ORIGINAL RESEARCH

Association Between Vitamin D Level and Respiratory Symptoms in Patients with Stable Chronic Obstructive Pulmonary Disease

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Purpose: Vitamin D insufficiency or deficiency is prevalent in patients with chronic obstructive pulmonary disease (COPD). However, the association between vitamin D levels and respiratory symptoms in patients with stable COPD has not been fully investigated. This study evaluated the association between vitamin D levels and respiratory symptoms in patients with stable COPD.

Patients and Methods: Patients with COPD who had their serum 25-hydroxyvitamin D (25-OH vitamin D) level measured within 6 months of spirometry between January 2016 and April 2020 were retrospectively included. Respiratory symptoms were assessed using the modified Medical Research Council (mMRC) scale and COPD assessment test (CAT) score.

Results: Of the 329 included patients, 193, 88, and 48 were categorized as having vitamin D deficiency (<20 ng/mL), insufficiency (20–29 ng/mL), and sufficiency (≥30 ng/mL), respectively. The mean serum 25-OH vitamin D level of each group was 13.45 ng/mL, 24.61 ng/mL, and 38.90 ng/mL, respectively. Patients with vitamin D insufficiency/deficiency showed higher CAT scores than those with vitamin D sufficiency (p = 0.004). In multivariable adjusted models, vitamin D insufficiency/deficiency was significantly associated with a CAT score of 10 or more (adjusted odds ratio [aOR] = 2.41, 95% confidence interval [CI] = 1.20–4.82, p = 0.013) and mMRC ≥ 2 (aOR = 2.39, 95% CI = 1.08–5.32, p = 0.032). Among CAT items, the amount of phlegm (p = 0.008), chest tightness (p = 0.030), breathlessness walking upstairs (p < 0.001), home activity limitations (p = 0.002), and lack of energy (p = 0.003) were significantly associated with vitamin D insufficiency/deficiency after adjustment for age, sex, body mass index, smoking history, Charlson comorbidity index, post-bronchodilator forced expiratory volume in 1 second, and season of blood draw.

Conclusion: Vitamin D insufficiency/deficiency were associated with worse respiratory symptoms in patients with stable COPD.

Keywords: chronic obstructive pulmonary disease, vitamin D, respiratory symptoms, COPD assessment test, modified Medical Research Council

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality and is projected to rise over 5.4 million annual deaths worldwide by 2060.[1,2] COPD is a progressive inflammatory lung disease involving the airways, alveoli, and pulmonary vasculature, leading to progressive deterioration of lung function, loss of exercise capacity, and frequent exacerbations.[3] These patients often have respiratory symptoms including chronic cough, sputum, breathlessness, and exercise limitations.[4,5] Accordingly, the Global Initiative for Chronic Obstructive Lung Disease

(GOLD)[6] recommends not only measuring lung function but also measuring symptoms of COPD with either the modified Medical Research Council (mMRC) scale or the COPD Assessment Test (CAT).

In recent years, the pleiotropic role of vitamin D has been highlighted in various diseases. As an immunomodulatory effector, vitamin D can boost innate immune responses upon infection and regulate adaptive immune responses.[7,8] Vitamin D metabolites support the induction of antiviral and antimicrobial effector mechanisms and attenuate inflammatory responses.[9,10] In line with this, a previous study showed that patients with a vitamin D level <10 ng/mL had 2.33-fold increased risk of hospital-acquired bloodstream infection.[11] Vitamin D insufficiency/deficiency has been linked to a broad range of diseases, including autoimmune diseases, allergic diseases, endocrine and metabolic disorders, cancer, infections, and cardiovascular disorders.[12,13]

Vitamin D insufficiency or deficiency is also found in a considerable proportion of patients with COPD. According to previous studies, low vitamin D levels are associated with low lung function,[14–16] increased dyspnea,[17] unfavorable quality of life assessments,[17,18] and increased number of exacerbations[16,19–22] in patients with COPD. A systematic review and meta-analysis showed that vitamin D3 administration decreased the rate of moderate/severe exacerbations of COPD in patients with baseline plasma 25-OH vitamin D levels below 25 ng/mL.[23] However, there are limited studies regarding the association between vitamin D deficiency and respiratory symptoms in COPD patients.[17,18] Moreover, the association between vitamin D insufficiency/deficiency (which is obviously more prevalent than deficiency alone) and detailed respiratory or non-respiratory symptoms has not been investigated. Thus, in this study, we aimed to determine the association between serum vitamin D insufficiency/deficiency (<30 ng/mL) and detailed respiratory and non-respiratory symptoms in stable COPD patients.

Materials and Methods
Study Population
This was a retrospective cohort study of COPD patients conducted at the Samsung Medical Center (a 1979-bed hospital with 11 pulmonary specialists in charge of the outpatient clinic in Seoul, South Korea) between January 2016 and April 2020. Electronic medical records contain routinely collected data on patient demographics, comprehensive clinical parameters, laboratory studies, and prescriptions. COPD was defined as a post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio <0.7, and we excluded patients with current asthma.

