International Journal of Chronic Obstructive Pulmonary Disease

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

The Role of Severe Vitamin D Deficiency in Predicting the Risk of Severe Exacerbation in Patients With Chronic Obstructive Pulmonary Disease

Li Zhou[1–4], Cunqiao Han[5], Yue Zhou[1–4]

[1]Department of Emergency Medicine, West China Hospital, Sichuan University, Chengdu, People's Republic of China; [2]West China School of Nursing, Sichuan University, Chengdu, People's Republic of China; [3]Disaster Medical Center, Sichuan University, Chengdu, People's Republic of China; [4]Nursing Key Laboratory of Sichuan Province, Chengdu, People's Republic of China; [5]Department of Emergency Medicine, Shangjinnanfu Hospital, West China Hospital, Sichuan University, Chengdu, People's Republic of China

Correspondence: Yue Zhou, Department of Emergency Medicine, West China Hospital, Sichuan University, No. 37 Guoxue Road, Chengdu, 610041, Sichuan, People's Republic of China, Tel +86-028-62539203, Email zhouyuesccd@163.com

Background: This study aims to investigate the association between vitamin D levels and the risk of severe acute exacerbations of chronic obstructive pulmonary disease (AECOPD).

Methods: We conducted a prospective observational study with 636 COPD patients admitted for exacerbations between January 2021 and December 2022. Patients were categorized based on serum 25-hydroxyvitamin D levels: severe deficiency (<10 ng/mL), deficiency (10–20 ng/mL), insufficiency (20–30 ng/mL), or sufficiency (>30 ng/mL). Severe exacerbation was defined when the patient visits an emergency room or is hospitalized due to COPD exacerbation. Multivariate Cox regression was used to evaluate the risk associated with vitamin D deficiency.

Results: Over an 18-month follow-up, 178 (28.0%) patients experienced at least one severe exacerbation. The severe deficiency group had the highest exacerbation rate (40.6%), followed by deficiency (27.8%), insufficiency (22.5%), and sufficiency (18.1%) groups ($P<0.01$). Multivariate Cox regression analysis showed that severe vitamin D deficiency was significantly associated with an increased risk of severe exacerbations (HR=2.74, 95% CI: 1.55–4.84; $P<0.01$) compared to vitamin D sufficiency.

Conclusion: Severe vitamin D deficiency is a significant predictor of severe COPD exacerbations, highlighting the importance of routine vitamin D assessment and supplementation in COPD management.

Keywords: acute exacerbations, COPD, risk factors, vitamin D deficiency

Introduction

Chronic obstructive pulmonary disease (COPD) is a long-term respiratory condition marked by enduring airflow obstruction and a heightened inflammatory response in the airways and lungs, typically due to exposure to harmful particles or gases.[1,2] It significantly contributes to global morbidity and mortality, with acute exacerbations being a major factor in the disease's burden.[3,4] Acute exacerbations of COPD (AECOPD) are episodes of sudden symptom worsening that require additional treatment and are linked to a swift decline in lung function, decreased quality of life, and increased mortality.[5,6] Thus, identifying modifiable risk factors for severe exacerbations is crucial for improving patient outcomes and reducing healthcare costs.

Vitamin D, a fat-soluble vitamin primarily known for its role in calcium and phosphate metabolism, has garnered increasing attention for its immunomodulatory and anti-inflammatory properties.[7] Evidence suggests that vitamin D exerts its effects on immune cells by regulating the production of antimicrobial peptides such as cathelicidin, modulating inflammatory cytokines, and promoting innate immune responses.[8] These mechanisms are critical in respiratory diseases where immune dysregulation and infection are key contributors to exacerbations.[9] Additionally, vitamin D deficiency has been linked to impaired lung function and increased susceptibility to respiratory infections, both of which are major triggers of

Received: 1 August 2024
Accepted: 28 December 2024
Published: 22 January 2025

AECOPD.[10] The prevalence of vitamin D deficiency is notably high among COPD patients, with reports indicating rates as high as 60%-90% depending on the population studied.[11]

Despite growing evidence on the link between vitamin D and COPD, the specific role of severe vitamin D deficiency (<10 ng/mL) in predicting severe AECOPD remains underexplored. Previous studies have shown inconsistent results, likely due to variability in cut-off values and study populations. Therefore, this study aims to clarify the association between severe vitamin D deficiency and the risk of severe exacerbations in COPD patients. We hypothesize that severe vitamin D deficiency is a significant predictor of severe AECOPD and that routine monitoring and intervention could mitigate exacerbation risks.

