

# Prevalence and Predictors of Osteoporosis in Patients of Interstitial Lung Disease: An Observational Study from North India

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## Abstract

**Background:** Osteoporosis has been widely reported in chronic respiratory diseases such as chronic obstructive pulmonary disease and cystic fibrosis. However, there is a scarcity of data on its prevalence and risk factors in interstitial lung disease (ILD), particularly in Indian patients. **Aims:** The present study was conducted to determine the prevalence and predictors of osteoporosis in ILD patients. **Materials and Methods:** We conducted a cross-sectional study, in which ILD patients presenting to the hospital were enrolled. After collecting demographic and clinical data, the patients underwent a dual-energy x-ray absorptiometry scan of the femoral neck to measure bone mineral density. Osteoporosis was diagnosed based on their T-scores, following the World Health Organization guidelines. Univariate and multivariate logistic regression analyses were performed to determine the risk factors of osteoporosis in ILD. **Results:** The mean age of the 97 ILD patients was 55.7 ± 12.6 years (range 28–84 years) with the predominance of females ( $n = 61$ ). Osteoporosis was detected in 39 (40.2%) patients. Female gender, duration of symptoms, and low hemoglobin level had a positive association with osteoporosis on univariate analysis ( $P < 0.05$ ). However, duration of symptoms (adjusted odds ratio [OR]-1.29; 95% confidence interval CI-1.02–1.63;  $P = 0.04$ ) and hemoglobin level (adjusted OR-0.59; 95% CI-0.39–0.89;  $P = 0.01$ ) were the independent risk factors of osteoporosis on multivariate analysis. **Conclusion:** Osteoporosis is common comorbidity seen in ILD patients. A longer duration of ILD symptoms and low hemoglobin level can predict the presence of osteoporosis in these patients.

**Keywords:** Bone mineral density, cross-sectional study, idiopathic pulmonary fibrosis, osteoporosis, predictors, prevalence, risk factors

## INTRODUCTION

Interstitial lung disease (ILDs) is a group of >200 diseases that is characterized by pulmonary fibrosis, often leading to progressive cough and breathlessness. Besides respiratory involvement, the disease is often associated with comorbidities such as coronary artery disease,<sup>[1]</sup> sleep-disordered breathing,<sup>[2]</sup> pulmonary hypertension,<sup>[3]</sup> gastro-esophageal reflux,<sup>[4]</sup> and depression,<sup>[5]</sup> that add to the symptoms and worsen the health-related quality of life of these patients.

Osteoporosis is clinically important comorbidity reported in different chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD),<sup>[6]</sup> cystic fibrosis,<sup>[7]</sup> and pulmonary hypertension.<sup>[8]</sup> Advanced age, lack of physical activity, poor nutritional status, tobacco smoking, long-term corticosteroid use, and systemic inflammation are some of the factors that increase the risk of osteoporosis in COPD

patients.<sup>[6,9,10]</sup> As many of these factors are also common in ILD patients, these patients may be at high risk of developing osteoporosis. Studies done outside India have shown a 13%–44% prevalence of osteoporosis in ILD patients. Old age, low body mass index (BMI), and Hispanic ethnicity are some of the factors that might increase the risk of osteoporosis in ILD.<sup>[11,12]</sup>

Recent studies have shown a significant burden of ILD among Indian patients.<sup>[13,14]</sup> However, studies evaluating bone mineral

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density (BMD) in ILD are lacking from this geographical region. The Western data cannot be extrapolated here due to differences in genetic makeup, lifestyles, and dietary habits. If the results are significant, management of osteoporosis will likely have significant clinical implications on the comprehensive treatment of ILD. Hence, the present study was conducted to determine the prevalence of osteoporosis as well as to evaluate its risk factors among ILD patients.