During the study period, 1025 COPD patients aged 40 years or older were identified, and 416 patients who had their serum 25-hydroxyvitamin D (25-OH vitamin D) levels measured within 6 months of spirometry were included. Among them, 84 patients without CAT scores within 1 month were excluded, and three patients with acute exacerbation at measurement of CAT and serum 25-OH vitamin D were excluded. Finally, 329 stable COPD patients were included in the analysis (Figure 1).

Measurements
We retrospectively obtained data from electronic medical records, including age, sex, smoking history, body mass index (BMI), mMRC dyspnea scale, CAT score, Inhaler use, and comorbidities including cardiovascular disease (CVD), diabetes mellitus, chronic kidney disease, liver disease, dementia, connective tissue disease, and peptic ulcer disease. Patients with CVD were defined as those who had been diagnosed with coronary arterial disease, cerebrovascular disease, congestive heart failure, or peripheral arterial disease. Patients with stable COPD were defined as those without moderate or severe exacerbations when the CAT score and vitamin D were measured. Moderate or severe exacerbations were defined as a worsening of symptoms that required oral corticosteroids and/or antibiotics and/or hospitalization.[24] Spirometry was performed and diffusing capacity for carbon monoxide (DLco) and lung volume were measured using Vmax 22 (SensorMedics, Yorba Linda, CA, USA) according to the American Thoracic Society and European Respiratory Society guidelines.[25,26] Absolute values of FEV_1, FVC, and DLco were obtained, and the percentage of predicted values (% pred) for FEV_1, FVC, and DLco were calculated using data obtained from a representative Korean sample.[27,28] The severity of COPD was based on the FEV_1 (% pred) according to GOLD grades.[6] Hyperinflation was measured using residual volume (RV)/total lung capacity (TLC).[29]
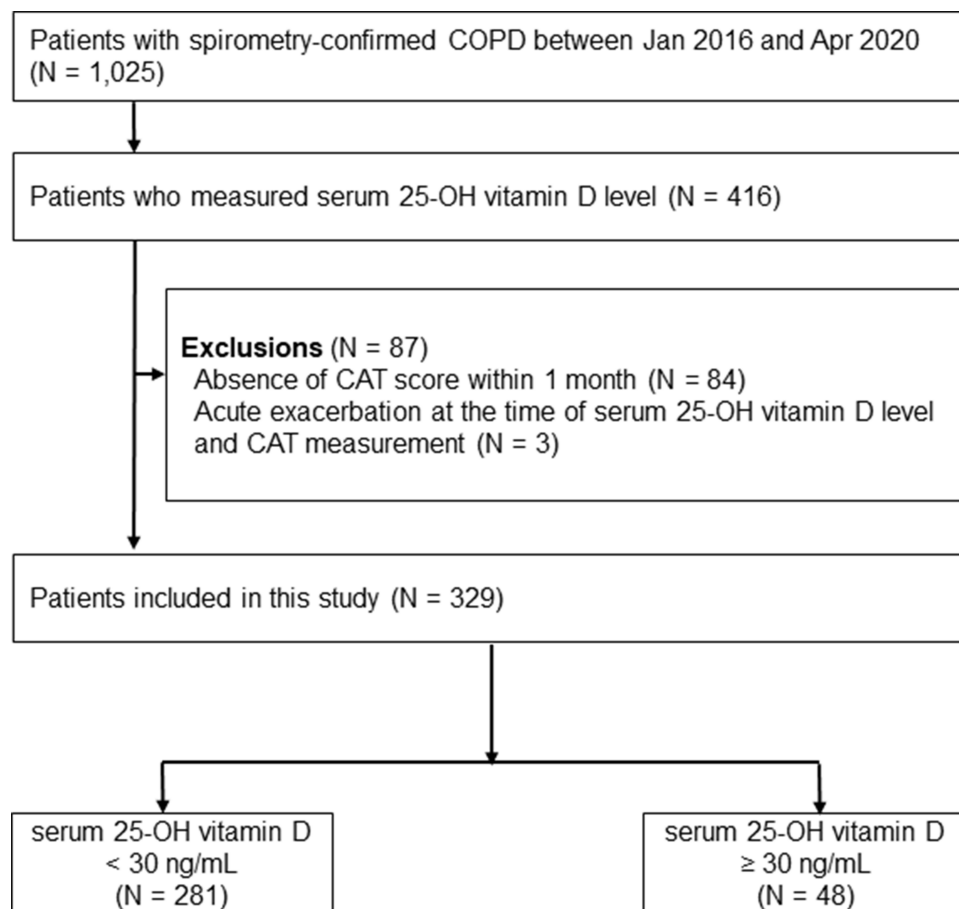
Figure 1 Flowchart of study population.
Abbreviations: COPD, chronic obstructive pulmonary disease; CAT, COPD assessment test.