Materials and Methods

Patients

This prospective, observational study involved patients admitted to our hospital for COPD exacerbations from January 2021 to December 2022. Inclusion criteria were patients aged 40 years and above with a confirmed COPD diagnosis per the 2020 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines,[12] with a post-bronchodilator FEV_1/FVC ratio below 0.7. Exclusion criteria included bronchial asthma, other chronic respiratory conditions, systemic illnesses requiring long-term corticosteroid use, malignancies, and pregnancy or peripartum status. To ensure the validity of the findings, patients who were taking medications that could influence serum vitamin D concentrations, such as corticosteroids, calcium, phosphorus, or vitamin D supplements, were excluded from the study.

Data Collection and Outcomes

Eligible patients were categorized into four groups based on their serum 25-hydroxyvitamin D (25-OHD) levels at admission: severe deficiency (<10 ng/mL), deficiency (10–20 ng/mL), insufficiency (20–30 ng/mL) or sufficiency (>30 ng/mL).[13–15]

Baseline demographic and clinical information including age, gender, body mass index (BMI), smoking habit, disease duration of COPD, the number of severe COPD exacerbations in the past 1 year, pulmonary function test, GOLD stage, GOLD group, COPD assessment test (CAT) score, blood eosinophil counts, inhalation therapies used, and comorbidities were documented. All subjects were followed up for 18 months.

The primary endpoint was severe exacerbation occurrence, assessed monthly via telephone interviews or medical record reviews. Patients lost to follow-up were censored at their last contact. According to the Rome classification,[16] AECOPD severity as mild when only symptoms are reported and the patient is treated with inhaled short-acting bronchodilators; moderate when the patient receives antibiotics, systemic corticosteroids, or both; and severe when the patient visits an emergency room or is hospitalized because of the event. In this study, severe exacerbations were selected as the primary endpoint due to their clear and consistent definition and significant clinical impact. Mild and moderate exacerbations, while valuable for a broader understanding of disease progression, were not included due to challenges in ensuring accurate and reliable data collection.

Statistical Analysis

To evaluate the association between baseline vitamin D levels and severe AECOPD, we primarily used Cox proportional hazards regression, as this method accounts for both the occurrence and the timing of events during the follow-up period. The proportional hazards assumption was tested and confirmed. For sensitivity analysis, we also performed logistic regression to assess the relationship between vitamin D levels and the occurrence of severe AECOPD as a binary outcome. Logistic regression analysis treated the occurrence of severe AECOPD as a single endpoint during the follow-up period, irrespective of the timing of events. Statistical significance was set at $P<0.05$ for all tests.

Statistical analyses were conducted using SPSS version 22.0 (IBM Corp., Armonk, NY).

Results

This study included 636 patients: 160 (25.2%) with severe vitamin D deficiency, 198 (31.1%) with deficiency, 173 (27.2%) with insufficiency, and 105 (16.5%) with sufficient levels. Table 1 provides the demographic and clinical

