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ORIGINAL RESEARCH

Association of Severe Vitamin D Deficiency with Hospitalization in the Previous Year in Hospitalized Exacerbated COPD Patients

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Purpose: Vitamin D deficiency (VDD, 25-hydroxyvitamin D < 20 ng/mL) has been reported associated with exacerbation of chronic obstructive pulmonary disease (COPD) but sometimes controversial. Research on severe vitamin D deficiency (SVDD, 25-hydroxyvitamin D < 10 ng/mL) in exacerbation of COPD is limited.

Patients and Methods: We performed a retrospective observational study in 134 hospitalized exacerbated COPD patients. 25-hydroxyvitamin D was modeled as a continuous or dichotomized (cutoff value: 10 or 20 ng/mL) variable to evaluate the association of SVDD with hospitalization in the previous year. Receiver operator characteristic (ROC) analysis was performed to find the optimal cut-off value of 25-hydroxyvitamin D.

Results: In total 23% of the patients had SVDD. SVDD was more prevalent in women, and SVDD group tended to have lower blood eosinophils counts. 25-hydroxyvitamin D level was significantly lower in patients who were hospitalized in the previous year (13.6 vs 16.7 ng/mL, $P = 0.044$), and the prevalence of SVDD was higher (38.0% vs 14.3%, $P = 0.002$). SVDD was independently associated with hospitalization in the previous year [odds ratio (OR) 4.34, 95% CI 1.61–11.72, $P = 0.004$] in hospitalized exacerbated COPD patients, whereas continuous 25-hydroxyvitamin D and VDD were not ($P = 0.1$, $P = 0.9$, separately). The ROC curve yielded an area under the curve of 0.60 (95% CI 0.50–0.71) with an optimal 25-hydroxyvitamin D cutoff of 10.4 ng/mL.

Conclusion: SVDD probably showed a more stable association with hospitalization in the previous year in hospitalized exacerbated COPD patients. Reasons for lower eosinophil counts in SVDD group needed further exploration.

Keywords: association, vitamin D, severe deficiency, hospitalization for exacerbation, COPD

Introduction

Chronic obstructive pulmonary disease (COPD) carries a heavy healthcare burden because of its increasing prevalence,[1] frequent exacerbations, and its requirement for hospital admission.[2] The current treatment options are insufficient because of the unclear underlying cellular and molecular mechanisms of COPD.[3,4]

Vitamin D deficiency (25-hydroxyvitamin D level < 20 ng/mL, VDD)[5] is prevalent in COPD.[6,7] It has been implicated as a risk factor for airflow limitation and pulmonary structure and function.[8–10] Its association with lung function decline and exacerbations in COPD is extensively reported, but sometimes controversial.[11,12] The Global Initiative for Chronic Obstructive (GOLD, 2024) recommends that all patients hospitalized for exacerbation of COPD be assessed and investigated for severe vitamin D deficiency (25-hydroxyvitamin D level < 10 ng/mL, SVDD),[5] followed by supplementation if required, based mainly on inference of meta-analysis.[13] However, real-world research about SVDD in severe COPD exacerbation is limited.

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Therefore, we performed a retrospective observational study in patients hospitalized for exacerbation of COPD to evaluate the association of SVDD with hospitalization for exacerbation.

Materials and Methods

Patients

Demographic and clinical data were retrospectively collected at Beijing Chao-Yang Hospital, Capital Medical University (Beijing, China) from January 2019 to October 2022. The inclusion criteria were age >40 years, a post-bronchodilator ratio of forced expiratory volume in 1 s to forced vital capacity (FEV_1/FVC) <0.7 at first diagnosis for COPD according to the diagnostic criteria of GOLD,[13] exacerbation of COPD as a primary discharge diagnosis (including both acute exacerbation of COPD defined as episodes of symptom worsening that have significant adverse consequences for patients[14] and pneumonic COPD with radiographic consolidation[15]), and available data on 25-hydroxyvitamin D. After excluding patients taking vitamin D supplements (n = 24), 134 patients were enrolled.

Data Collection

The demographic and clinical data of patients, including the discharge diagnosis, comorbidities, smoking habits, season in which 25-hydroxyvitamin D was examined, serum 25-hydroxyvitamin D level, lung function and fractional exhaled nitric oxide measured 6 months prior to admission, IgE, and blood eosinophils counts, were collected from the electronic medical records of the hospital. Comorbidities included pneumonia, respiratory failure, heart failure, diabetes, cerebral infarction, and hypoalbuminemia.[16] Serum 25-hydroxyvitamin D levels were analyzed by a chemiluminescence method using a 25-hydroxyvitamin D determination kit (YHLO, Shenzhen, China, C86023). Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2).

