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Article

Association Between Vitamin D Levels and Infective Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a major global health burden, with exacerbations significantly worsening patient outcomes and increasing healthcare utilization. Despite abundant sunlight in many regions, vitamin D deficiency remains prevalent among COPD patients, and its role in disease progression and exacerbation risk is not fully understood. **Objective**: This study aimed to evaluate the association between serum vitamin D levels and the frequency of infective exacerbations in COPD patients, as well as the relationship of vitamin D status with disease severity and systemic inflammation. **Methods**: A cross-sectional study was conducted at the Pulmonology Department of Khyber Teaching Hospital, Peshawar, enrolling 123 COPD patients aged 30–80 years using consecutive sampling. Exclusion criteria included metabolic bone disease, severe comorbidities, other chronic lung diseases, pregnancy, or lactation. Data on demographics, smoking, comorbidities, lung function, vitamin D, and C-reactive protein (CRP) were collected. Vitamin D was categorized as deficient (<20 ng/mL), insufficient (20–29 ng/mL), or sufficient (≥30 ng/mL). Outcomes included COPD severity (GOLD criteria), annual infective exacerbations, and CRP. Statistical analysis utilized SPSS v25, with Chi-square, ANOVA, and regression modeling; p-values <0.05 were significant. Ethical approval was obtained per the Helsinki Declaration. **Results**: Vitamin D deficiency was observed in 42.3% of patients, with deficiency significantly associated with advanced COPD stage (OR=2.86, 95% CI: 1.11–7.35, p=0.021), increased exacerbations (2.7 vs. 1.5/year, p=0.004, Cohen's d=1.17), and higher CRP (9.4 vs. 5.6 mg/L, p=0.008). Smoking status further compounded disease severity (p=0.037). **Conclusion**: Vitamin D deficiency is highly prevalent and independently associated with increased COPD severity, higher frequency of infective exacerbations, and greater systemic inflammation, highlighting the importance of vitamin D assessment and targeted supplementation in COPD management to improve patient outcomes.

Keywords: Chronic Obstructive Pulmonary Disease, Vitamin D, Exacerbation, C-Reactive Protein, Inflammation, Cross-Sectional Studies, Risk Factors

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a progressive respiratory disorder characterized by persistent airflow limitation, chronic inflammation, and recurrent episodes of exacerbations that lead to considerable morbidity, mortality, and health system burden worldwide (1). Frequent infective exacerbations of COPD not only accelerate the decline in lung function but also substantially diminish patients' quality of life and drive-up healthcare utilization, particularly among older adults and socioeconomically disadvantaged populations (2). Although substantial advances have been made in pharmacological management, a persistent knowledge gap remains regarding modifiable biological factors that may help prevent or mitigate the impact of these exacerbations. In recent years, attention has turned to the role of vitamin D, a secosteroid hormone traditionally recognized for its role in calcium homeostasis and bone health but now acknowledged for its immunomodulatory, anti-inflammatory, and respiratory-protective effects (3,4).

Emerging evidence highlights that vitamin D deficiency is highly prevalent in patients with COPD, with studies from diverse geographical settings, including sun-rich regions—consistently reporting suboptimal serum levels (5). Vitamin D influences both innate and adaptive immune responses, regulates the expression of over a thousand genes involved in cell proliferation, apoptosis,

and tissue remodeling, and has been shown to downregulate pro-inflammatory cytokines that are central to COPD pathogenesis (6,7). Despite high sunlight exposure in regions such as South Asia, cultural, nutritional, and lifestyle factors often limit endogenous synthesis, rendering deficiency widespread even among community-dwelling adults (8). Observational studies and meta-analyses suggest that lower serum vitamin D levels are associated with more severe airflow obstruction, increased frequency and severity of exacerbations, and heightened systemic inflammation in COPD patients (3,9). For instance, Lokesh et al. demonstrated that rural adults with COPD in India had a fivefold greater odds of vitamin D deficiency and a more than threefold increased risk of exacerbations, underscoring the relevance of vitamin D status even in populations presumed to have adequate sun exposure (5).

