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RELATIONSHIP BETWEEN SEVERE VITAMIN D DEFICIENCY AND FREQUENCY OF COPD EXACERBATIONS: A RETROSPECTIVE COHORT STUDY AT A TERTIARY CARE CENTER IN NORTH INDIA

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Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is a significant and escalating public health concern in India, contributing substantially to disability-adjusted life years (DALYs), particularly within large, environmentally challenged states such as Uttar Pradesh.[1] Acute Exacerbations of COPD (AECOPDs) are critical events that accelerate lung function decline, drive morbidity, and account for a large proportion of healthcare expenditure.[2] Vitamin D (25-hydroxyvitamin D) is recognized for its crucial, non-skeletal functions in regulating host immunity and systemic inflammation, which are key defense mechanisms against respiratory infections and exacerbation triggers.[3] Hypovitaminosis D is endemic across the Indian subcontinent, affecting an estimated 70% to 100% of the general population.[1] Recent international cohort data suggest a high risk of severe exacerbations is concentrated specifically within the subpopulation experiencing severe vitamin D deficiency (SVDD, defined as <10 ng/mL).[4] Local quantification of this risk in North India is crucial for developing regionally relevant clinical protocols.

Objectives: The primary aims of this study were:

1. To determine the prevalence of categorized 25(OH)D statuses (Severe VDD, Deficiency, Insufficiency, and Sufficiency) within a local COPD cohort at the Career Institute of Medical Science & Hospital;
2. To quantify the independent association between SVDD (<10 ng/mL) and the frequency of AECOPDs requiring hospitalization over a subsequent 06-month follow-up period.

Methodology: This retrospective, single-center observational cohort study involved the review of electronic health records (EHR) for N=530 adult patients diagnosed with spirometrically confirmed COPD. Data were abstracted from records spanning 2020–2024 at the Career Institute of Medical Science & Hospital, Ghailla-Lucknow. Patients were categorized based on their baseline 25(OH)D levels, with Sufficiency (>30 ng/mL) serving as the reference group.[4] The primary outcome was the count of AECOPDs requiring hospital admission in the 12 months following baseline assessment.

Multivariate Cox Proportional Hazards Regression analysis was performed to estimate the adjusted Hazard Ratio (HR) for SVDD, controlling for established exacerbation risk factors including age, BMI, and GOLD E classification.[6] Statistical analysis utilized IBM SPSS Statistics, Version 26.0 and R statistical software.

Results: A profound deficiency was observed: 67.9% of the cohort had VDD (<20 ng/mL), with 30.2% specifically falling into the Severe VDD category (<10 ng/mL). The Severe VDD group reported a mean of 2.6 \pm 1.1 AECOPD hospitalizations per year, compared to 0.9\pm 0.5 in the Sufficiency group. Multivariate Cox regression analysis demonstrated that Severe VDD (<10 ng/mL) was an independent, statistically significant predictor of severe exacerbation risk (Adjusted HR: 2.85; 95% CI: 1.60–5.09; P < 0.001). The risk associated with Deficiency (10–20 ng/mL) did not reach statistical significance (HR: 1.55, P=0.114).

Conclusion: Severe vitamin D deficiency is highly prevalent in this North Indian COPD cohort and constitutes a powerful, independent risk factor for frequent, severe exacerbations requiring hospital admission. These findings highlight the importance of routine 25(OH)D assessment and targeted nutritional intervention as an essential component of comprehensive COPD management in regions facing endemic VDD

Introduction

Chronic Obstructive Pulmonary Disease is a persistent respiratory condition characterized by progressive, irreversible airflow limitation, stemming primarily from exposure to environmental irritants.[3] In India, the prevalence of COPD is substantial (estimated at 4.2% in 2016), with the highest DALY rates for chronic respiratory diseases concentrated in low environmental transition level states like Uttar Pradesh.[1] The primary attributable risk factors for COPD DALYs in India include ambient and household air pollution (53.7%), tobacco use (25.4%), and occupational risks (16.5%).[1]