Table 1 Patients' Baseline Demographic and Clinical Profiles

	Vitamin D category				P value
	Severe deficiency (<10 ng/mL)	Deficiency (10–20 ng/mL)	Insufficiency (20–30 ng/mL)	Sufficiency (>30 ng/mL)	
N	160 (25.2%)	198 (31.1%)	173 (27.2%)	105 (16.5%)	
Age, years	69.4±3.0	69.1±3.1	68.8±3.4	68.9±2.8	0.29
Gender, n (%)					
Male	129 (80.6%)	151 (76.3%)	133 (76.9%)	75 (71.4%)	0.39
Female	31 (19.4%)	47 (23.7%)	40 (23.1%)	30 (28.6%)	
BMI, kg/m^2	24.3±1.4	24.6±1.3	24.4±1.2	24.3±1.2	0.15
Smoking status, n (%)					
Never-smoker	41 (25.6%)	57 (28.8%)	59 (34.1%)	29 (27.6%)	0.24
Ex-smoker	82 (51.2%)	96 (48.5%)	83 (48.0%)	44 (41.9%)	
Smoker	37 (23.1%)	45 (22.7%)	31 (17.9%)	32 (30.5%)	
Disease duration of COPD, n (%)					
<3 years	44 (27.5%)	45 (22.7%)	46 (26.6%)	36 (34.3%)	0.16
3–5 years	77 (48.1%)	107 (54.0%)	81 (46.8%)	54 (51.4%)	
>5 years	39 (24.4%)	46 (23.2%)	46 (26.6%)	15 (14.3%)	
Frequency of hospitalization due to AECOPD in the past 12 months, n (%)					
<2	105 (65.6%)	144 (72.7%)	131 (75.7%)	93 (88.6%)	<0.01
≥2	55 (34.4%)	54 (27.3%)	42 (24.3%)	12 (11.4%)	
Pulmonary function test					
FEV_1/FVC, %	52.2 ± 5.6	52.9 ± 6.0	52.0 ± 5.4	53.1 ± 6.3	0.29
FEV_1 pred, %	62.6 ± 9.2	62.2 ± 9.4	62.4 ± 9.3	63.0 ± 9.6	0.90
GOLD stage, n (%)					
Stage 1	9 (5.6%)	8 (4.0%)	9 (5.2%)	6 (5.7%)	0.74
Stage 2	38 (23.8%)	61 (30.8%)	52 (30.1%)	35 (33.3%)	
Stage 3	77 (48.1%)	89 (44.9%)	70 (40.5%)	46 (43.8%)	
Stage 4	36 (22.5%)	40 (20.2%)	42 (24.3%)	18 (17.1%)	
GOLD group, n (%)					
A	14 (8.8%)	19 (9.6%)	14 (8.1%)	11 (10.5%)	
B	69 (43.1%)	93 (47.0%)	98 (56.6%)	73 (69.5%)	<0.01
E	77 (48.1%)	86 (43.4%)	61 (35.2%)	21 (20.0%)	
CAT score, n (%)					
0–10	16 (10.0%)	21 (10.6%)	15 (9.1%)	15 (9.6%)	0.58
11–20	81 (50.6%)	91 (46.0%)	75 (43.4%)	46 (43.8%)	
21–30	50 (31.3%)	73 (36.9%)	62 (35.8%)	43 (41.0%)	
31–40	13 (8.1%)	13 (6.6%)	21 (12.1%)	9 (8.6%)	
Blood eosinophil counts					
<100	41 (25.6%)	43 (21.7%)	40 (23.1%)	25 (23.8%)	
100–300	84 (52.5%)	102 (51.5%)	94 (54.3%)	56 (53.3%)	0.93
≥300	35 (21.9%)	53 (26.8%)	39 (22.5%)	24 (22.9%)	
Inhalation therapies used					
ICS	11 (6.3%)	11 (5.6%)	9 (5.2%)	5 (4.8%)	
LAMA	8 (5.0%)	9 (4.5%)	10 (5.8%)	7 (6.7%)	
LABA/LAMA	16 (10.0%)	23 (11.6%)	20 (11.6%)	12 (11.4%)	0.32
ICS/LABA	67 (41.9%)	72 (36.4%)	73 (42.2%)	40 (38.1%)	
ICS/LABA+LAMA or ICS/LABA/LAMA	55 (34.4%)	71 (35.9%)	61 (35.3%)	34 (32.4%)	
Comorbidity, n (%)					
Diabetes	63 (39.4%)	56 (28.3%)	33 (19.1%)	18 (17.1%)	<0.01
Hypertension	60 (37.5%)	60 (30.3%)	43 (24.9%)	21 (20.0%)	<0.01
Cardiovascular diseases	87 (54.4%)	83 (41.9%)	77 (44.5%)	31 (29.5%)	<0.01

Notes: BMI, body mass index; COPD, chronic obstructive pulmonary disease; AECOPD, Acute Exacerbation of COPD; GOLD, Global Initiative for Chronic Obstructive Lung Disease; CAT, COPD assessment test; EV_1, forced expiratory volume in 1s; FVC, forced vital capacity; LABA, long-acting beta- agonists; LAMA, long-acting antimuscarinic antagonists; ICS, inhaled corticosteroids.