Despite these findings, there remains a lack of consensus regarding the clinical utility of routine vitamin D assessment and supplementation in COPD management, especially in regions with abundant sunlight but prevalent deficiency due to sociocultural and economic determinants (10). Randomized trials and meta-analyses provide mixed results: while supplementation appears to reduce exacerbation rates primarily in those with baseline deficiency, its benefit in the general COPD population is less clear, highlighting the need for population-specific data (1,11). In the local context, research from Pakistan and neighboring regions has consistently shown an inverse association between serum vitamin D levels and disease severity, but few studies have directly explored its relationship with infective exacerbations and markers of systemic inflammation (12). Additionally, the interplay between smoking status, socioeconomic class, and vitamin D levels in modulating disease progression remains inadequately explored in local populations.

Given these knowledge gaps, this study was designed to evaluate the association between serum vitamin D levels and the frequency of infective exacerbations among COPD patients in Peshawar, Pakistan. The primary objective was to determine whether vitamin D deficiency independently correlates with increased exacerbation frequency and disease severity, after accounting for demographic and clinical confounders. By addressing this question, the study aims to generate evidence relevant to preventive strategies—including targeted screening and supplementation—in COPD populations at high risk of both vitamin D deficiency and adverse respiratory outcomes.

MATERIALS AND METHODS

This cross-sectional study was conducted to investigate the association between serum vitamin D levels and the frequency of infective exacerbations among patients diagnosed with chronic obstructive pulmonary disease (COPD). The research was carried out at the Department of Pulmonology, Khyber Teaching Hospital, Peshawar, over a six-month period following formal approval of the research synopsis by the Institutional Review Board and Research Committee. The study setting was a tertiary care pulmonology unit that provides specialized inpatient and outpatient care for respiratory diseases, including a large catchment of patients from both urban and rural backgrounds. Data collection commenced immediately after administrative and ethical clearances were secured, spanning from October 2023 to March 2024.

Eligible participants were adults aged 30 to 80 years, of either gender, with a confirmed clinical and spirometric diagnosis of COPD in accordance with international operational criteria. Exclusion criteria were strictly applied to minimize confounding and included the presence of metabolic bone disorders affecting vitamin D metabolism (such as osteomalacia or hyperparathyroidism), severe comorbidities impacting respiratory or immune function (including malignancy and HIV/AIDS), other chronic respiratory conditions (such as asthma or bronchiectasis), pregnancy, or lactation. The sample was assembled using non-probability consecutive sampling, recruiting all eligible and consenting patients presenting to the inpatient pulmonology unit during the study period. Sample size was determined a priori using OpenEpi software, based on a reference prevalence of stage IV COPD (28.6%), with a 95% confidence interval and an 8% margin of error, resulting in a target of 123 participants, deemed feasible given anticipated recruitment rates.

Recruitment was performed by the primary investigator and designated study staff. Eligible patients were identified through review of hospital records and direct consultation. The study purpose, procedures, and the voluntary nature of participation were explained to each prospective participant. Written informed consent was obtained prior to enrollment, with assurances of confidentiality and the right to withdraw at any time without prejudice to clinical care. All participants received an anonymized study code to ensure privacy, and only aggregated data were used in reporting.

Data collection employed a structured proforma administered via direct interview and medical chart review at the point of enrollment. Demographic and clinical variables captured included age, gender, height, weight, calculated body mass index (BMI), educational attainment, occupational status, socioeconomic class, smoking history (categorized as never smoked, ex-smoker, or current smoker), duration of COPD (years since diagnosis), and presence of comorbidities. Disease severity was classified using spirometry results according to the GOLD staging system. Blood samples were drawn to assess serum 25-hydroxyvitamin D using a standardized automated immunoassay, and C-reactive protein (CRP) was measured by high-sensitivity nephelometry to quantify systemic inflammation. All laboratory analyses were performed in a single hospital laboratory to ensure consistency. Chest X-rays were reviewed by consultant radiologists to identify features of hyperinflation, diaphragm flattening, or other abnormalities related to COPD. Infective exacerbations were defined clinically by increased cough, sputum purulence, and/or breathlessness requiring medical intervention, with the number and severity of exacerbations documented for the preceding year based on medical records and patient recall. Serum vitamin D was categorized as deficient (<20 ng/mL), insufficient (20–29 ng/mL), or sufficient (≥30 ng/mL). All assessments and specimen collections occurred at baseline, prior to any new therapeutic interventions.