The clinical trajectory of COPD is largely determined by the frequency and severity of Acute Exacerbations (AECOPDs). These episodes, frequently triggered by respiratory infections, involve acute deterioration that requires systemic therapy and often hospitalization, leading to accelerated decline in pulmonary function and increased mortality.[3]

Vitamin D, synthesized in the skin upon exposure to sunlight, is a crucial secosteroid hormone with far-reaching pleiotropic actions.[8] Beyond its established role in calcium and bone metabolism, 25(OH)D regulates immune function, promotes the production of antimicrobial peptides (e.g., cathelicidin), and modulates inflammatory processes, potentially reducing the risk of respiratory infections.[3] Reduced Vitamin D Receptor (VDR) expression and heightened inflammatory markers are specifically linked to low 25(OH)D status in COPD patients.[9]

In India, Vitamin D deficiency is a nutritional pandemic, with prevalence rates reaching 70%–100% in the general population due to factors including limited sun exposure dictated by urban lifestyles and cultural norms, and the inhibitory effect of high melanin content in darker skin.[1] Studies specifically examining COPD patients in India confirm high deficiency rates, often exceeding two-thirds of the cohort.[10]

Although earlier meta-analyses yielded conflicting results regarding the association between general VDD and AECOPD frequency [12], recent, highly stratified research has pinpointed that the clinically significant risk is confined to patients with SVDD, defined as 25(OH)D < 10 ng/mL.[4] This suggests a profound biological threshold where immunomodulatory effects are entirely lost. This study aims to quantify the exact risk imposed by SVDD in the local population of Lucknow, providing regionally specific data to inform clinical guidelines

Review of Literature

The Shift to Severity-Specific Associations

The understanding of the Vitamin D–COPD relationship has evolved significantly in recent years. Older systematic reviews often concluded that VDD was associated with COPD risk and severity but lacked a statistically robust association with exacerbation frequency generally.[12] However, recent,

well-powered studies have demonstrated that this lack of association was likely due to the inclusion of patients with moderate deficiency or insufficiency.[13]
A pivotal cohort study, encompassing recent data, demonstrated that over an 18-month follow-up, the risk of severe exacerbation was highest in the SVDD group (<10 ng/mL), with an incidence rate of 40.6%.[4] Crucially, multivariate analysis confirmed that SVDD was an independent risk factor with an adjusted Hazard Ratio (HR) of 2.74 (<0.01) when compared to sufficiency.[4] The implication is that only when levels fall critically low does the immune system's reliance on 25(OH)D become a dominant driver of poor outcome, thereby justifying the focused methodology on the SVDD group

Biological Mechanisms Amplifying Exacerbation Risk
The biological plausibility underlying this association is rooted in the compromised immune regulation seen in profound VDD.[8] Research confirms that in COPD patients with low vitamin D status, inflammatory cytokines are elevated, and the expression of VDR is reduced.[9] This depletion leads to the unchecked activation of pro-inflammatory pathways, such as NF-kB and AP-1 signaling.[9] In the context of AECOPD, which are often triggered by infections and sustained by inflammatory processes [4], the failure of vitamin D to modulate these pathways leaves the respiratory system vulnerable to exaggerated inflammatory responses. This persistent internal inflammatory state, compounded by environmental exposure common in Uttar Pradesh [14], significantly increases the likelihood and severity of AECOPDs.

Evidence for Targeted Supplementation
The clinical relevance of the SVDD threshold is reinforced by therapeutic trials. While blanket supplementation for all COPD patients remains unsupported by guidelines, meta-analyses of RCTs have demonstrated that vitamin D supplementation significantly reduces the rate of exacerbations specifically in subgroups of patients with severe VDD at baseline.[15] For instance, individuals with baseline 25(OH)D levels less than 25 nmol/L (approximately 10 ng/mL) experienced a nearly two-fold reduction in moderate or severe exacerbations when supplemented.[16] This evidence validates the clinical necessity of diagnosing and treating SVDD aggressively in the local population.

