3% were severely deficient in 25-hydroxyvitamin D (< 10 ng/ml) (**Table 1**).

Table 1. Baseline characteristics ,pulmonary fuction and clinical characteristics of non-deficiency and deficiency groups of with COPD

Parameters	Non-Deficiency (n=33)	Deficiency (n=270)	P-Value
Age, years	69.6±7,1	66,6±8,6	0.053
Gender, m/f	31/2	226/44	0.038
GOLD A	10	28	
GOLD B	13	84	
GOLD D	10	158	
FEV1,% predectid	41 (IQR 25.5-48)	39 (IQR 26-54)	0.93
Baselinde plasma 25OH D vit	36.5 (IQR33.7-47.3)	11.1 (IQR 7.7-17.9)	0.0001
AECOPD (y/n)%	18.2(%)	45,2(%)	0.003
Number of mean AECOPD/ year	0,72±1,35	1,8±1,98	0,001
Hospitalization(y/n)%	24.2(%)	43.3(%)	0.03

There were significant sex differences across groups. The percentage of predicted FEV1 (39% vs 41%; P=0.93) was higher in the non-deficiency than in the deficiency group. Serum circulating 25-hydroxyvitamin D rates were weakly correlated with FEV1 in the COPD sub-group. (Pearson r=0.187, p=0.0013; **Figure 1**).

In patients with COPD, we found that 25-hydroxyvitamin D levels were significantly associated with the combined severity of the COPD stage. (**Figure 2**). Thirty-three (10.9%) of the patients had adequate serum 25-hydroxyvitamin D concentrations (≥30 ng/mL), while the remaining 270 (89.1%) were deficient in 25-hydroxyvitamin D (<30 ng/mL). Taken as a whole, this data clearly indicates that the reduction in 25-hydroxyvitamin D levels is correlated with the mMRC, exacerbation frequency, and COPD hospitalizations.

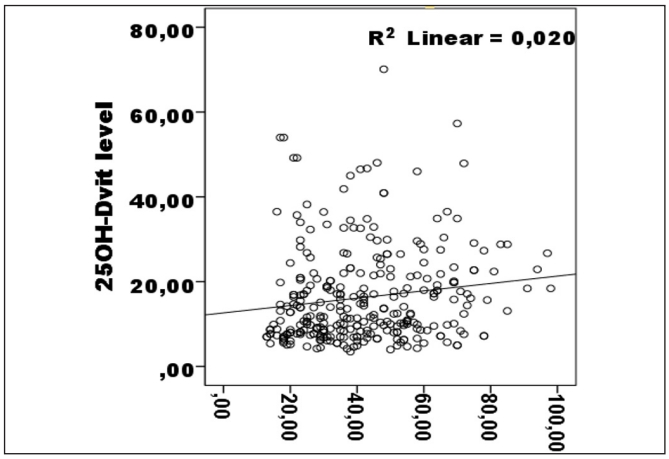


Figure 1. Correlation with D vit level and FEV1

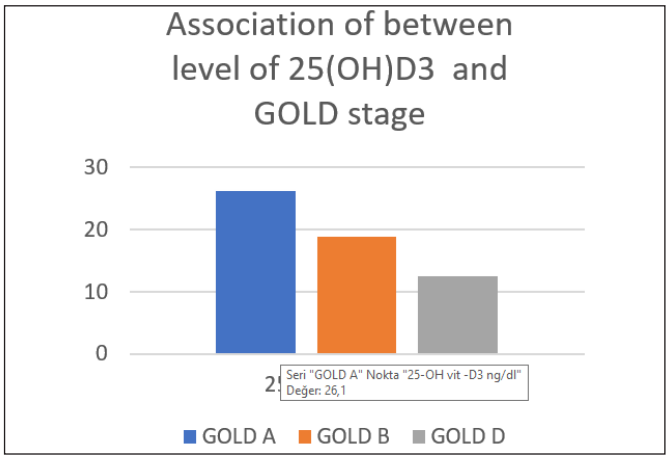


Figure 2: This figure showing 25-OHD levels according to the various GOLD (Global Initiative for Obstructive Lung Disease) stages. Serum 25(OH) D concentration among different grades of COPD (n= 37 for patients A group=98 for patients grade B COPD ; n=168 for patients with grade D COPD). All data were represented as mean ± SEM. *p<0.001

