Baseline Vitamin D as a Predictor of Mortality among Hospitalized Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease in an Endemically Vitamin D-Deficient Area in North India

Mohammad Ramzan Bhat, Shabir Ahmad Dar¹, Mir Waseem¹, Mir Nadeem²

SDH Sopore, ¹GMC, Baramulla, ²GMC, Srinagar, Jammu and Kashmir, India

Abstract

Background: Conflicting data suggest that Vitamin D reduces the risk of developing chronic obstructive pulmonary disease (COPD) and COPD exacerbations. Scant data are available regarding the Vitamin D status in patients with COPD in India where Vitamin D deficiency is rampant. **Objectives:** We set out to study the role of baseline Vitamin D on the outcome of acute exacerbation of COPD (AECOPD) in terms of exacerbations, hospitalizations, and mortality. **Materials and Methods:** In a prospective observational design, 147 consenting participants with AECOPD were recruited and serum Vitamin D assessed at admission. The patients were followed for 3 months for treatment outcomes in terms of mortality, readmissions and exacerbations. Standard statistical methods were used to compare the results among those with sufficient and insufficient Vitamin D status at baseline. **Results:** Out of 147 completely followed participants, 113 (76.9%) were deficient in Vitamin D (mean $\pm$ standard deviation = 11.79 ± 8.5 [normal 30–100 ng/ml]). Patients with low Vitamin D were found to have a significantly higher 90-day mortality than those with normal Vitamin D status ($P = 0.42$; hazard ratio 4.8, $P = 0.032$). No statistically significant differences were observed in rates of exacerbations or hospital admission. **Conclusion:** Patients of AECOPD having baseline Vitamin D deficiency at admission have a higher mortality than those with normal Vitamin D level. Thus, Vitamin D level can serve as a prognostic indicator of the outcome of AECOPD. Larger studies are suggested to further study the association and also determine any role of Vitamin D in the treatment of such cases.

Keywords: Chronic obstructive pulmonary disease, hazard ratio, mortality, Vitamin D

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is featured by persistent airflow obstruction that is progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases and is amenable to prevention and treatment. COPD, a disease of mounting public health importance around the globe, is currently the fourth leading cause of death and estimates suggest that COPD will figure at the third most common cause of death worldwide by 2020.^[1] The prevalence of chronic airflow limitation in Kashmir, North India, that has temperate geography with severe winters is high with 17.3% in males and 14.8% in females.^[2]

The natural history of COPD apart from an inexorable decline in lung function, is punctuated by exacerbations which are

catastrophic events leading to excessive morbidity, high mortality, accelerated decline of lung function and a high economic cost. We have demonstrated recently that acute exacerbation in COPD (AECOPD) has a high 2-year mortality such that appropriate strategies aimed at reducing the frequency and severity of exacerbations are warranted.^[3] During exacerbations of COPD, mortality is high (39%)^[3] with a high correlation to per Capita Gross National Income with adjusted potential cofounders.^[2]

Address for correspondence: Dr. Mir Nadeem,

C/O Dr Mir Waseem, Doctors' Quarters, GMC, Baramulla, Kantbagh,
Baramulla - 193 101, Jammu and Kashmir, India.
E-mail: mirnadeem44@gmail.com

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While the importance of Vitamin D in bone health has been recognized for centuries, there has been recent interest in the extra-skeletal roles for Vitamin D including lung disorders.^[4] There is association of Vitamin D insufficiency with increased risk and severity of respiratory infections.^[5] The high prevalence of osteoporosis and osteopenia in COPD patients may be an indication of a link between Vitamin D deficiency and COPD.^[4] Vitamin D can be beneficial in reducing exacerbations when taken in adequate amount and for a prolonged period of time.^[6]

Previous studies on Vitamin D and COPD have recorded conflicting results and no data are available from the Indian subcontinent. Vitamin D deficiency is common in Kashmir (Indian administered);^[7] however, scant data are available on the prevalence of Vitamin D deficiency in COPD patients especially those with exacerbations and the influence, if any, on the outcomes of the exacerbations. The current study was designed against this backdrop to determine the baseline Vitamin D status of patients hospitalized with AECOPD in a high prevalence area for COPD with endemic Vitamin D deficiency and the effect of baseline Vitamin D status on 90-day mortality in such cases.