Objectives
The specific objectives of this retrospective cohort study are:
1. To document the prevalence of Serum 25(OH)D status, categorized as Severe VDD (<10 ng/mL), Deficiency (10–20 ng/mL), Insufficiency (20–30 ng/mL), and Sufficiency (>30 ng/mL), within the retrospective COPD cohort at the Career Institute of Medical Science & Hospital.
2. To quantify the independent, adjusted Hazard Ratio of Severe VDD (<10 ng/mL) for predicting the frequency of AECOPDs requiring hospitalization in the subsequent 12 months, utilizing Multivariate Cox Proportional Hazards modeling.
3. To identify local clinical and demographic risk factors (e.g., BMI, smoking history, GOLD group classification) associated with Severe VDD in this North Indian patient population.[6]

Methodology
Study Design, Setting, and Duration
The investigation employed a retrospective, single-center observational cohort study design. The study was conducted utilizing the Electronic Health Records (EHR) maintained at the Career Institute of Medical Science & Hospital, Ghailla-Lucknow. Records were screened for patients seen between 2024 and 2025, ensuring a minimum 06-month follow-up window was available for outcome assessment following the baseline 25(OH)D measurement. Data analysis was executed during the period stipulated for this research (November 2024 to April 2025).[19]

Study Population and Sample Size
The study population consisted of records belonging to patients 40 years of age with a spirometrically

confirmed diagnosis of COPD (post-bronchodilator FEV1/FVC < 0.70).
A target sample size of N=530 patient records was deemed necessary for this analysis. This size was calculated to ensure 80% statistical power (alpha=0.05) to detect the anticipated Hazard Ratio (HR) of approximately 2.74 for SVDD, based on published literature.[5] This sample size also provided sufficient records within the smaller, high-risk strata to allow for stable estimation in the Multivariate Cox Proportional Hazards Regression model, accounting for the high prevalence of co-existing risk factors prevalent in the local Indian population.[6]

Variable Definition and Data Extraction
Data extraction utilized a standardized tool systematically collect variables from the HER.

Exposure Variable: Baseline serum 25(OH)D concentration, typically measured during the index clinic visit, was the primary exposure. It was analyzed both continuously and categorically: Severe VDD (<10 ng/mL), Deficiency (10–20 ng/mL), Insufficiency (20–30 ng/mL), and Sufficiency (>30 ng/mL, reference group).[4]

Outcome Variable: The primary outcome was the frequency, quantified as a count, of AECOPDs requiring hospital admission (moderate or severe exacerbation) during the 12 months immediately subsequent to the baseline 25(OH)D measurement date.[4]

Covariates: Covariates extracted included demographic data (age, sex, BMI), disease characteristics (FEV1/FVC, GOLD Group A-E classification), and established risk factors for exacerbation (smoking pack-years, comorbidities, and history of >2 AECOPD hospitalizations in the 12 months preceding baseline).[3]

Ethical Clearance
The study was conducted in accordance with the ethical standards of the Declaration of Helsinki.[22] Formal Institutional Ethics Committee (IEC) approval was secured from the Career Institute of Medical Science & Hospital.[23] Given the non-interventional, retrospective nature of the study relying exclusively on de-identified, existing clinical data, the requirement for written informed consent was waived by the IEC.[22]

5.5. Statistical Analysis
Data processing and analysis were performed using IBM SPSS Statistics, Version 26.0 and R statistical software (version 4.2).[19]
Baseline comparisons of the four Vitamin D categories were conducted using Chi-square tests for categorical variables and ANOVA for continuous variables (Table 1). The time-to-event data (AECOPD hospitalization) was initially assessed using Kaplan-Meier survival curves, with comparisons made via the Log-Rank test.
The primary analysis employed Multivariate Cox Proportional Hazards Regression to determine the independent association between Vitamin D status and the hazard of AECOPD hospitalization (Table 2). The model specifically adjusted for established and statistically significant confounders identified in the baseline analysis, including age, BMI, GOLD E status, and a history of >2 previous hospitalizations. The proportional hazards assumption was assessed using Schoenfeld residuals and was satisfied. A two-sided P-value of <0.05 was considered statistically significant

Inclusion and Exclusion Criteria
Inclusion Criteria
- Patient records of individuals aged ≥40 years at the time of baseline 25(OH)D measurement.
- Spirometrically confirmed COPD diagnosis (post-bronchodilator FEV1/FVC ratio < 0.70).
- Availability of a baseline serum 25(OH)D level measured between 2020 and 2024.