At every outpatient visit, patients were asked to complete the questionnaires for the mMRC dyspnea scale and CAT score, which were validated in the Korean language.[30,31] We used the mMRC dyspnea grades and CAT scores assessed on the day that 25-OH vitamin D levels were measured. The mMRC dyspnea scale is graded from 0 to 4, depending on the severity of the dyspnea, defined as mMRC ≥2 indicating more breathlessness.[32] The CAT consists of the following eight items: cough frequency, amount of phlegm, chest tightness, breathlessness walking upstairs, home activity limitations, not confident leaving home, sleep disturbance, and lack of energy.[33] Each item is presented on a semantic 6-point (0–5) differential scale, providing a total score of 40.[33] We defined a total CAT score ≥10 as a significant health impact.[34]

Patients were categorized into the vitamin D sufficiency group (plasma 25-OH vitamin D ≥30 ng/mL), vitamin D insufficiency group (plasma 25-OH vitamin D 20–29 ng/mL), and vitamin D deficiency group (plasma 25-OH vitamin D <20ng/mL).[35] We compared detailed respiratory and non-respiratory symptoms measured using the mMRC scale and CAT among patient groups based on vitamin D level (sufficiency group vs insufficiency/deficiency and sufficiency vs insufficiency vs deficiency group).

Statistical Analyses

All data are expressed as the number (percentage) for categorical variables and as mean ± standard deviation (SD) or median (interquartile range) for continuous variables. The Pearson chi-square test or Fisher's exact test was used to compare categorical variables, and Student's *t*-test, one-way analysis of variance, or Jonckheere trend test was used to compare continuous variables. Spearman correlation test was used to assess the relationship between serum 25-OH vitamin D level (continuous), total CAT score, and lung function parameters. Multivariable logistic regression was used

to evaluate the association between serum 25-OH vitamin D level (vitamin D sufficiency group vs insufficiency/ deficiency group) and respiratory symptoms (mMRC ≥2 and CAT ≥10). We calculated odds ratios (ORs) and 95% confidence intervals (CIs) after adjustment for age, sex, BMI, smoking history (never vs ever), Charlson comorbidity index (CCI), post-bronchodilator FEV$_1$ (≥50% vs <50% pred), and season of blood draw (spring/fall vs summer vs winter). Multivariable linear regression was used to calculate the difference in scores of each CAT item between the vitamin D sufficiency group and the insufficiency/deficiency group, with adjustment for the same variables as in the logistic regression model. Statistical significance was set at $p < 0.05$. SPSS (version 27.0; IBM Corp., Armonk, NY, USA) and Stata (version 14.2; StataCorp, College Station, TX, USA) was used for the statistical analyses.

Results

Baseline Characteristics

The mean (SD) serum 25-OH vitamin D level of the total study population (329 patients) was 20.15 (10.44) ng/mL, and levels ranged from 3.0 to 69.9 ng/mL (Figure 2). Using a cutoff value of 30 ng/mL, 281 patients were assigned to the vitamin D insufficiency/deficiency group and 48 patients to the vitamin D sufficiency group, with mean (SD) serum 25-OH vitamin D levels of 16.94 (6.40) ng/mL and 38.90 (9.79) ng/mL, respectively. The baseline characteristics of the 329 patients are summarized in Tables 1 and 2. No statistically significant differences were observed in the clinical characteristics (age, sex, BMI, smoking history, comorbidities, inhaler use, and previous exacerbation history) or pulmonary function parameters between the two groups.

In addition, among the 281 patients in the vitamin D insufficiency/deficiency group, 193 were further categorized into the vitamin D deficiency group with a mean (SD) serum 25-OH vitamin D of 13.45 (4.13) ng/mL. There were no statistically significant differences in the clinical characteristics and pulmonary function parameters when the patients were classified into three groups according to serum 25-OH vitamin D levels (Supplementary Table E1) or four groups by further subdividing the vitamin D deficiency group into those with vitamin D levels of 0–10 and 10–20 ng/mL (data not shown).
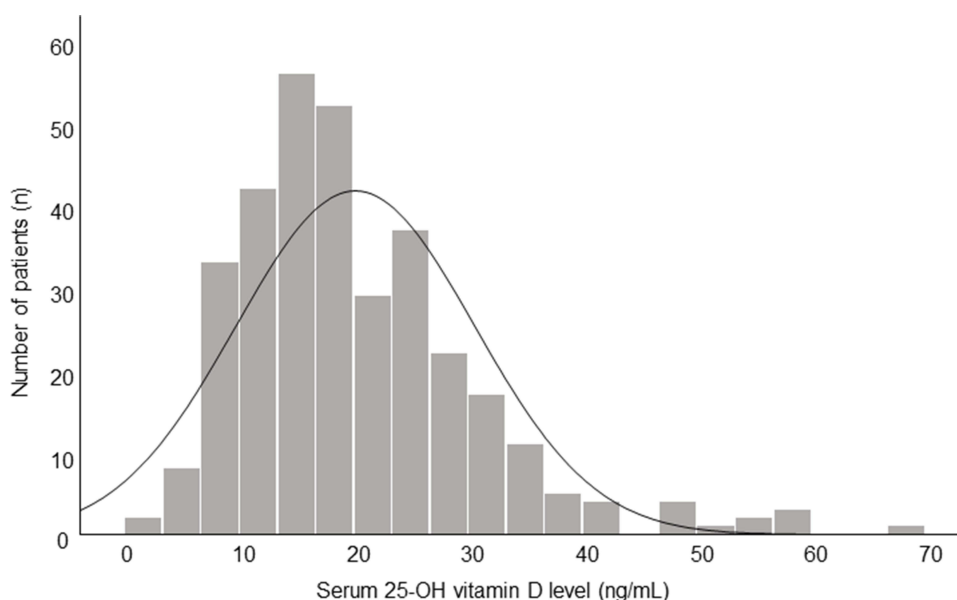

Figure 2 Histogram showing the distribution of 25-OH-vitamin D levels (ng/mL).