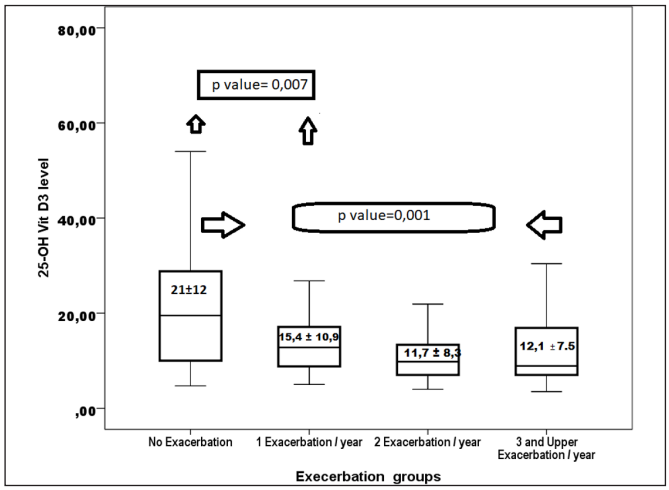
Association of 25-hydroxyvitamin D with Exacerbations and Hospitalization

In all, 181 participants experienced 493 AECOPDs over one year. A total of 122 participants (40.3%) remained AECOPD-free over one year; 53 (17.5%) had one AECOPD; 47 (15.5%) had two AECOPDs; and 81 (67%) had three or more AECOPDs.

The proportion of participants who were severely deficient in 25-hydroxyvitamin D increased with the number of AECOPDs (p < 0.001) (**Figure 3**).

Importantly, the levels of serum 25-hydroxyvitamin D were significantly higher in patients with COPD who had at least one exacerbation-related hospitalization than in those who had not been hospitalized . (**Figure 4**). Serum levels of vitamin 25-hydroxyvitamin D were associated with dyspnea perception on the mMRC scale (**Figure 5**).

The prevalence of severe 25-hydroxyvitamin D deficiencies was highest in frequent patients compared to those without frequent exacerbations. (55.5% vs. 27.4%, p<0.001).



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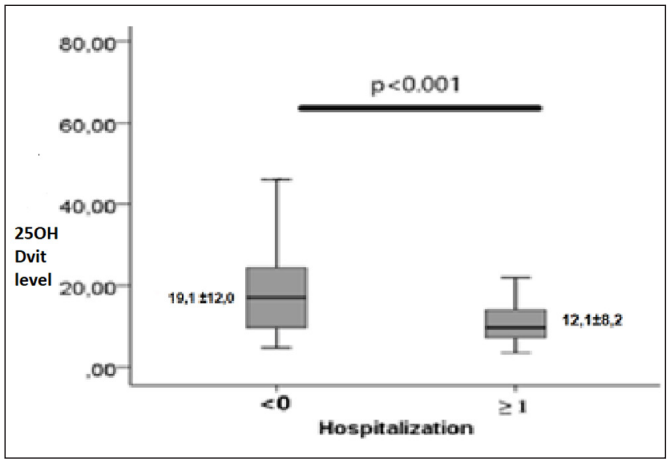

Figure 4. Comparison of serum 25-OH D3 vit concentration in COPD patients with ≥ 1 hospitalized exacerbation and those who were not hospitalized. The central horizontal line on each box represents the median, the ends of the boxes are 25 and 75 percentiles and error %5 and 95%. P values derived from the Mann -Whitney U test

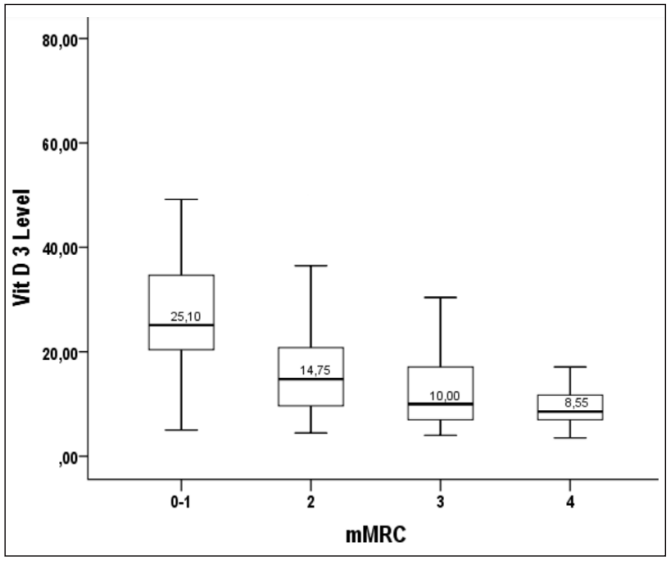

Figure 5. Serum levels of vitamin 25-OH D3 were associated with dyspnea perception on the mMRC scale

The mean number of exacerbations over one year were 2.3±2.1, 1.6±1.8, 0.8±1.6, and 0.7±1.3 in the patients with 25-hydroxyvitamin D concentrations of < 10 ng/dL, 10 ng/dL to 19.99 ng/dL, 20 ng/dL to 29.99 ng/dL, and > 30 ng/dL, respectively.