- Complete 12-month follow-up data available for AECOPD hospitalization outcomes.

Exclusion Criteria

- Records indicating concurrent severe, confounding respiratory diseases (e.g., active pulmonary tuberculosis, severe pulmonary fibrosis, or asthma-COPD overlap syndrome where asthma is the predominant feature).
- Documentation of high-dose vitamin D supplementation (defined as >10,000 IU/week) or high-dose systemic corticosteroid use within six months preceding the baseline 25(OH)D measurement.
- Known secondary causes of vitamin D deficiency (e.g., severe liver failure, end-stage renal disease, or diagnosed primary malabsorption syndromes).
- Incomplete data required for primary exposure assessment or covariate adjustment (e.g., missing BMI or smoking history).

Data Collection Tool

The standardized data abstraction form was utilized to ensure comprehensive and consistent retrieval of necessary variables and confounders from the existing medical records [3]:

Results and Analysis

Baseline Demographic and Clinical Characteristics

The cohort of N=530 COPD patients had a mean age of 65.8 years and exhibited a male predominance (70.8%).

The analysis of vitamin D status revealed a significant burden of deficiency in the local population. Only 11.3% (n=60) of patients were sufficient vitamin D (>30 ng/mL). Most of the cohort (67.9%) fell below the 20 ng/mL deficiency threshold. Importantly, the SVDD category (<10 ng/mL) represented 30.2% (n=160) of the total patient population.

Table 1 presents the baseline characteristics stratified by vitamin D status. Statistically significant differences (P<0.001) were observed between the groups regarding BMI, active smoking status, and GOLD E classification.[6] Patients with SVDD exhibited the lowest mean BMI (20.2 kg/m^2), a factor indicative of systemic inflammation and cachexia.[18] Furthermore, the highest proportion of patients categorized into the high-risk GOLD E group (59.4%) was found in the Severe VDD category. Mean AECOPD hospitalizations in the subsequent 06 months were highest in the SVDD group (2.6 ±1.1), contrasting sharply with the sufficiency group (0.9 ±0.5).

Table 1: Baseline Demographic and Clinical Characteristics of COPD Patients Stratified by Vitamin D Status (N=530)

Characteristic	Severe VDD (<10 ng/mL) (n=160)	Deficiency (10–20 ng/mL) (n=200)	Insufficiency (20–30 ng/mL) (n=110)	Sufficiency (>30 ng/mL) (n=60)	P-Value
Age, mean (SD)	64.9 (7.8)	65.5 (7.5)	66.1 (6.9)	68.5 (6.0)	0.08
Male Sex, N (%)	118 (73.8)	142 (71.0)	75 (68.2)	39 (65.0)	0.41
BMI (kg/m²), mean (SD)	20.2 (3.2)	21.6 (2.9)	22.8 (3.5)	24.1 (4.0)	<0.001

Active Smoker, N (%)	75 (46.9)	70 (35.0)	30 (27.3)	12 (20.0)	<0.001
GOLD E Group, N (%)	95 (59.4)	78 (39.0)	25 (22.7)	8 (13.3)	<0.001
Mean AECOPDs/ 06 Months	2.6 (±1.1)	1.9 (±0.9)	1.2 (±0.7)	0.9 (±0.5)	<0.001

Multivariate Cox Proportional Hazards Regression Analysis

The results of the multivariate Cox regression, adjusting for clinically significant confounders, are presented in Table 2.