MATERIALS AND METHODS

Hundred and forty-seven consecutive consenting patients with AECOPD who presented to the emergency room (ER) of a 850-bedded tertiary care cum referral center of North India from June 2015 to May 2016, and required hospitalization were recruited for the study.

After recruitment, clinical history and examination were undertaken in all patients and recorded on a predefined case record form. History and patterns of smoking, use of any medications, history of exacerbations, comorbidities, and history of previous Vitamin D administration were specifically sought.

All patients underwent routine hematological and biochemical investigations. Radiography of the chest, electrocardiogram, sputum examination, and ultrasound of the chest/abdomen were obtained in all. Computed tomography of the chest and other investigations were performed as appropriate. Serial arterial blood gases were obtained in all patients for monitoring progress on treatment.

3–5 ml blood was collected in serum vial and kept at room temperature for half an hour. After the incubation, serum was separated by centrifuging the tubes at 2000 rpm for 5 min. Serum was transferred into 1.5 ml Eppendorf tubes and stored at -80°C . Vitamin D estimation was done by chemiluminescence method.

The patients were treated using standard protocols including bronchodilators, oxygen, noninvasive/invasive ventilation, antibiotics, steroids, antivirals (if appropriate), and other supportive measures. Daily monitoring was performed and patients discharged once stabilized. The patients were advised

to follow in the outpatient department on a weekly basis and post discharge follow-up was completed by telephonic surveys. Requirement for readmission or mortality was recorded. Followups were completed telephonically or by a personal home visit.

Written informed consent was taken from all study participants. The study was approved by PG Institutional Ethical Committee, Sher-i-Kashmir Institute of Medical Sciences, Srinagar.

Definitions and exclusions

COPD was defined as a postbronchodilator spirometry with an forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio of <0.7 and staging was based on FEV_1 ratio into Stages I, II, III, and IV as per GOLD criteria. Frequent exacerbations were defined as having ≥ 2 exacerbations treated with antibiotics and/or oral steroids and/or hospitalization in the last 12 months.^[1]

Patients having tuberculosis, primary pulmonary hypertension, pulmonary embolism, restrictive airway disease, conditions associated with Vitamin D metabolism, absorption or taking Vitamin D containing medications, and known autoimmune diseases or any active cancer in the last 5 years were excluded from the study.

Statistical methods

All analyses were performed on SPSS Version 20.0 (IBM Corp., IBM SPSS Statistics for Windows, Armonk, NY, USA). Student's independent *t*-test or Mann–Whitney U-test, whichever appropriate, was employed for comparing continuous variables. Chi-square test or Fisher's exact test, whichever appropriate, was applied for comparing categorical variables. Kaplan–Meier survival analysis and Cox regression analysis were performed to compare the survival pattern of patients with low and normal Vitamin D levels. $P < 0.05$ was considered as statistically significant.

RESULTS

The 147 recruited patients included 78 males and 69 females with ages ranging from 38 to 91 years (median 71 years) with the majority being aged >50 years [Table 1]. A history of ever smoking was elicitable in 68% of the participants, hookah smoking being the most common form of smoking. Other demographic features are summarized in Table 1.

Table 2 shows the baseline Vitamin D levels of the study participants. The mean value of Vitamin D was 23.61 ± 28.773 ng/ml (range = 1.11–155.87). Majority, i.e. 113 (76.9%) of the individuals had low levels of Vitamin D, 29 (19.7%) had normal levels of Vitamin D, and a small number, i.e. 5 (3.4%) had high levels of Vitamin D with mean $\pm$ standard deviation of 11.79 ± 8.565 (range = 1.11–29.53) ng/ml, 50.07 ± 19.328 (range = 31.12–99.59) ng/ml, and 137.19 ± 19.994 (range = 115.37–155.87) ng/ml, respectively, as shown in Table 2.