The study was approved by the Ethics Committee of Beijing Chao-Yang Hospital, Capital Medical University (No. 2023-ke-390) in accordance with the Declaration of Helsinki. The subjects' sensitive information has been erased and de-identified in the statistical data to effectively protect their privacy and eliminate the risk of privacy breaches. Given the anonymous nature of the data, informed consent was waived for this study.

Statistical Analysis

A two-sample Student's *t*-test, the Mann–Whitney *U*-test, or the X^2 test was used to compare the prevalence of continuous or categorical variables between the groups. Bivariate logistic regression analysis models were used to determine the relationships between 25-hydroxyvitamin D levels (continuous or dichotomized) with hospitalization for COPD exacerbation in the previous year. Covariates in the multivariable model were selected on the basis of clinical relevance,[17] including sex, age, BMI, current smoking status, and the season in which 25-hydroxyvitamin D was examined. Receiver operator characteristic (ROC) analysis was performed to find the optimal cut-off value of 25-hydroxyvitamin D in relation to hospitalization for exacerbation in the prior year.

All analyses were performed using IBM SPSS Statistics 22.0. $P < 0.05$ was considered statistically significant for all the results.

Results

Patients' Characteristics

As presented in Table 1, the mean patient age was 70.0 years, 84% of patients were male, and 31% were current smokers. Severe COPD (GOLD stage III–IV) was present in 51% of 59 patients for whom lung function data in the 6 months prior to admission were available (75 without lung function data). The median 25-hydroxyvitamin D level was 15.2 ng/mL (95% CI = 10.4–21.2), with 97 patients (72%) having VDD and 31 patients (23%) having SVDD.

The comparison between the SVDD (n = 31) and non-SVDD (n = 103) groups revealed significant differences in sex ($P = 0.007$), the current-smoking status ($P = 0.040$), the season of 25-hydroxyvitamin D measurement ($P = 0.013$), and blood eosinophil counts ($P = 0.017$).

Table 1 Characteristics of Patients

Variable	Overall N = 134[a]	25-(OH)D<10 ng/mL N = 31[a]	25-(OH)D≥10 ng/mL N = 103[a]	*P*-value[b]
Sex, male	112 (84%)	21 (68%)	91 (88%)	0.007
Age	70.0 (64.0, 76.0)	70.0 (66.0, 79.0)	71.0 (63.0, 76.0)	0.6
BMI (kg/m^2)	22.6 (20.8, 24.5)	22.2 (21.3, 26.3)	22.8 (20.7, 24.2)	0.8
Current smoker	42 (31%)	5 (16%)	37 (36%)	0.040
GOLD stage				0.4
1	7 (12%)	2 (13%)	5 (11%)	
2	22 (37%)	7 (47%)	15 (34%)	
3	22 (37%)	6 (40%)	16 (36%)	
4	8 (14%)	0 (0%)	8 (18%)	
N/A	75	16	59	
25-(OH)D	15.2 (10.4, 21.2)	8.4 (7.9, 9.5)	17.1 (13.3, 22.8)	<0.001
25-(OH)D category				N/A
<10 ng/mL	31 (23%)	31 (100%)	0 (0%)	
10 to <20 ng/mL	66 (49%)	0 (0%)	66 (64%)	
20 to <30 ng/mL	31 (23%)	0 (0%)	31 (30%)	
≥30 ng/mL	6 (5%)	0 (0%)	6 (6%)	
Season of 25-(OH)D examined				0.013
Spring	40 (30%)	9 (29%)	31 (30%)	
Summer	40 (30%)	4 (13%)	36 (35%)	
Autumn	24 (18%)	5 (16%)	19 (18%)	
Winter	30 (22%)	13 (42%)	17 (17%)	
Comorbidities				
Pneumonia	46 (34%)	12 (39%)	34 (33%)	0.6
Respiratory failure	38 (28%)	9 (29%)	29 (28%)	0.9
Heart failure	24 (18%)	8 (26%)	16 (16%)	0.2
Diabetes	27 (20%)	8 (26%)	19 (18%)	0.4
Cerebral infarction	18 (13%)	3 (10%)	15 (15%)	0.5
Low serum albumin	79 (59%)	19 (61%)	61 (58%)	0.8
Eosinophils (x10^9/L)	0.1 (0.1, 0.3)	0.1 (0.1, 0.2)	0.2 (0.1, 0.3)	0.017
Eosinophils, %	1.8 (0.9, 3.2)	1.1 (0.6, 2.3)	2.1 (0.9, 3.5)	0.054
	N=70	N=18	N=52	
FEV1, pre-BD (L)	1.0 (0.7, 1.4)	1.1 (0.7, 1.3)	1.0 (0.7, 1.6)	0.9
FEV1%pred, pre-BD	47.6 (19.3)	52.6 (17.9)	45.8 (19.6)	0.1
FEV1/FVC%, pre-BD	46.3 (12.9)	45.7 (10.3)	46.5 (13.7)	0.9
	N=59	N=15	N=44	
FEV1, post-BD (L)	1.1 (0.8, 1.7)	1.1 (0.8, 1.4)	1.1 (0.8, 1.7)	0.6
FEV1%pred, post-BD	48.5 (32.5, 70.1)	56.1 (42.9, 63.0)	46.6 (30.4, 71.9)	0.3
FEV1/FVC%, post-BD	44.0 (36.5, 55.5)	48.0 (39.8, 52.5)	43.3 (35.1, 57.7)	0.8
	N=54	N=15	N=39	
FeNO (ppb)	24.0 (16.5, 34.0)	22.0 (13.0, 57.0)	25.0 (17.0, 35.0)	0.1
	N=80	N=15	N=65	
IgE (U/mL)	80.1 (23.8, 392.8)	257.0 (59.0, 759.5)	44.1 (16.3, 265.0)	0.8