Table 1 Baseline Characteristics of COPD Patients Stratified by Vitamin D Level

	Vitamin D Level			*P*-value
	Total (N=329)	< 30 ng/mL (N=281)	≥ 30 ng/mL (N=48)	
Age, year	70.89 (8.49)	70.73 (8.62)	71.83 (7.68)	0.404
Sex				0.554
Male	304 (92.4)	258 (91.8)	46 (95.8)	
Female	25 (7.6)	23 (8.2)	2 (4.2)	
BMI, kg/m^2	23.66 (3.20)	23.68 (3.22)	23.54 (3.12)	0.780
Smoking history				0.786
Current smoker	55 (16.7)	48 (17.1)	7 (14.6)	
Ex-smoker	241 (73.3)	206 (73.3)	35 (72.9)	
Never smoker	33 (10.0)	27 (9.6)	6 (12.5)	
Smoked pack-year	36.67 (24.46)	37.25 (24.73)	33.26 (22.77)	0.297
Comorbidity				
Coronary arterial disease	45 (13.7)	41 (14.6)	4 (8.3)	0.244
Cerebrovascular disease	24 (7.3)	22 (7.8)	2 (4.2)	0.550
Heart failure	22 (6.7)	18 (6.4)	4 (8.3)	0.542
Peripheral arterial disease	13 (4.0)	9 (3.2)	4 (8.3)	0.105
Diabetes mellitus	51 (15.5)	42 (14.9)	9 (18.8)	0.501
Chronic kidney disease	15 (4.6)	13 (4.6)	2 (4.2)	1.000
Liver disease	9 (2.7)	8 (2.8)	1 (2.1)	1.000
Dementia	4 (1.2)	3 (1.1)	1 (2.1)	0.470
Connective tissue disease	5 (1.5)	2 (0.7)	3 (6.3)	0.024
Peptic ulcer disease	10 (3.0)	10 (3.6)	0 (0.0)	0.368
CCI	5.14 (2.15)	5.05 (2.13)	5.65 (2.24)	0.076
Inhaler				
None	12 (3.6)	9 (3.2)	3 (6.3)	0.394
LABA or LAMA	17 (5.2)	13 (4.6)	4 (8.3)	0.288
LABA+LAMA	125 (38.0)	107 (38.1)	18 (37.5)	0.939
LABD+ICS	59 (17.9)	50 (17.8)	9 (18.8)	0.873
LABA+LAMA+ICS	116 (35.3)	102 (36.3)	14 (29.2)	0.339
Vitamin D level	20.15 (10.44)	16.94 (6.40)	38.90 (9.79)	<0.001
Previous Exacerbation, any				0.296
0	148 (45.0)	124 (44.1)	24 (50.0)	
1	107 (32.5)	96 (34.2)	11 (22.9)	
2≤	74 (22.5)	61 (21.7)	13 (27.1)	
Previous Exacerbation, severe				0.163
0	302 (91.8)	261 (92.9)	41 (85.4)	
1	18 (5.5)	14 (5.0)	4 (8.3)	
2≤	9 (2.7)	6 (2.1)	3 (6.3)	

Notes: Data are mean (standard deviation) or number (%).
Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; LABA, long-acting beta2-agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroids; LABD, Long acting bronchodilator (LAMA or LABA).

Vitamin D Levels According to Lung Function Parameters, Total CAT Score, and mMRC Grades

As shown in Figure 3, vitamin D levels showed a decreasing trend as GOLD grades increased (*p* for trend = 0.010) and total CAT score (*p* for trend < 0.001) and mMRC grades (*p* = 0.045) worsened. Analysis of vitamin D level as a continuous variable showed a weak but significant correlation with total CAT scores *(rs = −0.193, p < 0.001;* Figure 4A) and FEV$_1$ *(rs = 0.134, p = 0.015;* Figure 5A). However, there was no significant correlation between DLco, RV/TLC, and vitamin D levels (Figure 5B and C).