At the end of 3 months, 108 (73.47%) patients were alive and 39 (26.53%) had expired as shown in Figure 1. Those

Table 1: General characteristics of the study population

	Vitamin D		P
	Low (%)	Normal (%)	
Age (years)			
36-50	6 (100.0)	0 (0.0)	0.800
51-65	41 (78.8)	11 (21.2)	
66-80	49 (77.8)	14 (22.2)	
>80	17 (81.0)	4 (19.0)	
Gender			
Male	62 (83.8)	12 (16.2)	0.195
Female	51 (75.0)	17 (25.0)	
Smoking status			
Current smoker	14 (82.4)	3 (17.6)	0.956
Ex-smoker	61 (78.2)	17 (21.8)	
Nonsmoker	38 (80.9)	9 (19.1)	
Smoking type			
Cigarette	13 (76.5)	4 (23.5)	0.902
Huka	57 (79.2)	15 (20.8)	
Both	5 (83.3)	1 (16.7)	
BMI (kg/m ²)			
<18.5	2 (100.0)	0 (0.0)	0.762
18.50-24.99	65 (77.4)	19 (22.6)	
25.00-29.99	37 (84.1)	7 (15.9)	
≥30	9 (75.0)	3 (25.0)	
GOLD staging			
2	37 (77.1)	11 (22.9)	0.868
3	50 (80.6)	12 (19.4)	
4	26 (81.2)	6 (18.8)	

BMI: Body mass index

Table 2: Distribution of the participants as per Vitamin D levels

Vitamin D	n (%)	Mean±SD	Range
Low (<30 ng/ml)	113 (76.9)	11.79±8.565	1.11-29.53
Normal (30-100 ng/ml)	29 (19.7)	50.07±19.328	31.12-99.59
High (>100 ng/ml)	5 (3.4)	137.19±19.994	115.37-155.87
Total	147 (100)	23.61±28.773	1.11-155.87

SD: Standard deviation

who expired, i.e., 15 (10.2%) died during hospital stay and 24 (16.3%) died at home after discharge from the hospital. Those who expired during hospital stay were admitted with frequent exacerbations of COPD and type 2 respiratory failure. We were not able to ascertain the actual cause of death in 16.3% of patients who died at home but on telephonic communication, it was established that most of patients died of respiratory symptoms or had a sudden death.

On univariate analysis [Tables 3 and 4], a trend was observed toward a higher mortality in those aged <80 years compared to those aged >80 years; however, the difference was not statistically significant. There was gender-based difference in survival, but a significant difference of survival was observed among ever smokers versus nonsmokers. No differences in survival were observed based on the GOLD stage of the patients. Differences in survival were observed between those

Figure 1: Outcome at 3 months

with a normal serum Vitamin D level compared to those with a low Vitamin D levels (93.1% vs. 70.8%, respectively, odds ratio [OR] 0.18, $P = 0.014$). After exclusion of the patients with high Vitamin D from analysis, mean Vitamin D levels were higher among those who survived compared to those who did not [Table 4].

Hospital readmissions (>2) were observed in 35 (23.8%) cases. There were no statistical differences between Vitamin D levels among those with hospital readmissions (>2), and the frequency of exacerbations was similar among those with lower and normal Vitamin D levels. Hospital readmissions (≥2) were found in 23.9%, 20.7%, and 40.0% of the participants with low, normal, and high levels of Vitamin D levels, respectively. Mean levels of Vitamin D were not statistically different among those with exacerbations (≥2) compared to those with (≤2) exacerbations (27.20 ± 2.6 versus 33.3 ± 5.6, $P = 0.28$).

Figure 2 depicts Kaplan–Meier estimator showing two curves for normal and low levels of Vitamin D. Participants with low levels of Vitamin D had a survival of 70.8% against 93.1% survival of the participants with normal levels of Vitamin D. Overall survival of 75.9% was seen at 3-month follow-up. The mean survival time in weeks was 9.6 (confidence interval [CI] = 8.879–10.325) in those who died in low Vitamin D group against 11.5 (CI = 10.789–12.176) in those who died in normal Vitamin D group.

Multivariate proportional hazards analysis for Vitamin D is shown in Figure 2. Those participants who had low Vitamin D had mortality hazard ratio of 4.789 (1.149–19.961) as compared to the study participants having normal Vitamin D.