Notes: [a]All values represent mean (SD) or No. (%) or Median (IQR). [b]Student's *t*-test; Mann–Whitney-test; Chi-squared test.
Abbreviations: 25-(OH)D, 25-hydroxyvitamin D; BMI, body mass index; GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; BD, bronchodilator.

25-Hydroxyvitamin D Levels and SVDD Prevalence in Hospitalized in the Previous Year Participants

The 25-hydroxyvitamin D level was significantly lower in patients requiring hospitalization for exacerbation than in their counterparts [13.6 ng/mL, 95% confidence interval (CI) = 9.7–20.4 vs 16.7 ng/mL, 95% CI = 11.2–22.3, $P = 0.044$, Figure 1a], and rate of SVDD was also higher in patients requiring hospitalization (38.0% vs 14.3%, $P = 0.002$, Figure 1b).

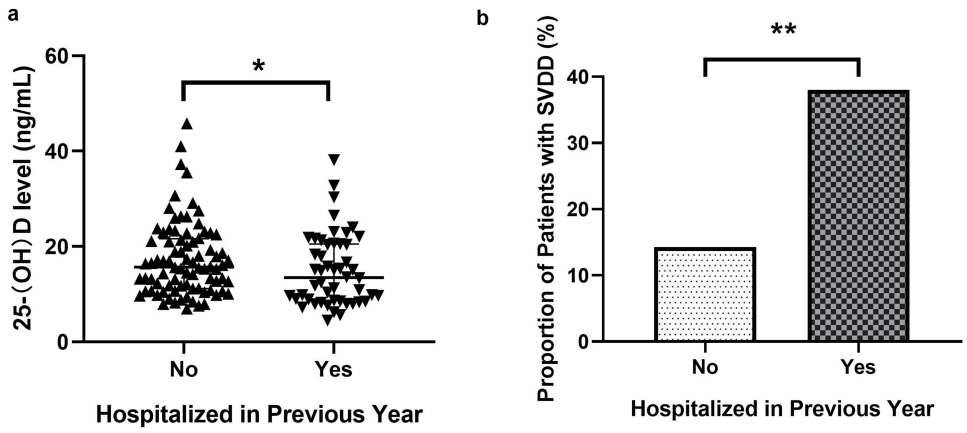

Figure 1 (**a**) 25-hydroxyvitamin D level and (**b**) proportion of patients with SVDD in participants with or without hospitalization in the previous year. *P<0.05, ** P < 0.01.

Association of SVDD with Hospitalization for Exacerbation in the Previous Year

After adjusting for sex, age, BMI, current smoking, and season of 25-hydroxyvitamin D examination, 25-hydroxyvitamin D as a continuous variable or dichotomized by 20 ng/mL did not show statistical significance in logistic regression analysis [odds ratio (OR) = 0.96, 95% CI = 0.91–1.01, P = 0.1 and OR = 1.05, 95% CI = 0.46–2.39, P = 0.9, separately]. However, 25-hydroxyvitamin D as a variable dichotomized by 10 ng/mL was independently associated with hospitalization for COPD exacerbation (OR = 4.34, 95% CI = 1.61–11.72, P = 0.004; Table 2).