Table 2 Baseline Pulmonary Function Parameters of COPD Patients Stratified by Vitamin D Level

	Vitamin D Level			*P*-value
	Total (N=329)	< 30 ng/mL (N=281)	≥ 30 ng/mL (N=48)	
Post-bronchodilator spirometry				
FVC, L	3.44 (0.81)	3.41 (0.81)	3.63 (0.81)	0.076
FVC, % pred	82.08 (15.02)	81.46 (15.25)	85.69 (13.17)	0.072
FEV$_1$, L	1.86 (0.62)	1.84 (0.62)	1.98 (0.63)	0.135
FEV$_1$, % pred	63.63 (18.23)	62.89 (18.10)	67.94 (18.57)	0.076
≥ 50, n (%)	259 (78.7)	222 (79.0)	37 (77.1)	0.764
FEV$_1$/FVC	53.66 (12.29)	53.55 (12.46)	54.31 (11.37)	0.692
RV/TLC, %	42.25 (10.45)	42.37 (10.55)	41.56 (9.99)	0.656
DLco, % pred	66.25 (20.80)	65.76 (20.79)	69.09 (20.83)	0.312
GOLD grade				0.073
1	53 (16.1)	40 (14.2)	13 (27.1)	
2	191 (58.1)	168 (59.8)	23 (47.9)	
3	65 (19.8)	54 (19.2)	11 (22.9)	
4	20 (6.1)	19 (6.8)	1 (2.1)	
CAT				
Cough frequency	1.85 (1.34)	1.90 (1.33)	1.52 (1.34)	0.067
Amount of phlegm	2.26 (1.40)	2.34 (1.41)	1.77 (1.21)	0.009
Chest tightness	1.86 (1.38)	1.93 (1.39)	1.44 (1.25)	0.021
Breathlessness walking upstairs	3.12 (1.46)	3.23 (1.44)	2.46 (1.43)	0.001
Home activities limitation	1.60 (1.50)	1.69 (1.52)	1.08 (1.25)	0.009
Not confident leaving home	1.64 (1.48)	1.69 (1.51)	1.33 (1.29)	0.120
Sleep disturbance	1.89 (1.41)	1.91 (1.42)	1.77 (1.33)	0.514
Lack of energy	2.36 (1.33)	2.43 (1.33)	1.94 (1.26)	0.018
CAT, total	16.58 (8.59)	17.14 (8.57)	13.31 (8.08)	0.004
CAT score ≥ 10	257 (78.1)	226 (80.4)	31 (64.6)	0.014
mMRC, total	1.37 (0.68)	1.41 (0.70)	1.19 (0.49)	0.039
mMRC ≥ 2	116 (35.3)	105 (37.4%)	11 (22.9%)	0.053

Notes: Data are mean (standard deviation) or number (%).
Abbreviations: FVC, forced vital capacity; FEV$_1$, forced expiratory volume in 1 second; RV, residual volume; TLC, total lung capacity; DLco, diffusing capacity of the lung for carbon monoxide; GOLD, global initiative for chronic obstructive lung disease; CAT, COPD assessment test; mMRC, modified Medical Research Council.

Association Between Respiratory Symptoms and Vitamin D Insufficiency/Deficiency

As shown in Table 2, the mean CAT score in patients with vitamin D insufficiency/deficiency was higher than in those with vitamin D sufficiency (17.14 ± 8.57 vs 13.31 ± 8.08, $p = 0.004$). The proportion of patients with a CAT score ≥ 10 was also higher in the vitamin D insufficiency/deficiency group than in the vitamin D sufficiency group (80.4% vs 64.6%, $p = 0.014$). Similarly, the mean mMRC grade in patients with vitamin D insufficiency/deficiency was higher than in those with vitamin D sufficiency (1.41 ± 0.70 vs 1.19 ± 0.49, $p = 0.039$), and the proportion of patients with an mMRC ≥ 2 was higher in the vitamin D insufficiency/deficiency group than in the vitamin D sufficiency group (37.4% vs 22.9%, $p = 0.053$). This association of CAT score and mMRC with vitamin D level was similar when the patients were classified into three groups based on the serum 25-OH vitamin D level (Supplementary Table E2) or four groups by further subdividing the vitamin D deficiency group into those with vitamin D levels of 0–10 and 10–20 ng/mL (data not shown), except that there was no statistically significant difference in the proportion of patients with mMRC ≥2 among three or four groups.