## MATERIAL AND METHODS

It was a cross-sectional study conducted in a tertiary care hospital of North India for 2 years (March 2018 to March 2020). All ILD patients (both newly diagnosed and those already on treatment) reporting to Pulmonary Medicine OPD were consecutively enrolled. The diagnosis of ILD was based on clinical, radiological, and pathological features using a multidisciplinary approach, as per the standard guidelines.<sup>[15,16]</sup> Based on the prevalence figures (13%–44%) from previous studies,<sup>[11,12]</sup> a sample size of 81 ILD patients was required to detect a 30% prevalence of osteoporosis with a 10% margin of error at 95% confidence level. After compensating for dropouts/incomplete data, it was decided to enroll 90 patients in the study. ILDs patients with concomitant COPD, patients with current or recent (in preceding 6 weeks) lower respiratory tract infection and acute exacerbation of ILD in the preceding 6 weeks and other chronic disorders such as congestive heart failure, renal or liver dysfunction, and malignancies that could affect BMD were excluded from the study. Informed and written consent was obtained from all patients. The study was approved by the institutional ethics committee of our teaching hospital (No. IEC/2017/70 dated 14/12.2017)

A detailed history was taken from the patients emphasizing the type and duration of symptoms, presence of diabetes, previous antituberculosis therapy, smoking history, and occupational/environmental exposure to probable inciting agents. Duration of symptom was calculated from the time of the first ILD-related symptom (cough or breathlessness). Wherever available, the patient's management records were checked to confirm the duration and type of symptoms. Detailed treatment history, especially focusing on the dose and duration of steroids was elucidated verbally and by checking medical records. A patient was said to have a history of significant steroid use if he had ever consumed the equivalent of > 10 mg prednisone for >3 months.<sup>[11]</sup> All patients underwent complete blood count, renal, and liver function tests. The disease severity was evaluated in terms of routine spirometry values, arterial oxygen saturation (SaO<sub>2</sub>), and 6-min walk distance (6-MWD). Spirometry was performed on RMS Helios 401 PC-based spirometer, in which forced expiratory volume in first second (FEV<sub>1</sub>), forced vital capacity (FVC), and FEV<sub>1</sub>/FVC values were recorded, as per the recent ATS guidelines.<sup>[17]</sup> Six-minute walk test (6MWT) was performed as per recommended guidelines, in which the distance covered by the patient (6MWD) as well as any change in oxygen saturation was recorded at the end of the test.<sup>[18]</sup>

A dual-energy x-ray absorptiometry (DEXA) scan of the femoral neck was performed to measure the BMD of the patients. The test was performed on the Hologic DXA system (Model: Discovery Wi; software: Apex). BMD was expressed as absolute values (grams per centimeter squared) and as standard deviations (SD) of means of T and Z scores. The T score is a standard deviation compared to a young adult, sex-matched control population. The Z score is a standard deviation compared to an age- and sex-matched control population. Diagnosis of osteoporosis was made using the World Health Organization guidelines according to which osteoporosis was defined when a T score is >-2.5.<sup>[19]</sup>

Results were analyzed as the number (%) of ILD patients having osteoporosis. Based on the existing evidence from previous studies<sup>[8,11,12]</sup> and the author's experience, certain patient and disease-related factors, i.e., age, gender, BMI, duration of symptom, severity parameters such as FVC, SaO<sub>2</sub>, 6-MWD, hemoglobin level, and diabetes were analyzed for their possible association with osteoporosis using logistic regression analysis.

## Statistical analysis

Quantitative variables were summarized as mean ± SD or median (interquartile range [IQR]) and qualitative variables as frequency/percentage. Unpaired student *t*-test/Mann-Whitney *U*-test and Chi-square test/Fisher's exact test were used, as appropriate, to compare continuous and nominal variables between ILD patients, with and without osteoporosis. Multivariate logistic regression analysis using the forward LR approach was used to find an association between different patient, disease, and therapy-related factors and the presence of osteoporosis. Multivariate model was used to measure the odds ratios (OR) with their 95% confidence intervals (CI), for different factors predicting osteoporosis. *P* value was considered statistically significant at <0.05. All statistical calculations were done using the computer program SPSS (IBM SPSS Statistics 21.0; Armonk, NY, USA).

## RESULTS

A total of 97 stable ILD patients were enrolled. The mean age of the study cohort was 55.7 ± 12.6 years (range 28–84 years) with a predominance of females (*n* = 61). Elderly patients comprised one-third of the total subjects (*n* = 36). Out of 97 patients, 35 (36.1%) were overweight/obese and 7 had BMI <18.5 kg/m<sup>2</sup>.