ROC Analysis

The ROC curve for 25-hydroxyvitamin D levels in relation to hospitalization for COPD exacerbation in the previous year yielded an area under the curve (AUC) of 0.60 (95% CI = 0.50–0.71). The optimal cutoff was 10.4 ng/mL (Figure 2).

Discussion

In this retrospective study of 134 hospitalized exacerbated COPD patients, the prevalence of SVDD was 23%, and SVDD was more prevalent in women. Season of 25-(OH)D examined varied between SVDD group and non-SVDD group. Comorbidities did not vary between these two groups. As reported before, women had a higher prevalence of vitamin

Table 2 Logistic Regression Modeling [a] of Associations Between 25-(OH)D and Hospitalization for Exacerbation in Previous Year

Characteristics	Hospitalized for AECOPD in Previous Year								
	Continuous 25-(OH)D			Dichotomized 25-(OH)D by 20 ng/mL			Dichotomized 25-(OH)D by 10 ng/mL		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
25-(OH)D	0.96	0.91,1.01	0.1	1.05	0.46, 2.39	0.9	4.34	1.61, 11.72	0.004
Sex, male	1.45	0.51,4.12	0.5	1.25	0.44, 3.53	0.7	1.94	0.63, 5.99	0.2
Age	1.00	0.95,1.04	0.8	0.99	0.95, 1.04	0.7	0.99	0.95, 1.04	0.7
BMI	0.94	0.85, 1.04	0.3	0.95	0.86, 1.05	0.3	0.94	0.84, 1.04	0.2
Current-smoking	0.25	0.10,0.63	0.003	0.26	0.10, 0.65	0.004	0.28	0.11, 0.72	0.008
Season of 25-(OH)D examined									
Spring									
Summer	0.55	0.21,1.46	0.2	0.50	0.19, 1.32	0.2	0.60	0.22, 1.62	0.3
Autumn	0.38	0.12,1.24	0.1	0.33	0.11, 1.06	0.062	0.32	0.09, 1.07	0.063
Winter	0.52	0.18,1.49	0.2	0.57	0.20, 1.61	0.3	0.39	0.13, 1.20	0.1

Notes: [a] Adjusted for all covariates in table N=134.
Abbreviations: 25-(OH)D, 25-hydroxyvitamin D; BMI, body mass index; OR, odds ratio; CI, confidence interval.

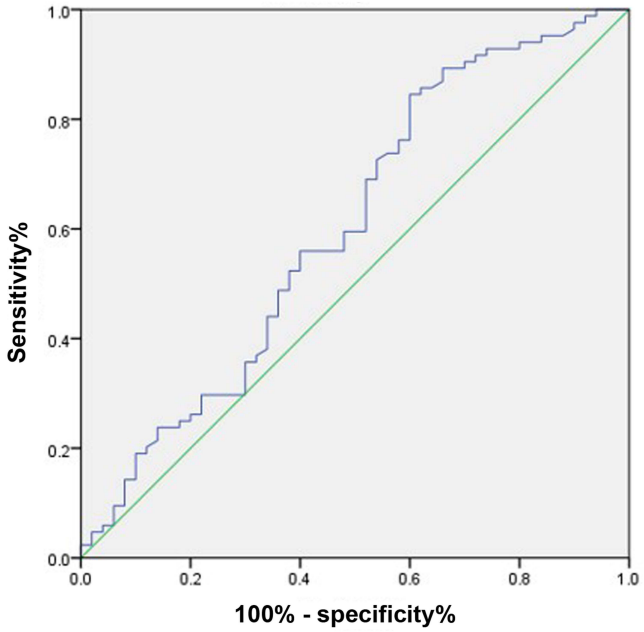

Figure 2 Receiver operating characteristic curve for hospitalization in the previous year.

D deficiency and insufficiency.[18,19] In addition, vitamin D deficiency was reported to be more prevalent in winter and spring by a cross-sectional study of urban Beijing residents.[20] Besides, COPD patients with vitamin D deficiency were reported to have no significant differences in the severity of comorbidities as their counterparts without vitamin D deficiency in a study of 236 patients with COPD.[21] These were consistent with our observations.