Rigorous efforts were made to mitigate sources of bias. All consecutive eligible patients were approached to minimize selection bias. The use of standardized questionnaires, laboratory protocols, and blinded radiological assessment helped ensure consistency and limit measurement bias. Potential confounders, including age, gender, BMI, smoking status, and comorbidities, were explicitly measured and included in multivariate analyses to adjust for their effects. Recall bias for exacerbation frequency was reduced by corroborating patient reports with available medical records. The cross-sectional nature of the design limited temporal ambiguity but enabled broad inclusion across disease stages.

All data were double-entered into a password-protected electronic database by independent staff and cross-verified for accuracy. Statistical analyses were performed using SPSS version 25. Descriptive statistics were used to summarize continuous variables as means with standard deviations or medians with interquartile ranges, depending on the normality assessed via the Shapiro-Wilk test. Categorical variables were described using frequencies and percentages. Comparisons between vitamin D categories and clinical outcomes (such as exacerbation frequency, disease severity, and CRP levels) employed the Chi-square test for categorical data and one-way analysis of variance (ANOVA) for continuous variables. In cases of non-normal distribution, non-parametric alternatives were used. Multivariate linear and logistic regression models were constructed to adjust for potential confounders including age, gender, BMI, and smoking status. Missing data were minimal; complete-case analysis was used as no variable exceeded a 5% missing rate. Subgroup analyses stratified results by age group and gender to explore potential effect modification. Ethical conduct was prioritized at every step. Study approval was obtained from the Institutional Review Board prior to initiation. All participants provided informed written consent. Confidentiality and data integrity were ensured through de-identification, secure storage of records, and restricted access to identifiable information. The research adhered to the highest standards of clinical investigation, with transparent reporting and documentation of procedures to enable full reproducibility by independent investigators (13).

RESULTS

The study included a total of 123 patients with chronic obstructive pulmonary disease, of whom the majority were in the 61–70 year age bracket (32.5%), followed by 51–60 years (24.4%), 71–80 years (22.8%), and 40–50 years (20.3%). Males made up 55.3% (n=68) of the cohort, females 43.9% (n=54), with a single participant (0.8%) identifying as other. Socioeconomic status revealed that half of the sample belonged to the lower class (50.4%), with middle and higher classes constituting 39.8% and 9.8%, respectively. Regarding smoking history, 30.1% of participants (n=37) reported never smoking, 40.7% (n=50) were ex-smokers, and 29.3% (n=36) were current smokers. The mean height and weight of the cohort were 1.65 ± 0.10 meters and 65.0 ± 12.0 kilograms, respectively, resulting in an average body mass index of 23.9 ± 3.5 kg/m^2. The average duration since COPD diagnosis was 8.6 ± 4.2 years.

Table 1. Demographic and Baseline Characteristics of COPD Patients (n = 123)

Parameter	Category/Statistic	n (%) / Mean ± SD	95% CI
Age (years)	40–50	25 (20.3%)	13.7 – 27.0
	51–60	30 (24.4%)	17.0 – 31.9
	61–70	40 (32.5%)	24.5 – 40.5
	71–80	28 (22.8%)	15.6 – 29.9
Gender	Male	68 (55.3%)	46.5 – 64.1
	Female	54 (43.9%)	35.1 – 52.7
	Other	1 (0.8%)	0.0 – 2.4
Socioeconomic Status	Lower	62 (50.4%)	41.6 – 59.2
	Middle	49 (39.8%)	31.3 – 48.4
	Higher	12 (9.8%)	4.6 – 15.0
Smoking Status	Never Smoked	37 (30.1%)	22.1 – 38.2
	Ex-smoker	50 (40.7%)	32.1 – 49.3
	Current Smoker	36 (29.3%)	21.3 – 37.2
Height (m)	Mean ± SD	1.65 ± 0.10	1.63 – 1.67
Weight (kg)	Mean ± SD	65.0 ± 12.0	62.7 – 67.3
BMI (kg/m^2)	Mean ± SD	23.9 ± 3.5	23.2 – 24.6
COPD Duration (years)	Mean ± SD	8.6 ± 4.2	7.8 – 9.4