The analysis determined that Severe VDD (<10 ng/mL) was independently and significantly associated with an increased risk of AECOPD hospitalization. When compared to the Sufficiency group, the adjusted Hazard Ratio was 2.85 (95% CI: 1.60–5.09; P < 0.001). This result is consistent with recent international findings that identify SVDD as the critical risk factor.[5]

Crucially, after adjustment for covariates, the hazard ratios for Deficiency (10 to 20 ng/mL, HR 1.55, P=0.114) and Insufficiency (20–30 ng/mL, HR 1.10, P=0.725) were not statistically significant predictors of exacerbation risk. This outcome affirms the notion of a severe biological threshold existing below 10 ng/mL, rather than a linear relationship across the full deficiency spectrum.

As expected, high-risk disease markers were the strongest predictors of future exacerbation: GOLD E classification (HR 7.60) and a history of >2 AECOPD hospitalizations in the past 12 months (HR 2.90) were both highly significant risk factors (P<0.001).[4] The fact that SVDD maintains a high and significant HR (2.85) even when controlling for the profound exacerbation risk conferred by the GOLD E group demonstrates that severe nutritional deficiency is an independent, additive risk factor that must be addressed separately.

Table 2: Multivariate Cox Proportional Hazards Regression Analysis for Time to Next Severe COPD Exacerbation

Variable	**Adjusted Hazard Ratio (HR)**	**95% Confidence Interval (CI)**	**P-Value**
Vitamin D Status (Ref: Sufficiency >30 ng/mL)			
Severe VDD (<10 ng/mL)	2.85	1.60–5.09	<0.001
Deficiency (10–20 ng/mL)	1.55	0.90–2.67	0.114
Insufficiency (20–30 ng/mL)	1.10	0.65–1.87	0.725
Established Confounding Factors			
Age (per 10 years increase)	1.10	1.01–1.20	0.041
BMI (per unit decrease)	1.05	1.00–1.11	0.049

GOLD E Classification	7.60	3.05–19.00	<0.001
>2 AECOPD Hospitalizations (Past 12 Months)	2.90	2.05–4.10	<0.001

Discussion and Interpretation

Contextualizing the Deficiency Epidemic

The 67.9% prevalence of VDD (<20 ng/mL) and 30.2 % SVDD observed in this cohort confirms that hypovitaminosis D is an endemic condition among COPD patients in the Lucknow area, reflecting broader epidemiological data from Uttar Pradesh and the Indian subcontinent.[1] This high background deficiency rate amplifies the clinical significance of any systemic risk factor identified in this population.

The core finding is the highly robust, independent association between SVDD and AECOPD hospitalization risk. The adjusted HR of 2.85 rivals the predictive power of a history of frequent prior exacerbations (HR 2.90) and highlights the critical systemic vulnerability SVDD imposes.[4] This strong predictive link is crucial because it indicates that SVDD is not merely an indicator of general poor health or severe lung disease, but rather an independent, biologically meaningful, and potentially modifiable driver of exacerbation frequency.

Synergistic Pathophysiology: Environment and Nutrition

The high exacerbation risk quantified in this study can be interpreted within the unique high-risk environment of North India. The leading attributable risk factor for COPD DALYs in this region is air pollution.[1] High levels of particulate matter induce significant airway and systemic inflammation. Severe VDD cripples the host's capacity for anti-inflammatory regulation, specifically by impairing VDR signaling and failing to suppress pro-inflammatory pathways.[9] The resulting high AECOPD hazard is therefore understood because of a dual failure: relentless external inflammatory stress (pollution) meeting a severely compromised internal immunomodulatory system (SVDD).

Furthermore, the significant negative correlation between SVDD status and low BMI suggests that SVDD may be involved in the systemic consequences of advanced COPD, such as cachexia and muscle wasting.[18] Recognizing and addressing VDD may thus offer synergistic benefits beyond immunomodulation, potentially supporting respiratory muscle function and overall systemic health.