https://doi.org/10.2147/COPD.S489650

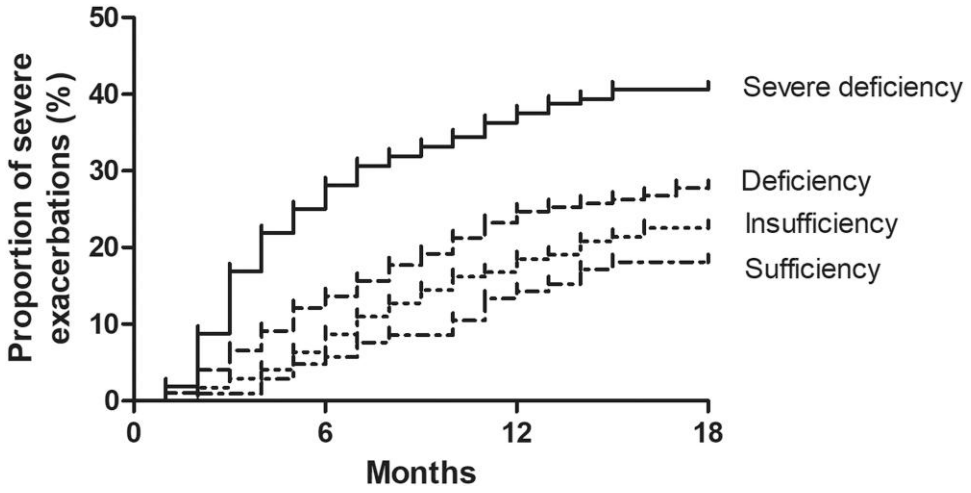

Figure 1 Kaplan-Meier survival curves for the time to the next severe exacerbation of chronic obstructive pulmonary disease in patients with different vitamin D levels. Severe deficiency: Vitamin D<10 ng/mL, deficiency: 10–20 ng/m, insufficiency: 20–30 ng/mL, sufficiency: >30 ng/mL.

characteristics. Patients with severe deficiency had significantly higher rates of ≥2 AECOPD hospitalizations, GOLD E classification, diabetes, hypertension, and cardiovascular diseases compared to those with sufficient vitamin D (all $P<0.01$). Other baseline characteristics did not differ significantly among the groups (all $P>0.05$).

Over an 18-month follow-up, 178 (28.0%) patients experienced at least one severe exacerbation. The highest proportion was in the severe deficiency group (40.6%), followed by deficiency (27.8%), insufficiency (22.5%), and sufficiency (18.1%) groups ($P<0.01$). The Kaplan-Meier survival curve (Figure 1) showed a significantly higher risk of the next severe COPD exacerbation in the severe deficiency group compared to the deficiency group (HR=2.77, 95% CI: 1.66–4.62; $P<0.01$).

Multivariate Cox proportional hazards regression analysis (Table 2) revealed that, after adjusting for confounders, severe vitamin D deficiency (HR=2.74, 95% CI: 1.55–4.84; $P<0.01$) was significantly associated with a higher risk of

Table 2 Multivariate Cox Regression Analysis Exploring the Association of Vitamin D Levels With the Risk of the Next Severe Exacerbation of Chronic Obstructive Pulmonary Disease

	Multivariate Analysis		
	Hazard ratio	**95% CI**	**P value**
Vitamin D groups			
Sufficiency	Reference		
Insufficiency	1.07	0.60–1.92	0.82
Deficiency	1.44	0.84–2.48	0.19
Severe Deficiency	2.74	1.55–4.84	<0.01
Age	1.00	0.95–1.06	0.89
Gender			
Male	Reference		
Female	0.80	0.56–1.16	0.24
BMI	1.04	0.92–1.17	0.57
Smoking status			
Never-smoker	Reference		
Ex-smoker	1.09	0.76–1.57	0.63
Smoker	1.25	0.81–1.94	0.32

(*Continued*)

Table 2 (Continued).