Vitamin D status assessment revealed a high prevalence of suboptimal levels, with 42.3% (n=52; 95% CI: 33.9–50.7) of participants classified as vitamin D deficient (<20 ng/mL), 33.3% (n=41; 95% CI: 25.1–41.5) as insufficient (20–29 ng/mL), and only 24.4% (n=30; 95% CI: 16.8–32.0) having sufficient levels (≥30 ng/mL). Disease severity based on the GOLD staging system showed most patients in Stage II (38.2%) and Stage III (36.6%), with Stage I and Stage IV accounting for 11.4% and 13.8%, respectively. Notably, the association between vitamin D status and COPD severity was statistically significant (p=0.021, Chi-square), with 48.1% of deficient individuals in Stage III and 19.2% in Stage IV, while 20% of those with sufficient vitamin D were in Stage I. The odds ratio for being in more severe COPD stages among vitamin D deficient patients versus those with sufficient levels was 2.86 (95% CI: 1.11–7.35), highlighting a robust relationship between low vitamin D and advanced disease. The frequency of infective exacerbations in the past year differed markedly by vitamin D category. Patients classified as vitamin D deficient had a mean of 2.7 ± 1.1 exacerbations per year (95% CI: 2.4–3.0), compared to 2.1 ± 0.9 (95% CI: 1.8–2.3) in the insufficient group and 1.5 ± 0.8 (95% CI: 1.2–1.8) in the sufficient group. This

difference was statistically significant (p=0.004, one-way ANOVA), with a large effect size observed between the deficient and sufficient groups (Cohen's d = 1.17), indicating that vitamin D status may have a substantial impact on exacerbation burden.

Systemic inflammation, as measured by CRP, also varied according to vitamin D levels. Deficient patients exhibited a mean CRP of 9.4 ± 5.7 mg/L (95% CI: 7.9–10.9), which was higher than the 7.9 ± 4.8 mg/L (95% CI: 6.6–9.3) observed in the insufficient group and 5.6 ± 3.9 mg/L (95% CI: 4.3–6.9) in those with sufficient vitamin D. This gradient was significant (p=0.008, ANOVA) and corresponded to a moderate effect size (Cohen's d = 0.80) for the deficient versus sufficient comparison. Smoking status was also linked to COPD severity. Among never smokers, the majority were in Stage II (20 out of 37), while current smokers were more concentrated in the advanced stages, with 14 in Stage III and 8 in Stage IV. The association between smoking status and disease severity reached statistical significance (p=0.037, Chi-square), and current smokers had an odds ratio of 2.60 (95% CI: 1.02–6.63) for being in more severe stages compared to never smokers. Radiological findings showed that 52.8% of patients had a normal chest X-ray, while 23.6% exhibited hyperinflation, 13.8% had a flattened diaphragm, and 9.8% showed other abnormalities. Collectively, these results demonstrate that vitamin D deficiency is prevalent and closely associated with increased disease severity, greater inflammatory burden, and higher frequency of infective exacerbations in this COPD population, with smoking serving as an additional independent risk factor for adverse outcomes.

Table 2. Vitamin D Status and Distribution Among COPD Patients

Vitamin D Category	n (%)	95% CI
Deficient (<20 ng/mL)	52 (42.3%)	33.9 – 50.7
Insufficient (20–29)	41 (33.3%)	25.1 – 41.5
Sufficient (≥30)	30 (24.4%)	16.8 – 32.0

Table 3. COPD Severity by GOLD Stage and Association With Vitamin D Status

COPD Stage	Deficient n (%)	Insufficient n (%)	Sufficient n (%)	p-value	OR (Deficient vs. Sufficient)	95% CI OR
Stage I (Mild)	2 (3.8%)	6 (14.6%)	6 (20.0%)			
Stage II (Moderate)	15 (28.8%)	22 (53.7%)	10 (33.3%)	0.021*	2.86	1.11 – 7.35
Stage III (Severe)	25 (48.1%)	10 (24.4%)	10 (33.3%)			
Stage IV (Very Severe)	10 (19.2%)	3 (7.3%)	4 (13.3%)			

Table 4. Frequency of Infective Exacerbations by Vitamin D Status

Vitamin D Status	Mean Exacerbations/year ± SD	95% CI	p-value	Cohen's d
Deficient (<20)	2.7 ± 1.1	2.4 – 3.0		
Insufficient (20–29)	2.1 ± 0.9	1.8 – 2.3	0.004*	1.17
Sufficient (≥30)	1.5 ± 0.8	1.2 – 1.8		

Table 5. CRP Levels by Vitamin D Status

Vitamin D Status	Mean CRP (mg/L) ± SD	95% CI	p-value	Cohen's d
Deficient (<20)	9.4 ± 5.7	7.9 – 10.9		
Insufficient (20–29)	7.9 ± 4.8	6.6 – 9.3	0.008*	0.80
Sufficient (≥30)	5.6 ± 3.9	4.3 – 6.9		