Comparison to International Standards and Guidelines

This study aligns with the newest international cohort analyses focusing on the SVDD threshold, providing a vital regional validation of a critical risk metric.[4] By differentiating between the lack of association in general deficiency and the highly significant risk in severe deficiency, this research provides the necessary evidence base for advocating targeted screening and supplementation, particularly since clinical trials show supplementation efficacy is restricted primarily to this severely deficient subgroup.[15]

Recommendations and Future Scope

Recommendations and Clinical Protocol

The high prevalence of SVDD and the quantified risk mandate a change in clinical practice at the Career Institute of Medical Science & Hospital.

- **Targeted Screening Protocol:** All patients diagnosed with COPD, particularly those categorized into GOLD Groups D or E, or those presenting with a history of >2 AECOPD hospitalizations in the past year, should undergo routine screening for serum 25(OH)D levels.[6]
- **Aggressive Supplementation:** Patients identified with Severe VDD (<10 ng/mL) should be prioritized for immediate, standardized high-dose Vitamin D replacement therapy, as this is the population most likely to experience a reduction in exacerbation frequency following intervention.[15]

This targeted approach ensures that scarce healthcare resources are utilized effectively, focusing intervention where the clinical return is highest.[25]

Future Scope for Research

- **Local RCT for Optimal Dosing:** The next phase of research should involve a prospective Randomized Controlled Trial (RCT) conducted locally, focusing exclusively on patients with SVDD (<10 ng/mL) to determine the optimal, effective, and safe dosage and duration of Vitamin D supplementation necessary to maintain target 25(OH)D levels (>30 ng/mL) and reduce AECOPD frequency in the North Indian cohort.[15]
- **Air Quality and Deficiency Correlation:** Further epidemiological studies are needed to quantitatively examine the influence of ambient air pollution (AQI data) in the Ghailla-Lucknow vicinity on Vitamin D status and exacerbation rates, enabling the development of comprehensive public health strategies that address both environmental and nutritional risks concurrently.[1]

Conclusion

Severe vitamin D deficiency, affecting nearly one-third of the COPD patients studied at this North Indian tertiary care center, is confirmed as a critical and independent prognostic indicator of frequent severe exacerbations requiring hospitalization, carrying an adjusted Hazard Ratio of 2.85. This systemic nutritional deficit should be viewed as an actionable risk factor. Proactive screening and targeted supplementation in high-risk COPD patients in the Lucknow vicinity are essential public health measures that hold significant promises for mitigating the substantial morbidity and healthcare burden associated with AECOPDs in the Uttar Pradesh region.

Application to Practical Findings

The results provide a tangible, evidence-based criterion for clinical resource management that is immediately applicable within the vicinity of the Career Institute of Medical Science & Hospital.

Given the high cost and logistical challenge of treating frequent AECOPDs, prioritizing preventative efforts is imperative. By demonstrating that the extreme SVDD group—representing 30.2% of the cohort—is responsible for a disproportionate share of the exacerbation risk, the study allows clinicians to focus their resources on this sub-population.[26] Instead of implementing costly universal screening, the institution can limit testing and high-dose supplementation to patients already identified as high-risk exacerbators (GOLD D/E), thereby offering the highest return on investment in preventative nutritional care.

Furthermore, these findings necessitate that COPD management protocols reflect the dual challenge of high environmental pollution and systemic deficiency common in this region.[1] Incorporating nutritional assessment and treatment for SVDD provides a systemic intervention that complements pharmaceutical management, ensuring a more holistic and robust approach to patient care in this specific geographical and epidemiological context.

Limitations of the Study

The inherent limitations of a retrospective design include the potential for residual confounding from unmeasured factors, such as genetic polymorphisms influencing vitamin D metabolism, or undocumented environmental exposures.[27] The reliance on hospitalization data limits the analysis to severe exacerbations, potentially obscuring any marginal effect of VDD on less severe, outpatient-managed AECOPDs.[28] While efforts were made to control for seasonality by utilizing data spanning multiple years (2020–2024), temporal variations in 25(OH)D levels remain a subtle bias in any single baseline measurement.[27] Finally, as a single-center study, the generalizability of the absolute prevalence of SVDD may be restricted to populations with similar access to tertiary care in the Lucknow area.

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