	Multivariate Analysis		
	Hazard ratio	**95% CI**	**P value**
Disease duration of COPD, years			
<3	Reference		
3–5	0.75	0.52–1.07	0.11
>5	1.03	0.67–1.59	0.90
Frequency of hospitalization due to AECOPD in the past 12 months			
<2	Reference		
≥2	2.85	2.04–3.98	<0.01
Pulmonary Function Test			
FEV_1/FVC	0.99	0.96–1.03	0.72
FEV_1 pred	1.01	0.98–1.03	0.58
GOLD stage			
Stage 1	Reference		
Stage 2	1.64	0.64–4.19	0.30
Stage 3	1.80	0.72–4.51	0.21
Stage 4	1.74	0.67–4.50	0.25
GOLD group, n (%)			
A	Reference		
B	2.08	0.80–5.411	0.13
E	7.51	2.99–18.9	<0.01
CAT score			
0–10	Reference		
11–20	1.39	0.77–2.53	0.28
21–30	0.97	0.52–1.81	0.93
31–40	1.41	0.67–2.94	0.37
Blood eosinophil counts			
<100	Reference		
100–300	0.71	0.46–1.09	0.11
≥300	2.28	1.50–3.46	<0.01
Inhalation therapies used			
ICS	Reference		
LAMA	1.10	0.42–2.87	0.85
LABA/LAMA	1.46	0.65–3.27	0.36
ICS/LABA	1.74	0.88–3.45	0.11
ICS/LABA+LAMA or ICS/LABA/LAMA	1.69	0.84–3.39	0.14
Comorbidity			
Diabetes	0.77	0.54–1.11	0.16
Hypertension	1.26	0.91–1.74	0.16
Cardiovascular diseases	1.21	0.89–1.65	0.23

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; AECOPD, Acute Exacerbation of COPD; GOLD, Global Initiative for Chronic Obstructive Lung Disease; CAT, COPD assessment test; EV_1, forced expiratory volume in 1s; FVC, forced vital capacity; LABA, long-acting beta-agonists; LAMA, long-acting antimuscarinic antagonists; ICS, inhaled corticosteroids. In the multivariate analysis, potential confounders were controlled including age, gender, BMI, smoking habit, disease duration of COPD, the number of severe COPD exacerbations in the past 1 year, pulmonary function test, GOLD stage, GOLD group, the number of severe COPD exacerbations in the past 1 year, CAT score, blood eosinophil counts, inhalation therapies used, and comorbidities.

severe exacerbation compared to sufficiency. Additionally, ≥2 AECOPD hospitalizations in the past 12 months (HR=2.85, 95% CI: 2.04–3.98; P<0.01), GOLD E group (HR=7.51, 95% CI: 2.99–18.9; P<0.01), blood eosinophil counts ≥300 (HR=2.28, 95% CI: 1.50–3.46; P<0.01) were also risk factors.

 https://doi.org/10.2147/COPD.S489650

Consistently, logistic regression analysis (Table 3) revealed a similar association, with severe vitamin D deficiency significantly associated with the occurrence of severe AECOPD as a binary outcome (OR=3.40, 95% CI: 1.57–7.35; $P<0.01$). These complementary results reinforce the robustness of our findings.

Table 3 Multivariate Logistic Regression Analysis Exploring the Association of Vitamin D Levels With the Risk of the Next Severe Exacerbation of Chronic Obstructive Pulmonary Disease

	Multivariate Analysis		
	Odds ratio	**95% CI**	**P value**
Vitamin D groups			
Sufficiency	Reference		
Insufficiency	1.16	0.54–2.51	0.70
Deficiency	1.53	0.73–3.19	0.26
Severe Deficiency	3.40	1.57–7.35	<0.01
Age	1.00	0.92–1.08	0.92
Gender			
Male	Reference		
Female	0.88	0.53–1.48	0.63
BMI	1.06	0.89–1.25	0.51
Smoking status			
Never-smoker	Reference		
Ex-smoker	1.12	0.67–1.89	0.67
Smoker	1.24	0.66–2.33	0.50
Disease duration of COPD, years			
<3	Reference		
3–5	0.84	0.50–1.41	0.51
>5	1.15	0.62–2.11	0.67
Frequency of hospitalization due to AECOPD in the past 12 months			
<2	Reference		
≥2	4.46	2.78–7.17	<0.01
Pulmonary Function Test			
FEV_1/FVC	0.99	0.96–1.03	0.72
FEV_1 pred	1.01	0.98–1.03	0.58
GOLD stage			
Stage 1	Reference		
Stage 2	1.77	0.57–5.50	0.33
Stage 3	2.17	0.72–6.55	0.17
Stage 4	2.66	0.84–8.44	0.10
GOLD group, n (%)			
A	Reference		
B	2.45	0.82–7.31	0.11
E	12.83	4.39–37.50	<0.01
CAT score			
0–10	Reference		
11–20	1.84	0.81–4.21	0.15
21–30	1.08	0.46–2.53	0.87
31–40	2.60	0.90–7.55	0.08
Blood eosinophil counts			
<100	Reference		
100–300	0.76	0.44–1.32	0.33
≥300	3.79	2.07–6.93	<0.01

(*Continued*)

Table 3 (Continued).