In multivariable adjusted models, vitamin D insufficiency/deficiency was significantly associated with a CAT score ≥10 (adjusted OR [aOR] = 2.41, 95% CI = 1.20–4.82, $p = 0.013$) and mMRC ≥2 (aOR = 2.39, 95% CI = 1.08–5.32, $p = 0.032$) (Table 3).
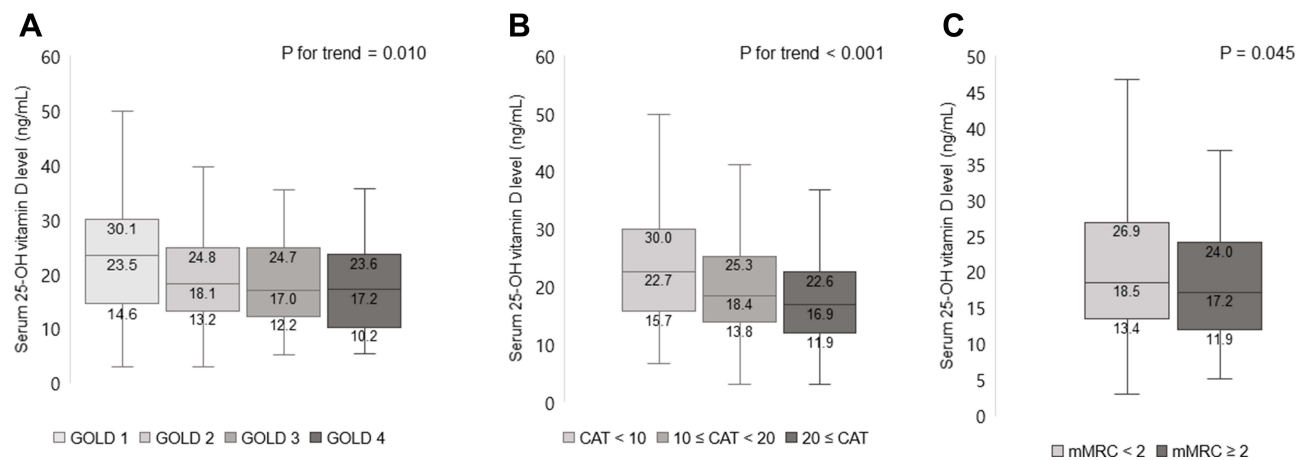
Figure 3 Serum 25-OH vitamin D level (median with IQR) by (**A**) GOLD grade, (**B**) CAT score categories, (**C**) mMRC grade (<2 vs ≥2).
Abbreviations: IQR, interquartile range; GOLD, Global Initiative for Chronic Obstructive Lung Disease; COPD, chronic obstructive pulmonary disease; CAT, COPD assessment test; mMRC, modified Medical Research Council.
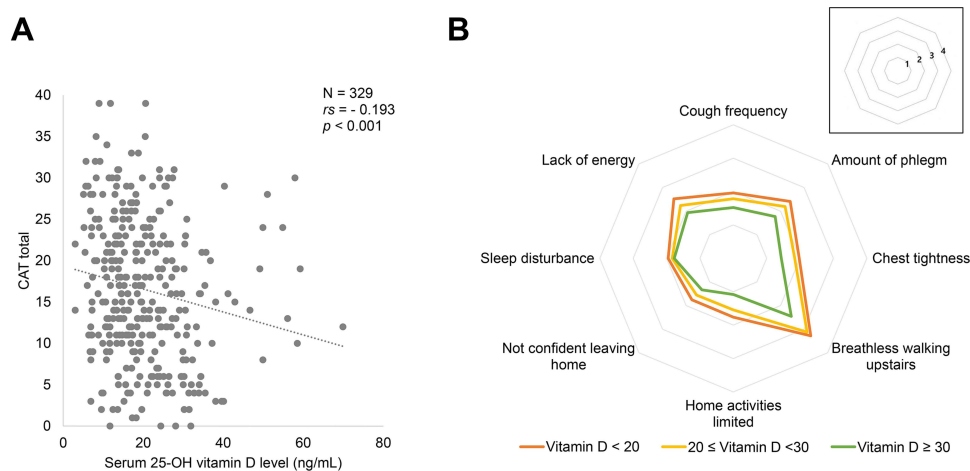

Figure 4 Association between serum 25-OH vitamin D level and CAT score. (**A**) Correlation between serum 25-OH vitamin D level and total CAT score. (**B**) Distribution of mean score for each CAT item according to serum 25-OH vitamin D level groups.
Abbreviations: COPD, chronic obstructive pulmonary disease; CAT, COPD assessment test.

Association Between Individual CAT Items and Vitamin D Insufficiency/Deficiency

When each item constituting the CAT score was analyzed individually, patients with vitamin D insufficiency/deficiency showed higher scores in the amount of phlegm ($p = 0.009$), chest tightness ($p = 0.021$), breathlessness walking upstairs ($p = 0.001$), home activity limitations ($p = 0.009$), and lack of energy ($p = 0.018$) than those with vitamin D sufficiency (Table 2). The difference in these five CAT items between the vitamin D insufficiency/deficiency and vitamin D sufficiency groups remained significant even after adjustment for age, sex, BMI, smoking history, CCI, post-bronchodilator FEV_1 (≥50% vs <50% pred), and season of blood draw (spring/fall vs summer vs winter) (Table 4). The distribution of the mean score for each CAT item in the three groups classified according to serum 25-OH vitamin D level also showed a prominent difference in breathlessness walking upstairs and limitations in home activities (Figure 4B).
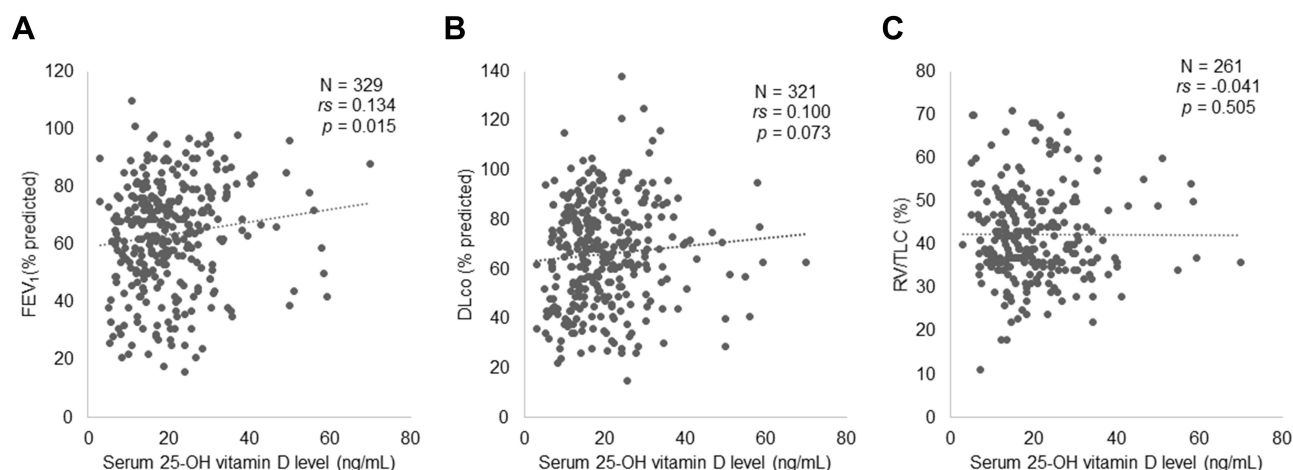
Figure 5 Correlation between serum 25-OH vitamin D level and lung function parameters in terms of (**A**) airflow limitation (FEV₁, % pred), (**B**) diffusing capacity (DLco, % pred), and (**C**) hyperinflation (RV/TLC, %).