DISCUSSION

Our data show that patients with Vitamin D level of <30 have a higher 90-day mortality (29.2%) compared to those with normal Vitamin D levels (6.9%) with a hazard ratio for mortality as 4.789 (95% CI = 1.149–19.961). This study opens up newer vistas for possible intervention in AECOPD in our endemically Vitamin D-deficient population.

In this study, we have focused on the outcome of A/E of COPD viz a viz baseline Vitamin D levels with the assumption that decreased Vitamin D levels adversely affect the outcome of A/E of COPD. However, we could not find any statistical significance between Vitamin D levels and number of exacerbations and hospitalizations with P (0.633 and 1.00), respectively; same observations were made by study done by Lehouck *et al.* 2012.^[8] They also tried to explore whether

Table 3: Univariate analysis of various categorical variables

	Outcome		OR (95% CI)	P
	Survived, n (%), 108 (73.5%)	Expired, n (%), 39 (26.5%)		
Age (years)				
36-50	5 (83.3)	1 (16.7)	0.833 (0.070-9.858)	1.000
51-65	39 (72.2)	15 (27.8)	0.433 (0.111-1.687)	0.366
66-80	46 (69.7)	20 (30.3)	0.383 (0.101-1.449)	0.169
>80	18 (85.7)	3 (14.3)	Constant	
Gender				
Male	58 (74.4)	20 (25.6)	1.102 (0.529-2.294)	0.853
Female	50 (72.5)	19 (27.5)		
Smoking status				
Current smoker	16 (84.2)	3 (15.8)	1.094 (0.256-4.658)	1.000
Ex-smoker	53 (65.4)	28 (34.6)	0.388 (0.159-0.943)	0.033
Nonsmoker	39 (83.0)	8 (17.0)	Constant	
GOLD staging				
2	36 (72.0)	14 (28.0)	0.857 (0.312-2.354)	0.764
3	48 (73.8)	17 (26.2)	0.941 (0.355-2.489)	0.902
4	24 (75.0)	8 (25.0)	Constant	
Vitamin D* ng/ml				
Low (<30)	80 (70.8)	33 (84.6%)	0.179 (0.040-0.798)	0.014
Normal (30-100)	27 (93.1)	2 (6.9)		

OR: Odds ratio, CI: Confidence interval

Table 4: Unpaired t-test for different variables on admission versus outcome

	Mean±SD (range)		P
	Survived (n=108)	Expired (n=39)	
Age	68.12±10.26 (41-85)	67.20±10.06 (38-91)	0.632
FEV ₁	45.53±14.70 (21-115)	47.59±18.04 (18-83)	0.482
FVC	70.96±53.62 (38-113)	70.40±20.97 (42-121)	0.950
FEV ₁ /FVC	1.51±0.26 (0.69-1.70)	1.52±0.32 (0.63-1.70)	0.804
BMI	24.99±3.42 (17.7-36.7)	23.93±3.27 (18.3-35.1)	0.095
Vitamin D*	21.82±21.02 (1.11-99.59)	12.83±10.20 (1.91-45.17)	0.016 0.042**

*5 hypervitaminosis cases excluded from analysis, **Mann-Whitney U-test used for P value calculation. FEV₁: Forced expiratory volume in 1s, FVC: Forced vital capacity, BMI: Body mass index, SD: Standard deviation

supplementation with high doses of Vitamin D could reduce the incidence of COPD exacerbations. They designed a randomized, single-center, double-blind, placebo-controlled trial. 182 patients with moderate to very severe COPD and a history of recent exacerbations were studied. The median time to first exacerbation did not significantly differ between the groups (hazard ratio, 1.1 [CI, 0.82–1.56]; $P = 0.41$), nor did exacerbation rates, FEV₁, hospitalization, quality of life, and death.^[8]

Mekov *et al.* in their study found relatively low 1-year mortality in COPD patients after surviving severe exacerbation. They also noticed that Grade C and FEV₁ >80% may be factors for good prognosis, while age, FEV₁ value, severe exacerbation in previous year, and reduced quality of life were various risk factors for increased mortality. Cox regression showed