	Multivariate Analysis		
	Odds ratio	**95% CI**	**P value**
Inhalation therapies used			
ICS	Reference		
LAMA	0.79	0.21–2.92	0.72
LABA/LAMA	1.01	0.33–3.11	0.99
ICS/LABA	1.37	0.52–3.65	0.53
ICS/LABA+LAMA or ICS/LABA/LAMA	1.16	0.42–3.18	0.78
Comorbidity			
Diabetes	0.67	0.40–1.11	0.12
Hypertension	1.21	0.75–1.94	0.44
Cardiovascular diseases	1.24	0.80–1.95	0.34

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; AECOPD, Acute Exacerbation of COPD; GOLD, Global Initiative for Chronic Obstructive Lung Disease; CAT, COPD assessment test; EV_1, forced expiratory volume in 1s; FVC, forced vital capacity; LABA, long-acting beta-agonists; LAMA, long-acting antimuscarinic antagonists; ICS, inhaled corticosteroids. In the multivariate analysis, potential confounders were controlled including age, gender, BMI, smoking habit, disease duration of COPD, the number of severe COPD exacerbations in the past 1 year, pulmonary function test, GOLD stage, GOLD group, the number of severe COPD exacerbations in the past 1 year, CAT score, blood eosinophil counts, inhalation therapies used, and comorbidities.

Discussion

Vitamin D deficiency in COPD patients can be attributed to multiple factors. One primary cause is inadequate sunlight exposure, as vitamin D is predominantly synthesized in the skin through ultraviolet B (UVB) radiation.[17] COPD patients often have limited outdoor activity due to respiratory symptoms, which contributes to lower sun exposure. Moreover, smoking, which is a common risk factor for COPD, has been shown to impair vitamin D metabolism and lower serum levels.[18] Additionally, older age, common in COPD patients, is associated with reduced skin synthesis of vitamin D.[19] Furthermore, nutritional deficiencies, particularly inadequate dietary intake of vitamin D-rich foods, can also play a significant role.[20] Given these factors, patients with COPD are at heightened risk for vitamin D deficiency, which may exacerbate the severity of the disease. Our findings indicate that severe vitamin D deficiency is significantly associated with a higher risk of severe AECOPD, even after adjusting for potential confounders including age, gender, BMI, smoking habit, disease duration of COPD, the number of severe COPD exacerbations in the past 1 year, pulmonary function test, GOLD stage, GOLD group, the number of severe COPD exacerbations in the past 1 year, CAT score, blood eosinophil counts, inhalation therapies used, and comorbidities. This underscores the importance of monitoring and managing vitamin D levels in COPD patients to potentially mitigate the risk of severe exacerbations.

The role of vitamin D deficiency in AECOPD remains a subject of debate. Kunisaki et al conducted a study involving 973 COPD patients prone to exacerbations and found no association between baseline vitamin D levels and subsequent AECOPD risk.[21] Similarly, Puhan et al reported no link between severe vitamin D deficiency and exacerbations, nor any effect of vitamin D supplementation on AECOPD outcomes.[22] Conversely, two other studies suggested that severe vitamin D deficiency is independently associated with poor clinical outcomes.[10,14] A key reason for these inconsistencies may be the different cut-off points used to define severe vitamin D deficiency. Our findings confirm that severe vitamin D deficiency (<10 ng/mL) is significantly associated with an increased risk of COPD exacerbations.