Exertional dyspnea was the most common presenting symptom (*n* = 90), followed by cough (*n* = 78). The median duration of symptoms was 2 years (IQR 1–4 years). One or more extra-pulmonary symptoms were seen in 72 (74.2%) patients. Thirty-six patients (37.1%) had a history of significant steroid use that was being given as a part of ILD treatment. In comparison, osteoporotic patients were more likely to be females (*P* = 0.03), anemic (*P* = 0.005), and had a longer duration of ILD symptoms (*P* = 0.04) [Table 1].

**Table 1: Baseline features of interstitial lung disease patients with and without osteoporosis**

Patient parameters	Osteoporosis group (n=39)	No osteoporosis (n=58)	P
Age (years)	54.9±11.8	56.2±13.3	0.61
Females	30 (76.9)	31 (53.4)	0.03
BMI (kg/m <sup>2</sup> )	23.9±4.4	23.5±3.0	0.54
Duration of symptoms (years), median (IQR)	3 (1-6)	1.5 (0.7-3.0)	0.04
Previous ATT	4 (10)	9 (15.7)	0.55
Significant steroid use	16 (41)	20 (34.4)	0.61
Diabetes	6 (15.3)	15 (25.8)	0.22
Ever smokers	5 (12.8)	8 (13.8)	0.77
SaO <sub>2</sub>	93.1±4.1	94.0±4.5	0.42
FVC (% predicted)	70.8±16.6	68.9±15.8	0.56
6MWD (m)	284±72	317±91	0.06
Hemoglobin (g/dl)	11.7±1.7	12.9±1.3	0.005

Values are mentioned as mean±SD or n (%) unless otherwise specified. BMI: Body mass index, ATT: Anti-tubercular therapy, SaO<sub>2</sub>: Arterial oxygen saturation, FVC: Forced vital capacity, IQR: Interquartile range, SD: Standard deviation, 6MWD: 6-min walk distance

### Subtypes of ILD

Hypersensitivity pneumonitis was the most common type of ILD seen in the study cohort (n = 23), followed by idiopathic pulmonary fibrosis (IPF) (n = 19) and connective tissue disease-associated ILD (CTD-ILD) (n = 16) [Figure 1].

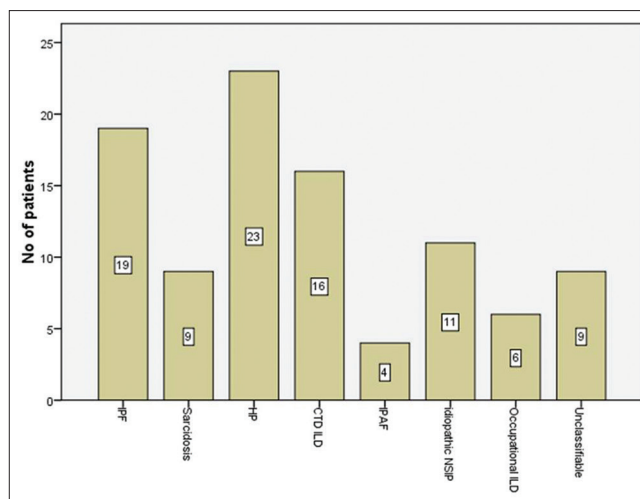
### Bone mineral density and its predictors in interstitial lung disease patients

Mean T-score of the study group was -2.12 + 1.1 [Table 2]. Osteoporosis was diagnosed in 39 (40.2%) patients on the DEXA scan. On univariate logistic analysis, duration of symptoms, female gender, and low hemoglobin were positively associated with osteoporosis (P < 0.05), whereas on multivariate logistic regression analysis, duration of symptoms (adjusted OR-1.29; 95% CI-1.02–1.63; P = 0.04) and hemoglobin level (adjusted OR-0.59; 95% CI-0.39–0.89; P = 0.01) were the factors that independently predicted osteoporosis in ILD patients [Table 3].

## DISCUSSION

The present study showed a high prevalence of low bone density among ILD patients with a 40.2% prevalence of osteoporosis. The results also demonstrated that a longer duration of ILD symptoms and low hemoglobin levels were positively associated with an increased likelihood of osteoporosis.