An analysis of AECOPD levels stratified according to 25-hydroxyvitamin D levels showed that participants with severe 25-hydroxyvitamin D deficiency (<10 ng/ml) had a higher average AECOPD rate than the others. The discrepancy is statistically significant. (p=0.001).

DISCUSSION

In our research, we found that the serum 25-hydroxyvitamin D levels were associated with important clinical correlates of COPD such as the exacerbation frequency, the mMRC symptom scales, and the hospitalization frequency score. Most importantly, Serum levels of 25-hydroxyvitamin D were significantly reduced in patients with COPD who had experienced at least one exacerbation in the previous year. Severe deficiency of 25-hydroxyvitamin D was associated with frequent exacerbations the following year, as documented in our clinic. We also showed that measures of 25-hydroxyvitamin D levels can provide a predictive tool for evaluating the frequency of exacerbations associated with hospitalizations in COPD patients.

However, the association of serum 25-hydroxyvitamin D levels with the frequency of exacerbation is uncertain (18). Our results are consistent with research done by Sanket et al. (19) which have shown COPD to be associated with an increased risk for 25-hydroxyvitamin D deficiency. A meta-analysis by Zhu et al. (9) found no associations. Zhu et al. (9) studied the association between serum levels of 25 hydroxyvitamin D in the host and the severity of COPD and found that low serum levels of 25-hydroxyvitamin D were not associated with sensitivity to COPD but high deficiency rate 25-hydroxyvitamin D had been linked to the severity of COPD. Indeed, two studies have shown 25-hydroxyvitamin D deficiency to be associated with more frequent exacerbations (20,21) while others have not found this association (15,22,23). The relationship between 25-hydroxyvitamin D deficit and exacerbation of COPD is controversial. Puhan et al. (23) informed a trend whereby patients suffering from severe 25-hydroxyvitamin D deficiency were sensitive to exacerbations without statistically significant relationship. Martineau et al. (24) recommended that 25-hydroxyvitamin D supplementation was protective of moderate to severe exacerbation in COPD patients with 25-hydroxyvitamin D deficiency. In our study, we found a retrospective cohort in which severe 25-hydroxyvitamin D deficiency (<10 nmol/L) was associated with more frequent exacerbation of COPD in the year preceding 25-hydroxyvitamin D measurements. A longitudinal study by Persson et al. (25)

showed that patients with COPD and hypovitaminosis D. (< 50 nmol/L, n=142) had more severe COPD, and more frequent exacerbations.

There are several mechanisms that can explain the contribution of 25-hydroxyvitamin D deficiency to COPD exacerbation. First, VDR (25-hydroxyvitamin D receptor) dysfunction, dependent on 25-OH D deficiency, is thought to decrease the innate immune function which increases the susceptibility to infections (26). Also, airway epithelial and immune cells in the lung express VDR. Other researchers have found higher levels of vitamin D3-binding proteins in COPD patients. associated with macrophage activation and neutrophil chemotaxis (underlying COPD pathogenesis mechanisms). A dysregulated immune-inflammatory response causes chronic inflammation and lung structural destruction. Secondly, 25-hydroxyvitamin D may regulate the expression of antimicrobial peptides as a response to infections (27,28). Quint et al. (22) noticed that the 25-hydroxyvitamin D deficiency is associated with COPD and increased susceptibility to infections among the general population. 25-hydroxyvitamin D deficiency can help initiate bacterial or viral infections and lead to acute COPD exacerbations. Exacerbations are predominantly initiated by infections, and patients with frequent exacerbations have impaired daily activities, spend less time outdoors (29), have rapid disease progression (30), and present a higher mortality rate (31) than patients with infrequent exacerbations.

NHANES III research has shown an inverse dose-response relationship between 25-hydroxyvitamin D levels and upper respiratory tract infections in asthmatics., and a similar association was observed for COPD cases (although not significant after adjustments) (32). In this study, we found a link between exacerbation frequencies and measured 25-hydroxyvitamin D levels. According to our research results, patients with 25-hydroxyvitamin D deficiency (<10 nmol/L) had the highest risk for exacerbations (2.3±2.1 exacerbations per year), suggesting the deficiency is a risk factor for exacerbations.