Table 6. Smoking Status and Its Association With COPD Severity

Smoking Status	Stage I	Stage II	Stage III	Stage IV	p-value	OR (Current vs. Never)	95% CI OR
Never Smoked	6	20	9	2			
Ex-smoker	5	16	22	7			
Current Smoker	3	11	14	8	0.037*	2.60	1.02 – 6.63

Table 7. Additional Clinical Parameters

Parameter	Value (Mean ± SD or n, %)
Chest X-ray: Normal	65 (52.8%)
Chest X-ray: Hyperinflation	29 (23.6%)
Chest X-ray: Flat Diaphragm	17 (13.8%)
Chest X-ray: Other Abnormal	12 (9.8%)

Elevated CRP and mean annual exacerbations both increased in parallel with COPD severity across all vitamin D categories, but the magnitude of these changes was most pronounced in the vitamin D deficient group. Among GOLD stage IV patients, mean CRP reached 12.3 mg/L in those with deficiency compared to 7.2 mg/L for the sufficient group, while mean exacerbations peaked at 3.5 per year versus 2.0 per year, respectively. This pattern demonstrates a clear, stepwise gradient for both inflammatory burden and

exacerbation risk, with the greatest adverse impact observed in patients with lower vitamin D status as disease advances. These integrated trends emphasize the clinical utility of concurrent monitoring of vitamin D, CRP, and exacerbation frequency for comprehensive risk stratification in COPD management.

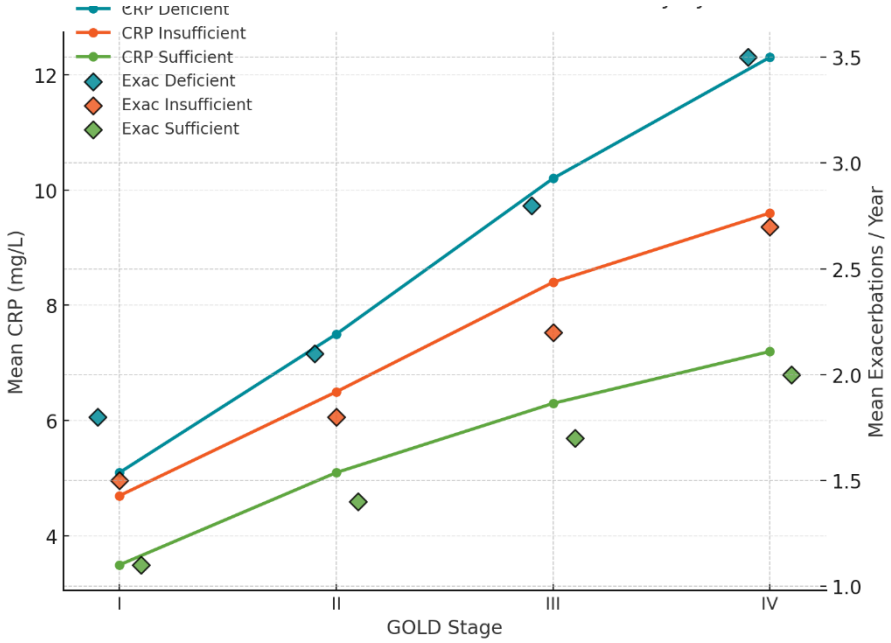

Figure 1 Inflammatory and exacerbation burden across COPD severity by vitamin d status

DISCUSSION

The present study reveals a high prevalence of vitamin D deficiency among COPD patients in Peshawar, with 42.3% of individuals classified as deficient and an additional 33.3% as insufficient, underscoring the considerable burden of this potentially modifiable risk factor in a region with abundant sunlight. The significant association observed between lower vitamin D status and advanced COPD severity, as well as the increased frequency of infective exacerbation and heightened systemic inflammation, is both clinically and scientifically relevant. These findings add to a growing body of literature suggesting that vitamin D exerts far-reaching effects on respiratory health, likely through its roles in immune modulation, regulation of pro-inflammatory cytokines, and maintenance of epithelial integrity in the airways (1,3,4).