Osteoporosis is a skeletal disorder characterized by low bone mass with microarchitectural deterioration of bone tissue that compromises bone strength and increases the risk of fracture.<sup>[20]</sup> Low bone fragility has been found to be widespread in COPD patients.<sup>[6]</sup> However, the data in other chronic respiratory diseases, particularly ILD, are insufficient to validate the association. Caplan-Shaw *et al.* measured BMD



**Figure 1:** Bar chart showing distribution of different subtypes of interstitial lung diseases in the study population. HP: Hypersensitivity pneumonitis, CTD-ILD: connective tissue disease-associated interstitial lung disease, IPAF: Idiopathic pneumonia with autoimmune features, NSIP: Nonspecific interstitial pneumonia

in 86 ILD patients (excluding sarcoidosis) referred for lung transplantation and found a prevalence of 13% osteoporosis in their study.<sup>[11]</sup> Another study from Saudi Arabia found a prevalence of 44% osteoporosis among 196 newly diagnosed ILD patients.<sup>[12]</sup> Even though the patient profile and subtypes of ILD were different in the study,<sup>[12]</sup> but a high prevalence of osteoporosis seen in it, in concordance with the present study, highlights the extent of the problem and calls for the universal management of osteoporosis in ILD patients.

Osteoporosis is widely prevalent in apparently healthy adults both in India and outside. Conservative estimates suggest that around 20% of Indian women and about 10%–15% of men above 50 years of age have osteoporosis.<sup>[21]</sup> A recent retrospective analysis of BMD in 31,238 adults showed a prevalence of 18.3% osteoporosis in the healthy Indian population.<sup>[22]</sup> Keeping these figures in mind, a prevalence of 40.2% seen in our cohort suggests a possible causal role of disease-specific factors in predisposing osteoporosis. We, therefore, analyzed different patient, disease, and therapy-related parameters that could increase the risk of osteoporosis in these patients.

Duration of symptoms is a surrogate marker of the length or chronicity of the disease. In the present study, the duration of the first ILD symptom predicted osteoporosis in ILD patients. The plausible explanation for this association could be the persistent inflammatory/immune response seen in different subtypes of ILD, particularly IPF,<sup>[23]</sup> hypersensitivity pneumonitis,<sup>[24]</sup> and non-IPF idiopathic interstitial pneumonia<sup>[25]</sup> that facilitated bone resorption through certain chemical mediators resulting in osteoporosis. Transforming growth factor-beta is one such mediator seen in patients with pulmonary fibrosis that increases bone turnover by increasing the activity of osteoblasts and osteoclasts, leading to osteoporosis.<sup>[26]</sup> Apart from this finding,

**Table 2: Bone mineral density measurements in interstitial lung disease patients**

BMD parameters	Minimum	Maximum	Mean±SD
T score	-5.10	0.60	-2.12±1.1
Z score	-4.90	2.10	-1.22±1.42
BMD	0.505	1.115	0.80±0.146

BMD: Bone mineral density, SD: Standard deviation

**Table 3: Association of osteoporosis with different factors in interstitial lung disease patients**

Patient parameters	Univariate logistic regression, OR (95% CI)	P	Multivariate logistic regression, adjusted OR (95% CI)	P
Age	0.9 (0.96-1.02)	0.61		
female gender	2.9 (1.2-7.1)	0.02		
BMI	1.04 (0.92-1.16)	0.53		
Duration of symptom	1.24 (1.03-1.48)	0.02	1.29 (1.02-1.63)	0.04
Diabetes	0.51 (0.18-1.4)	0.21		
Significant steroid use	1.36 (0.49-3.7)	0.55		
FVC (% predicted)	0.99 (0.97-1.02)	0.56		
6MWD	1.01 (0.99-1.01)	0.20		
Hemoglobin	0.59 (0.40-0.87)	0.009	0.59 (0.39-0.89)	0.01
Non-IPF diagnosis	0.91 (0.26-3.2)	0.88		