Several mechanisms may explain the link between severe vitamin D deficiency and increased risk of severe exacerbations.[1] Vitamin D has been shown to enhance innate immunity by promoting the production of antimicrobial peptides and modulating inflammatory responses.[23] Deficiency in vitamin D could impair these immune functions, leading to a higher susceptibility to respiratory infections, which are a common trigger for COPD exacerbations.[24] Additionally, vitamin D deficiency has been associated with reduced lung function, which could predispose patients to more frequent and severe exacerbations.[25]

Our study also identified other significant risk factors for severe exacerbations. Specifically, patients with a history of ≥2 AECOPD hospitalizations within the past year had a 2.85 times higher risk of experiencing severe exacerbations, further emphasizing the critical role of recent exacerbation history as a strong predictor of future exacerbations. Additionally, patients classified under the GOLD E group were at significantly higher risk, likely due to their advanced disease stage and more compromised lung function. Elevated blood eosinophil counts (≥300 cells/μL) were also identified as a significant risk factor, which aligns with previous studies suggesting that eosinophilic inflammation plays a key role in the pathogenesis of AECOPD and exacerbation frequency. The presence of eosinophils may reflect an inflammatory subtype of COPD that is more prone to severe exacerbations. While vitamin D deficiency remains an important factor, these additional findings highlight the multifaceted nature of AECOPD exacerbations, where multiple clinical factors must be considered when assessing the risk of severe exacerbations.

The strengths of our study include a well-defined patient cohort and a prospective design, allowing for a clear temporal relationship between vitamin D levels and exacerbation risk. However, several limitations should be noted. First, our study specifically focuses on COPD patients with a recent exacerbation, as they represent a high-risk population with substantial morbidity and mortality. This group is particularly vulnerable to subsequent events, making them highly relevant for investigating predictors such as vitamin D deficiency. However, the generalizability of our findings to stable COPD populations may be restricted. Moreover, vitamin D results were not blinded to the patients. Although no supplementation was recommended by treating physicians as part of the study, it is possible that some patients independently sought vitamin D supplementation after being informed of their deficiency. However, vitamin D levels were measured only at baseline, and fluctuations in these levels during the follow-up period were not accounted for, potentially introducing bias. Lastly, only data on severe AECOPD cases, where hospitalization served as a reliable indicator, were included in the analysis. Data on mild and moderate AECOPD were incomplete and insufficiently robust for accurate classification and evaluation. Future studies should include a broader spectrum of COPD patients, monitor vitamin D levels longitudinally, and evaluate their dynamic impact on exacerbation risks across varying severities to provide a more comprehensive understanding of these associations.

In conclusion, our study highlights that severe vitamin D deficiency (<10 ng/mL) is significantly associated with an increased risk of severe AECOPD in patients with a recent exacerbation. These findings emphasize the importance of routine assessment and management of vitamin D levels in high-risk COPD populations to mitigate exacerbation risks. While other factors, such as frequent prior exacerbations, eosinophilia, and GOLD group E classification, also play a pivotal role in exacerbation risks, addressing modifiable factors like vitamin D deficiency remains a promising avenue for improving patient outcomes. Future studies are warranted to evaluate the longitudinal impact of vitamin D status and supplementation across broader COPD populations and varying severities of exacerbations.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of West China Hospital. All procedures were conducted according to the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All patients gave written informed consents.