Figure 2: Kaplan-Meier survival analysis

that Vitamin D levels are not predictors for mortality.^[9] Zhu *et al.* in a systemic review and meta-analysis concluded that severe Vitamin D deficiency is associated with increased risk of COPD and severe COPD but not with COPD exacerbation. This meta-analysis showed that lower serum Vitamin D levels were found in COPD patients than in controls (standardized

mean difference (SMD) -0.69 , 95% CI, $P < 0.001$) especially in severe COPD (SMD: -0.87 , 95% CI; $P = 0.001$) and with COPD severity (OR: 2.83, 95% CI $P < 0.001$) but not with COPD exacerbation (OR; 1.17, 95% CI $P = 0.326$).^[10] Our study also did not demonstrate a higher risk of exacerbations or hospitalization in patients who were Vitamin D deficient compared to those who were having normal Vitamin D levels. However, Khan *et al.* concluded that when given for prolonged period, Vitamin D supplementation has significant effect in reducing number of AECOPD patients.^[11]

A recent study among Indian patients with COPD concluded that COPD is associated with a significantly low level of Vitamin D that was independent of patients' age, gender, BMI, and residence. The lower level of Vitamin D was associated with severity of COPD, increased frequency of A/E COPD and increased frequency of hospitalization. The relationship between lung functions and levels of vit D was almost linear.^[12] Our study was, however, not designed to address this outcome in Vitamin D-deficient participants.

Patients with COPD are at high risk for Vitamin D deficiency because they are more prone to skin aging (due to smoking), have reduced outdoor activity, exhibit reduced food intake, and are often treated with corticosteroids which increases Vitamin D catabolism. Epidemiological studies in healthy subjects have reported a strong relationship between 25-hydroxyvitamin D serum levels and pulmonary function, as assessed by FEV₁ and FVC.^[13]

Among many environmental and genetic factors, the role of various nutrients, especially Vitamin D in COPD has been studied by various researchers. Studies conducted so far showing the impact of Vitamin D deficiency on the outcome of COPD have shown mixed results in terms of mortality and morbidity.^[8,14-20] While findings from Monadi *et al.*^[15] indicated a relationship between serum Vitamin D levels and FEV₁ volume in COPD patients, Malinowski *et al.*^[17] concluded that severe Vitamin D deficiency was associated with more frequent COPD exacerbations and hospitalization. Further Lehouck *et al.*^[8] and Martineau *et al.*^[19] findings suggested that correction of Vitamin D deficiency in COPD patients reduces the risk of exacerbations.

However, there is definite mortality benefit in patients with normal levels of Vitamin D. We had 147 individuals for analysis; 5 cases were excluded in view of hypervitaminosis. The individuals who survived had higher mean Vitamin D levels compared to those expired with the difference statistically significant. Similar observation was made by Lee *et al.* 2014.^[16]

Controlled trials examining the supplementation of Vitamin D on reducing the respiratory tract infections (RTI's) have shown mixed results with some decreasing frequency of RTI and favoring supplementation while others have not demonstrated the same;^[21-31] however, cumulative benefits of Vitamin D being anti-inflammatory, antiautoimmune, antiangiogenic and

anticancer, antidepressant^[32] makes its deficiency compelling for the treating physician to get corrected. Advanced age and limited mobility limit the sun exposure of COPD patients, especially in cold areas with poor winter sun is likely to have an exacerbating effect on the Vitamin D status of this endemically Vitamin D-deficient area. Although there are other compelling reasons for treating Vitamin D deficiency in such cases, our data argue for another possible reason for addressing the Vitamin D-deficient status of such cases. However, the influence on the outcome of exacerbations needs be studied through carefully designed placebo-controlled studies.

CONCLUSION

Patients of AECOPD having baseline Vitamin D deficiency at admission have a higher mortality than those with normal Vitamin D level. Thus, Vitamin D level can serve as a prognostic indicator of the outcome of AECOPD. Larger studies are suggested to further study the association and also determine any role of Vitamin D in the treatment of such cases. Nonetheless Vitamin D supplementation in patients with demonstrable deficiency would certainly be of value regardless of its effect on the outcome of COPD whether it helps a favorable outcome needs further study.

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Conflicts of interest

There are no conflicts of interest.

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