BMI: Body mass index, FVC: Forced vital capacity, 6MWD: 6-min walk distance, CI: Confidence interval, OR: Odds ratio, IPF: Idiopathic pulmonary fibrosis, FEV<sub>1</sub>: Forced expiratory volume in 1 s

the results also showed that disease severity indices such as lung function test, arterial oxygen saturation, and 6MWD had no association with osteoporosis. Taken together, the findings imply that it is the chronicity of ILD and not its severity that increases the risk of osteoporosis. The results are also backed by previous studies which did not find any of these severity indicators as predictors of osteoporosis.<sup>[11,12]</sup>

Females are generally at higher risk of developing osteoporosis because of the hormonal changes occurring during menopause.<sup>[27,28]</sup> In the present study too, 23 (50%) out of the 46 females who were in the menopausal age group (>45 years) had osteoporosis at presentation. However, similar to previous studies,<sup>[11,12]</sup> the association was not statistically significant in multivariate analysis. Low hemoglobin level was the third variable that showed a significant association with osteoporosis in the study. Anemia, an indicator of poor nutritional status,<sup>[29]</sup> is an independent risk factor for osteoporosis in the general population.<sup>[30]</sup> However, its role in predicting osteoporosis in ILD has not been evaluated previously. Instead, low BMI, an anthropometric indicator of malnutrition has been observed to be an independent risk factor for osteoporosis previously (adjusted OR, 1.3; 95% CI, 1.1–1.6; *P* 0.007).<sup>[11]</sup> Incidentally, BMI values were not statistically different between

the two osteoporosis groups in our cohort. Nevertheless, the results suggest that poor nutrition might increase the risk of osteoporosis, and hence nutritional management should be an integral part of the treatment of ILD patients.

Older age is an established risk factor of osteoporosis in the general population. However, its role in ILD patients has yielded mixed results in earlier studies.<sup>[11,12]</sup> The present study also did not find a significant association between age and osteoporosis. This could be due to the narrow age range (middle age and elderly being common in ILD) of enrolled patients that apparently concealed the plausible association between age and osteoporosis. Long-term use of corticosteroids is a proven risk factor of osteoporosis.<sup>[8,31]</sup> However, similar to prior results on ILD patients,<sup>[11,12]</sup> we could not elicit the association between steroid use and osteoporosis. This might be because only 36 (37%) subjects in the study cohort were on steroid treatment which could have diluted its role in predisposing osteoporosis. Finally, the etiology of ILD (IPF v/s non-IPF) also did not have any association with the presence of osteoporosis in ILD patients in the study.

To the best of our knowledge, it is the first study from India to evaluate BMD in ILD patients. The results gave a clear insight into the prevalence and predictors of osteoporosis in ILD. Osteoporosis, by virtue of bony pains and an increased tendency for fractures, can add to the morbidity due to ILD. Further longitudinal studies are required to evaluate the long-term impact of osteoporosis on disease progression, health-related quality of life, and mortality. Our study had a few limitations as well. The cross-sectional design with a lack of a control arm in the study limited the strength of the association between ILD and osteoporosis. Nevertheless, comparing the prevalence of osteoporosis in ILD patients in our study (40.2%) with healthy controls from previous Indian studies (10%–18.3%)<sup>[21,22]</sup> showed a clear difference that served to validate the association between ILD and osteoporosis. The present study included the hospital-based data of ILD patients that might be different from population-based figures. However, the results derived in the hospital-based setting are more clinically relevant and practically actionable. Prior calcium and/or Vitamin D supplementation was not studied in the patients which might have affected the results of the study. Finally, the level of physical activity was not assessed in the study participants which could have confounded the results. Instead, we evaluated 6-MWD, a marker of functional exercise capacity, which did not have any association with osteoporosis [Table 3].

## CONCLUSION

Osteoporosis seems to be a common extra-pulmonary manifestation of ILD. Apart from general risk factors, the long duration of ILD and low hemoglobin level might predict osteoporosis in these patients. The results advocate for universal assessment of BMD in ILD patients. The findings also call for future research in the form of large sample-sized

studies with a longitudinal design that not only serves to assess the long-term impact of osteoporosis on ILD but also evaluates different treatment options for managing both conditions comprehensively.

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### Conflicts of interest

There are no conflicts of interest.

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