Abbreviations: FEV₁, forced expiratory volume in 1 second; pred, predicted; DLco, diffusing capacity of the lung for carbon monoxide; RV, residual volume; TLC, total lung capacity.

Discussion

In this study, the majority of patients with stable COPD had vitamin D insufficiency/deficiency, and patients with vitamin D insufficiency/deficiency showed worse respiratory symptoms and quality of life than those with vitamin D sufficiency. Vitamin D levels were also positively associated with lung function, as measured by FEV₁. In a further analysis of each CAT item according to vitamin D status, vitamin D insufficiency/deficiency was associated with not only respiratory symptoms such as amount of phlegm, chest tightness, and breathlessness walking upstairs, but also non-respiratory symptoms such as home activity limitations and lack of energy, indicating that vitamin D insufficiency/deficiency might reflect poor general health status of COPD patients.

Consistent with previous studies,[17,18] our study showed an association between vitamin D deficiency/insufficiency and worse respiratory symptoms and low FEV₁. Interestingly, Burkes et al showed that vitamin D levels were associated with respiratory symptoms in middle-aged patients with COPD.[18] Contrary to Burkes' study, we found an association between vitamin D and respiratory symptoms only in older patients, but not in middle-aged patients (Supplementary Tables E3 and E4 and Supplementary Figure 1). This difference might be explained by the difference in COPD severity between middle-aged patients (<65 years old) and older patients (≥65 years old). In the Burkes study, lung function and respiratory symptoms were worse in middle-aged patients than in older patients, whereas they were worse in older patients than in middle-aged patients in our study. Thus, we speculated that the association between vitamin D levels and respiratory symptoms might be more pronounced as a function of COPD severity than as a function of age itself.

Table 3 The Association Between Respiratory Symptoms and Vitamin D Level < 30ng/mL

	Unadjusted		Adjusted*	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Total CAT score ≥ 10				
Vitamin D ≥ 30 ng/mL (N = 48)	Reference			
Vitamin D < 30 ng/mL (N= 281)	2.34 (1.17–4.68)	0.016	2.41 (1.20–4.82)	0.013
mMRC ≥ 2				
Vitamin D ≥ 30 ng/mL (N = 48)	Reference			
Vitamin D < 30 ng/mL (N= 281)	2.01 (0.98–4.10)	0.056	2.39 (1.08–5.32)	0.032

Notes: *Adjusted for age, sex, body mass index and smoking history (never vs ever), Charlson comorbidity index, post bronchodilator FEV₁ (≥ 50% vs < 50% pred), and season of blood draw (spring/fall vs summer vs winter).

Abbreviations: OR, odds ratio; CI, confidence interval; CAT, COPD assessment test; mMRC, modified Medical Research Council.

Table 4 The Total Score and Each Item of CAT by Vitamin D Level (< 30ng/mL Vs ≥ 30ng/mL)

	Vitamin D Level		Difference Between < 30 ng/mL vs ≥ 30 ng/mL (95% CI)*	P-value
	< 30 ng/mL (N=281)	≥ 30 ng/mL (N=48)		
CAT score, total	17.14 (8.57)	13.31 (8.08)	3.92 (1.51–6.34)	0.002
Cough frequency	1.90 (1.33)	1.52 (1.34)	0.33 (−0.07–0.74)	0.108
Amount of phlegm	2.34 (1.41)	1.77 (1.21)	0.57 (0.15–0.99)	0.008
Chest tightness	1.93 (1.39)	1.44 (1.25)	0.45 (0.04–0.86)	0.030
Breathlessness walking upstairs	3.23 (1.44)	2.46 (1.43)	0.74 (0.34–1.15)	<0.001
Home activities limitation	1.69 (1.52)	1.08 (1.25)	0.65 (0.23–1.06)	0.002
Not confident leaving home	1.69 (1.51)	1.33 (1.29)	0.40 (−0.02–0.82)	0.060
Sleep disturbance	1.91 (1.42)	1.77 (1.33)	0.21 (−0.22–0.63)	0.348
Lack of energy	2.43 (1.33)	1.94 (1.26)	0.58 (0.20–0.96)	0.003

Notes: *Adjusted for age, sex, body mass index and smoking history (never vs ever), Charlson comorbidity index, post bronchodilator FEV_1 (≥ 50% vs < 50% pred), and season of blood draw (spring/fall vs summer vs winter).
Abbreviations: CI, confidence interval; CAT, COPD assessment test.