Hospitalization for exacerbation is recognized as a major event in the natural history of COPD because of its negative effects on lung function, survival, the risk of readmission, and quality of life.[16] Among participants hospitalized in the previous year, 25-hydroxyvitamin D levels were lower than non-hospitalized patients, and prevalence of SVDD was higher. Through regression analysis, we observed that SVDD was independently associated with hospitalization in the previous year. A previous retrospective observational cohort study had reported the same results. They observed that SVDD was related to more frequent COPD exacerbation and hospitalization during the year prior to the measurement of vitamin D in 97 patients with COPD not taking vitamin D supplements.[19]

However, continuous and dichotomized (cutoff, 20 ng/mL) 25-hydroxyvitamin D did not show significant association with hospitalization in the previous year. Previously published studies have reported the association between VDD and exacerbation in COPD, but the results were inconsistent. An analysis of the SPIROMICS cohort modeled 25-hydroxyvitamin D as a continuous and dichotomized variable (<20 ng/mL vs ≥20 ng/mL) reported that VDD was associated with worse cross-sectional and longitudinal lung function and increased rates of COPD exacerbation in patients in clinical centers.[11,22] While another study conducted in the primary care setting reported no association of VDD with COPD exacerbation and mortality.[12] Differences in 25-hydroxyvitamin D levels and COPD populations included in these studies were noted. Here in our study, we focused specifically on SVDD and hospitalized COPD patients. Our results extended the association of 25-hydroxyvitamin D with exacerbation by revealing a possibly more stable relationship between SVDD and hospitalization in the previous year, rather than continuous 25-hydroxyvitamin D or a dichotomy based on a cutoff at 20 ng/mL.

The ROC curve revealed that the optimal 25-hydroxyvitamin D cut-off value in relation to hospitalization in the previous year was 10.4 ng/mL, which supported the results of the association between SVDD and hospitalized for exacerbation in the previous year.

The effect of vitamin D supplementation on COPD exacerbation was inconsistent.[23–25] A post-hoc analysis of a double-blind, randomized controlled trial (RCT) of 30 participants with SVDD demonstrated that vitamin

D supplements reduced the risk of COPD exacerbation.[26] But it was with very small sample size. Our study highlighted the need of further RCTs of vitamin D supplementation in hospitalized patients with COPD and SVDD.

Blood eosinophil counts were lower in the SVDD group. It has been reported by a cohort of 6163 healthy people in China that, blood eosinophil counts were lower in patients with SVDD than in those with VDD, 25-hydroxyvitamin D insufficiency, and normal 25-hydroxyvitamin D levels.[27] This was consistent with our observation, but the reasons were not clear currently. Active vitamin D has been reported to prolong human eosinophil survival by upregulating C-X-C chemokine receptor type 4 expression.[28] At the same time, vitamin D was considered to exert a direct effect on reducing necrosis in eosinophils.[29] These might be potential mechanisms underlying, and further research is needed.

This study had several limitations. First, severity of COPD can be evaluated by objective measures such as the BODE index. A regression model with the BODE index would be meaningful to consider the confounding effect of COPD severity. Nevertheless, it is important to note that this is a retrospective observational study. The data on four factors in the BODE index are incomplete, particularly regarding exercise tolerance assessed through a 6-minute walk test. Second, lung function data were incomplete, and thus, the distribution of GOLD stages in the cohort at baseline was unclear. Finally, 25-hydroxyvitamin D levels were measured at the end of the observation period rather than at the beginning, and its levels might differ between these time points. Generally, serum vitamin D levels remained stable if patients' living environments and food intake habits did not change.[30] Patients involved in the present study were generally Beijing residents, and those taking vitamin D supplement were excluded from this study. Therefore, it might be speculated that the levels of vitamin D measured in the present study were similar to those in the prior year. At the same time, a retrospective study could avoid the criticism of not treating patients with SVDD.[19]

Conclusion

In this study, SVDD was more prevalent in women, and SVDD group tended to have lower blood eosinophils counts. 25-hydroxyvitamin D levels were significantly lower in participants hospitalized in the previous year, and proportion of SVDD was higher in this group. SVDD showed an independent association with hospitalization for exacerbation in the previous year after adjusting relevant covariates, rather than continuous 25-hydroxyvitamin D or a dichotomy based on a cutoff at 20 ng/mL. We extended the recognition by revealing that SVDD might behave in a potentially more stable way. Lower eosinophil counts in SVDD group needs for further exploration.

Abbreviations

25-(OH)D, 25-hydroxyvitamin D; VDD, vitamin D deficiency; SVDD, severe vitamin D deficiency; BMI, body mass index; GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; BD, bronchodilator; OR, odds ratio; CI, confidence interval.

Ethics Approval and Informed Consent

The study was approved by the Ethics Committee of Beijing Chao-Yang Hospital, Capital Medical University (No. 2023-ke-390) in accordance with the Declaration of Helsinki. The subjects' sensitive information has been erased and de-identified in the statistical data to effectively protect their privacy and eliminate the risk of privacy breaches. Given the anonymous nature of the data, informed consent was waived for this study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree 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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