In our research, we found a low correlation between 25-hydroxyvitamin D levels and lung function tests. The Third National Health And Nutritional Exam Survey in the United States United has shown that the difference between the highest and lowest quintiles of 25-hydroxyvitamin D was greater in people diagnosed with emphysema or chronic bronchitis than in others, which suggests a stronger association between 25-hydroxyvitamin D and FEV1 levels in COPD patients compared to the general population (33). In a previous study on patients with COPD by Janssens et al. (13) they found that a strong association between the GOLD stage and the presence of 25-hydroxyvitamin D deficiency suggested the presence of airway obstruction. These researchers suggested the existence of a strong association between 25-hydroxyvitamin D and COPD. However, our study could not find a similarly strong correlation between FEV1 and 25-hydroxyvitamin D levels. Based on our results, the exacerbation and hospitalization frequencies are good predictors of deficient 25-hydroxyvitamin D levels. Thus, the fact that these 25-hydroxyvitamin D levels were associated with AECOPD exacerbation or hospitalization rates suggests that serum 25-hydroxyvitamin D can be used to predict risk of future exacerbations in COPD patients. Possible explanations include the fact that 25-hydroxyvitamin D has been involved in tissue remodeling via collagen synthesis and fibroblast proliferation, and modulation of matrix metalloproteinase levels (34). In addition, undiagnosed osteoporosis resulting in spinal compressions can result in loss of height, decreased thoracic mobility and reduced lung function (35). In an article by Black et al. (33), 25-hydroxyvitamin D levels were strongly associated with FEV1 and FVC, with standardized data for sex, age, ethnic origin, smoking history and body mass index (BMI).

Patients with COPD experience increased skin aging due to smoking and decreased sun exposure due to restrictions on outdoor activities, and these conditions lead to reduced 25-hydroxyvitamin D serum levels (13). Patients with COPD are frequently treated with corticosteroids, which increase vitamin D catabolism.

In our study, there was a statistically significant difference in 25-hydroxyvitamin D levels in male. (16.7±11.2) and female (13.8±10.3) with COPD, similar to the results of previous studies (**Table 2**). For example, Black et al. (14) reviewed the information from the NHANES III research undertaken in the USA on 14, 091 individuals and female were found to have significantly lower average levels of 25-hydroxyvitamin D compared to men (28.72 ng/mL versus 31.37 ng/mL). It was suggested that these results could be attributed to women's preference for clothing. that covered most of their body for religious reasons, or due to the use of sun creams for cosmetic reasons or for skin cancer protection.

Table 2. Coefficients from multiple linear regression and logistic regression models ,showing the relationship between baseline predictors and serum levels of 25(OH)D3(<30 mg/dl) in COPD patients

Risk factor	RR (%95 CI)	P value
Age	1.03 (0.99-1.09)	0.03
Gender	2.6 (0.58-11.9)	0.20
Season		
Autumn	2.6(0.8-8.1)	0.08
Winter	0.5(0.1-2.9)	0.50
Spring	1.8(0.7-4.8)	0.19
Summer		
Exacerbation frequency(y/n)	4.0(1.6-10.2)	0.003

For the both linear and lositic regression models a backward stepwise procedure was used the fallowing variables include at start: age,sex,season and exacerbation (yes/no)

Seasonality, as a confounding factor, can influence overall study results. Several researchers have demonstrated that seasonality affects 25-hydroxyvitamin D levels, but we did not find a similar phenomenon (7) (**Table 3**). Therefore, the seasons did not influence on 25-hydroxyvitamin D levels in our research.

Table 3. Seasonal variatioon of baseline plasma 25-OH VitD3 levels

Season	n	Median(IQR %25-75), ng/mL	P-value
September-November	103	10.2 (IOR 7.1- 17.2)	0,052[1]
December-Febraury	45	12.7 (IOR 7.8- 23.4)	
March-May	43	11.4 (IOR 8.6- 17.9)	
June-November	112	15.8 (IOR 8.6- 23.3)	

SD, standart deviation.1: There is not significant statistical diffrence beetwen season and plasma 25-OH VitD3 levels(p value=0,052). ANOVA used for variation with season.

The major weakness of this study is its retrospective design. Secondly since we chose to focus on 25-hydroxyvitamin D effects on AECOPD patients with 25-hydroxyvitamin D defiency, our results could not be generalized to all AECOPD patients. There are other limitations: a relatively small patient population; a failure to include all possible factors affecting 25-hydroxyvitamin D levels in individuals (Like nutrition, sunlight exposure time, and clothing style.); a failure to apply a food frequency questionnaire; and a failure to account for seasonality.

CONCLUSION

Our research findings confirm that 25-hydroxyvitamin D deficiency is associated with the severity of COPD. According to our results, Vitamin D deficiency was significantly related to higher rates of exacerbation and hospitalization for COPD. Larger clinical trials with similar evidence is needed to make conclusions about the link between 25-hydroxyvitamin D and the risk of exacerbation. Further research is needed to identify the benefits of the strategies aimed at preventing COPD exacerbations, including the use of vitamin D supplementation.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Keçiören Training and Research Hospital Ethics Committee (Date: 23.11.2021, Decision No: 15-2409).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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