Our study further investigated the association between vitamin D levels and individual items constituting the CAT score. In particular, the CAT scores corresponding to sputum, chest tightness, breathlessness going up hills/stairs, home activity limitations, and feeling a lack of energy were significantly higher in patients with vitamin D insufficiency/ deficiency than in those with vitamin D sufficiency. In addition to respiratory symptoms, we showed that non-respiratory symptoms such as home activity limitations and feeling a lack of energy were significantly higher in patients with vitamin D insufficiency/deficiency than in those with vitamin D sufficiency. Given the nature of the cross-sectional study, we cannot ascertain the causality between vitamin D and these respiratory and non-respiratory symptoms, but as a lower level of vitamin D might result in poor muscle function, weakness, and myalgia,[36] respiratory muscle weakness may contribute to respiratory impairment. Furthermore, skeletal muscle weakness and exertional dyspnea result in decreased outdoor physical activity, which in turn leads to a decrease in sun exposure.

Several other mechanisms could be considered regarding the influence of vitamin D insufficiency or deficiency on respiratory symptoms in COPD patients. Vitamin D has antibacterial and antiviral effects. Several studies have indicated a clinical association between vitamin D insufficiency and respiratory infections. A Finnish study conducted on 800 healthy men reported that subjects with 25-OH vitamin D levels <40 nmol/L had significantly more days of absence from duty because of respiratory infections.[37] In a study carried out in 2135 patients with prehospitalization vitamin D measurements, patients with vitamin D <10 ng/mL had 2.33 times more hospital-acquired bloodstream infections.[11] A recent meta-analysis of data from 46 randomized controlled trials of vitamin D supplementation for the prevention of acute respiratory infections revealed a protective effect of this intervention.[38] Second, vitamin D has various immuno-modulatory effects.[7–10] The dysregulated immune response attributed to vitamin D insufficiency/deficiency leads to the development of chronic inflammation and aggravation of clinical symptoms.

In addition, among the stable COPD patients included in our study, the median 25-OH vitamin D level was 20.2 ng/ mL, and 85.2% had vitamin D insufficiency/deficiency. Various causes, including lower food intake, skin aging with reduced capacity for vitamin D synthesis, absence of sun exposure, increased catabolism by glucocorticoids, impaired activation due to renal dysfunction, and lower storage capacity in muscles or fat could contribute to defective vitamin D status in patients with COPD.[13]

Our study has several limitations. First, given the observational nature of the study, there is always the possibility that selection bias or confounding might have influenced our findings. Second, this cross-sectional study could not explain the causal relationship between vitamin D levels and COPD. Additional prospective studies are needed to determine whether vitamin D insufficiency/deficiency leads to worsening of clinical symptoms or whether severely symptomatic patients acquire vitamin D insufficiency/deficiency. More prospective studies are necessary to determine whether vitamin D intake improves clinical symptoms.

Conclusion

This study adds to the existing evidence of an association between vitamin D deficiency and worse respiratory symptoms in patients with COPD by demonstrating that vitamin D insufficiency/deficiency (which is obviously more prevalent than deficiency alone) is also associated with more dyspnea and a higher impact of COPD symptoms on health status compared with vitamin D sufficiency. In addition, we showed that increasing levels of vitamin D are significantly correlated with the total CAT score as well as individual CAT items, especially breathlessness, home activity limitations, and lack of energy. Although current GOLD reports recommend assessment of vitamin D status for patients hospitalized for exacerbation of COPD and vitamin D supplementation only for those with severe deficiency, this study suggests that vitamin D supplementation might improve respiratory symptoms and health status in stable COPD patients with vitamin D insufficiency. Further studies are warranted to validate this finding, but meanwhile, clinicians should pay more attention to vitamin D insufficiency/deficiency in stable COPD patients with respiratory symptoms.

Abbreviations

COPD, chronic obstructive pulmonary disease; mMRC, modified Medical Research Council; CAT, COPD assessment test; CVD, cardiovascular disease; DLco, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; BMI, body mass index; OR, odds ratio; CI, confidence interval; CCI, Charlson comorbidity index.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding authors (Hye Yun Park or Jun Hyeok Lim) in response to reasonable requests.

Ethics Approval

This study was approved by the Institutional Review Board of Samsung Medical Center, and the requirement for informed consent was waived because of the retrospective nature of the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Author Contributions

Chaiyoung Lee and Sun Hye Shin are co-first authors of this study. Hye Yun Park and Jun Hyeok Lim contributed equally to this work and supervised the work.

All authors made a significant contribution to the work, including the conception, study design, execution, acquisition of data, analysis, and interpretation; participated in drafting, revising, or critically reviewing the manuscript; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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