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.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J*. 2009;33(5):1165–1185. doi:10.1183/09031936.00128008
2. Agusti A, Hogg JC. Update on the Pathogenesis of Chronic Obstructive Pulmonary Disease. *N Engl J Med*. 2019;381(13):1248–1256. doi:10.1056/NEJMra1900475
3. Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. *Lancet*. 2007;370(9589):786–796. doi:10.1016/S0140-6736(07)61382-8
4. Rabe KF, Watz H. Chronic obstructive pulmonary disease. *Lancet*. 2017;389(10082):1931–1940. doi:10.1016/S0140-6736(17)31222-9
5. Miravitlles M, Anzueto A. Insights into interventions in managing COPD patients: lessons from the TORCH and UPLIFT studies. *Int J Chron Obstruct Pulmon Dis*. 2009;4:185–201.
6. Mullerova H, Agusti A, Erqou S, Mapel DW. Cardiovascular comorbidity in COPD: systematic literature review. *Chest*. 2013;144(4):1163–1178. doi:10.1378/chest.12-2847
7. Hewison M. Vitamin D and the immune system: new perspectives on an old theme. *Rheum Dis Clin North Am*. 2012;38(1):125–139. doi:10.1016/j.rdc.2012.03.012
8. LB E, Ismailova A, Dimeloe S, Hewison M, White JH. Vitamin D and Immune Regulation: antibacterial, Antiviral, Anti-Inflammatory. *JBMR Plus*. 2021;5(1):e10405. doi:10.1002/jbm4.10405
9. Herr C, Greulich T, Koczulla RA, et al. The role of vitamin D in pulmonary disease: COPD, asthma, infection, and cancer. *Respir Res*. 2011;12(1):31. doi:10.1186/1465-9921-12-31
10. Lokesh KS, Chaya SK, Jayaraj BS, et al. Vitamin D deficiency is associated with chronic obstructive pulmonary disease and exacerbation of COPD. *Clin Respir J Apr*. 2021;15(4):389–399. doi:10.1111/crj.13310
11. Zhu M, Wang T, Wang C, Ji Y. The association between vitamin D and COPD risk, severity, and exacerbation: an updated systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis*. 2016;11:2597–2607. doi:10.2147/COPD.S101382
12. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: 2020 Report. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Availabe From: https://goldcopd.org/gold-reports/. Acessed january 13, 2025
13. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(7):1911–1930. doi:10.1210/jc.2011-0385
14. Malinovschi A, Masoero M, Bellocchia M, et al. Severe vitamin D deficiency is associated with frequent exacerbations and hospitalization in COPD patients. *Respir Res*. 2014;15(1):131. doi:10.1186/s12931-014-0131-0
15. Shen B, Liu B, Wang Y, Wang R, Gu D. Severe Vitamin D Deficiency is Associated with Mortality Risk in Critically Ill Patients with Acute Kidney Injury. *Int J Gen Med*. 2024;17:5153–5162. doi:10.2147/IJGM.S477114
16. Celli BR, Fabbri LM, Aaron SD, et al. An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations: the Rome Proposal. *Am J Respir Crit Care Med*. 2021;204(11):1251–1258. doi:10.1164/rccm.202108-1819PP
17. Young AR, Morgan KA, Harrison GI, et al. A revised action spectrum for vitamin D synthesis by suberythemal UV radiation exposure in humans in vivo. *Proc Natl Acad Sci U S A*. 2021;118(40). doi:10.1073/pnas.2015867118
18. Lange NE, Sparrow D, Vokonas P, Litonjua AA. Vitamin D deficiency, smoking, and lung function in the Normative Aging Study. *Am J Respir Crit Care Med*. 2012;186(7):616–621. doi:10.1164/rccm.201110-1868OC
19. Bocheva G, Slominski RM, Slominski AT. The Impact of Vitamin D on Skin Aging. *Int J mol Sci*. 2021;22(16). doi:10.3390/ijms22169097
20. Kiani AK, Dhuli K, Donato K, et al. Main nutritional deficiencies. *J Prev Med Hyg*. 2022;63(2 Suppl 3):E93–E101. doi:10.15167/2421-4248/jpmh2022.63.2S3.2752
21. Kunisaki KM, Niewoehner DE, Connett JE, Network CCR. Vitamin D levels and risk of acute exacerbations of chronic obstructive pulmonary disease: a prospective cohort study. *Am J Respir Crit Care Med*. 2012;185(3):286–290. doi:10.1164/rccm.201109-1644OC
22. Puhan MA, Siebeling L, Frei A, Zoller M, Bischoff-Ferrari H, Ter Riet G. No association of 25-hydroxyvitamin D with exacerbations in primary care patients with COPD. *Chest*. 2014;145(1):37–43. doi:10.1378/chest.13-1296
23. Aranow C. Vitamin D and the immune system. *J Investig Med*. 2011;59(6):881–886. doi:10.2310/JIM.0b013e31821b8755
24. Jolliffe DA, Griffiths CJ, Martineau AR. Vitamin D in the prevention of acute respiratory infection: systematic review of clinical studies. *J Steroid Biochem mol Biol*. 2013;136:321–329. doi:10.1016/j.jsbmb.2012.11.017
25. Kunisaki KM, Niewoehner DE, Singh RJ, Connett JE. Vitamin D status and longitudinal lung function decline in the Lung Health Study. *Eur Respir J*. 2011;37(2):238–243. doi:10.1183/09031936.00146509