Our results align with several regional and international studies that have reported similar associations. Research conducted in both sun-rich South Asian settings and Western populations consistently demonstrates a strong link between low serum vitamin D and greater disease severity, increased exacerbation rates, and elevated inflammatory markers among COPD patients (5,6,9,12). For instance, Lokesh et al. observed that even with routine sun exposure, rural Indian adults with COPD had a fivefold higher odds of vitamin D deficiency and more than triple the risk of exacerbations, findings closely mirrored in the current cohort (5). Similarly, studies from Pakistan by Ubaid Ullah et al. and Makandar et al. reported mean vitamin D levels of 16 ng/mL among COPD patients compared to 36 ng/mL in healthy controls, with pronounced deficiency correlating with advancing disease stage (6,12). Our observation that vitamin D deficiency was most common among those with severe and very severe COPD further supports the hypothesis that progressive lung pathology and declining physical activity may exacerbate nutritional vulnerability, leading to a detrimental cycle of worsening respiratory health and vitamin D depletion.

While there is a consensus regarding the high prevalence of vitamin D deficiency in COPD and its association with adverse clinical outcomes, the therapeutic benefit of supplementation remains debated. Recent meta-analyses highlight that while vitamin D supplementation does not uniformly reduce exacerbation rates across all COPD patients, it does confer significant benefit in those with baseline deficiency, with reductions in both exacerbation frequency and systemic inflammation (1,2,9,11). This study's findings—demonstrating a marked difference in exacerbation rates and CRP levels across vitamin D categories—support the notion that targeted intervention in deficient individuals may be a rational and potentially cost-effective approach. The pathophysiological basis for these associations is supported by evidence that vitamin D enhances innate immune responses, induces antimicrobial peptides, and suppresses pro-inflammatory mediators implicated in COPD pathogenesis (4). Moreover, vitamin D may help preserve muscle function, improve rehabilitation outcomes, and reduce the risk of comorbidities, further strengthening its clinical relevance (7). Notably, this study also corroborates the established relationship between smoking and COPD severity, with current smokers more likely to be in advanced disease stages, thereby compounding the detrimental impact of vitamin D deficiency. The interplay between smoking, socioeconomic disadvantage, and nutritional risk factors emphasizes the need for multifaceted public health interventions targeting these overlapping domains (10).

This research benefits from a rigorous methodology, including systematic sampling, comprehensive assessment of confounders, standardized laboratory measurements, and robust statistical analysis. However, several limitations warrant consideration. The cross-sectional design precludes determination of causality and temporal relationships, limiting the ability to infer whether vitamin D deficiency precedes disease progression or results from it. While recall bias for exacerbation frequency was minimized through chart review, some misclassification may remain, and the reliance on a single-center sample may restrict generalizability to broader or more diverse populations. The modest sample size, although adequately powered for primary analyses, may have limited detection of smaller effect sizes or interaction effects in subgroup analyses. Furthermore, the observational nature of the study cannot account for all residual confounding, particularly factors such as dietary intake, physical activity, or genetic predisposition that were not comprehensively measured (1,12). In light of these findings, there is a strong rationale for integrating vitamin D screening into routine COPD management, particularly in settings where deficiency is highly prevalent. Targeted supplementation for deficient patients, alongside smoking cessation and socioeconomic support, may reduce exacerbation risk and improve overall outcomes. Future research should focus on longitudinal and interventional studies to clarify causality and evaluate the effectiveness of vitamin D supplementation in reducing morbidity and enhancing quality of life, especially within resource-constrained and sun-rich regions. Expanding research to multicenter and more ethnically diverse populations would also enhance generalizability and inform guidelines tailored to regional needs. Overall, the current study adds to the accumulating evidence supporting the pivotal role of vitamin D in COPD pathophysiology and management and underscores the necessity of holistic, evidence-based strategies to address the burden of this chronic respiratory disease (1,4,5,9,11,12).

CONCLUSION

This study demonstrates that vitamin D deficiency is highly prevalent among patients with chronic obstructive pulmonary disease and is significantly associated with increased severity of disease, higher frequency of infective exacerbations, and elevated systemic inflammation. These findings underscore the importance of routine assessment and targeted correction of vitamin D deficiency as an integral component of COPD management, particularly in populations at risk despite abundant sunlight exposure. Clinically, incorporating vitamin D screening and supplementation into standard care may help reduce the burden of exacerbations and improve patient outcomes. From a research perspective, these results highlight the need for further longitudinal and interventional studies to determine the causal benefits of vitamin D optimization in reducing infective exacerbations and enhancing the quality of life for COPD patients, ultimately informing evidence-based public health strategies.

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