Investigation of osteoporosis and its influencing factors in a group of Chinese patients with Interstitial Lung Disease

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Abstract

Background

Interstitial lung disease (ILD) seriously influences patient's quality of life (QOL) due to an abnormally repaired lung structure and damaged lung function, as well as its many complications. Osteoporosis is a systemic bone disease characterized by low bone mineral density (BMD) and may impair QOL and increase mortality in ILD patients. We conducted this study to investigate osteoporosis in Chinese ILD patients.

Methods

We performed a cross-sectional survey of 179 Chinese ILD patients. BMD levels were evaluated, and the clinical variables of the patients were recorded. The physical activity and QOL of patients were evaluated by a questionnaire when enrolled. Regression analysis was used to identify factors affecting BMD in ILD patients.

Results

In total, 68.2% of the included patients had an abnormal BMD, 24.6% had osteoporosis, and 43.6% had osteopenia. Decreased of BMD in ILD patients was associated with multiple factors, of which sex, height, weight, ILD subtypes and serum parathyroid hormone (PTH) were most significantly. The QOL of ILD patients with osteoporosis is dramatically declining.

Conclusions

Osteoporosis and osteopenia have high prevalence rates in ILD patients and seriously affect patients' QOL. The development of osteoporosis and low BMD in ILD patients are influenced by multiple factors. Early identification and interventions are expected to benefit the QOL of ILD patients.

Introduction

Interstitial lung disease (ILD) is a group of diffuse pulmonary parenchymal diseases characterized by different degrees of inflammation and pulmonary fibrosis, eventually leading to irreversible damage to the lung structure and a dramatic decline in the patient's lung function[1]. The primary purposes of ILD treatment include extending the patient's lifespan and improving the patient's quality of life (QOL), both of which remain challenging [2, 3]. Growing evidence indicates that the QOL of ILD patients is affected not only by the severity of ILD but also by comorbidities.

Osteoporosis is a systemic bone disease characterized by low bone mineral density (BMD) and the degeneration of the bone tissue microstructure, resulting in increased bone fragility and an increased incidence of fractures, which is a serious consequence of osteoporosis that is associated with a high mortality rate [4]. The onset of osteoporosis is often insidious, without clinical manifestations [5]. Osteoporosis is common in all ethnicities and regions, and imposes substantial health and economic burdens on individuals, families and societies. In the United States, approximately 10 million people have osteoporosis, and approximately 18 million people have low bone mass. In Italy, 4.5 million individuals have osteoporosis, and in China, 35% of the people over the age of 65 have osteoporosis [5–7]. Ethnicity, age, sex, malnutrition, lifestyle and glucocorticoid use are commonly associated with the risk of osteoporosis.

Patients with ILDs may have high prevalences of osteoporosis and osteopenia [8, 9]. Their advanced mean age, reduced level of daily activity, chronic hypoxia due to dyspnea, and excessive use of glucocorticoids are risk factors for osteoporosis, which may explain the high prevalence of osteoporosis in ILD patients [10].

There have been few studies on the status of and factors influencing osteoporosis in Chinese ILD patients, whose ethnic background and eating habits differ from those of Western populations. Therefore, we designed this cross-sectional study to investigate the status of osteoporosis in Chinese ILD patients, the influencing factors and the impact of osteoporosis on these patients' QOL. The identification of the high-risk population would facilitate the provision of effective prevention and treatment in clinical practice, which could improve patients' QOL.

Methods

Study design and subjects

In this cross-sectional study, ILD patients in the Department of Pulmonary and Critical Care Medicine, Beijing Chaoyang Hospital, Capital Medical University, who met the diagnostic criteria from December 2018 to December 2019 were enrolled. The diagnosis of ILDs was based on the international consensus definition, according to clinical (manifestations, exposure history, smoking history, associated diseases, pulmonary function, and laboratory results) and chest high-resolution computed tomography (HRCT) features, and pathological examination of the lung was performed for patients with atypical imaging [1]. Patients with osteogenesis imperfecta, hyperparathyroidism, a history of organ transplant, multiple myeloma or other hematologic tumors, short bowel syndrome or other inflammatory bowel diseases, and acromegaly or Marfan's syndrome were excluded. Other exclusion criteria included renal insufficiency (creatinine clearance less than 50 milliliters/minute), hemodialysis, participation in any drug trials, pregnancy or breastfeeding, and lack of informed consent.

Collection of demographics and clinical characteristics

We collected the demographic data of the enrolled patients, including the following information: age, sex, height, weight, body mass index (BMI), education, economic status and smoking status. BMI was calculated as the weight in kilograms divided by the height in meters squared.

The duration of disease, history of fragility fractures, pulmonary function, HRCT findings and ILD subtype were also recorded. Pulmonary function was measured in all enrolled patients in accordance with the international guidelines, and the values of the pulmonary function test were recorded as shown in Table 2 and Table 3[11]. The scores for ground-glass opacities and fibrosis on chest HRCT in both lungs were determined by two observers who were blinded to the identify of the patients. Three sections were scored, namely, the level of the aortic arch, the carina, and 1 cm above the diaphragm [12, 13]. The average values for ground-glass opacities and fibrosis were calculated, and the score range for ground-glass opacities and fibrosis was 0 ~ 5 according to the extent of the lesions on the image. The higher the score was, the greater the extent of the lesions.

Osteoporosis-associated clinical examination

BMD was examined by dual energy X-ray absorptiometry (DXA), which was completed at the time of entry into this study. The diagnosis of osteoporosis was based on the T value calculation of BMD measured by DXA according to the World Health Organization (WHO). A T value lower than or equal to -2.5 was defined as osteoporosis, a T value between -1.0 and -2.5 was defined as osteopenia, and a T value greater than -1.0 was defined as normal bone density [6]. We measured BMD at the lumbar spine and femoral subregions using the same DXA device in all subjects at the time of enrollment. Three representative BMD results were obtained: lumbar spine (LS), femoral neck (FN) and total hip (TH). The T value was calculated as follows: (measured value-peak BMD of normal young people of the same race and same sex) / standard deviation of peak BMD of normal young people of the same race and same sex [6]. The levels of serum intact parathyroid hormone (PTH) and 25-hydroxyvitamin D₃ (25(OH)VitD₃) were recorded. According to the clinical guidelines of the Endocrine Society, vitamin D deficiency was defined as a 25(OH)VitD₃ level less than 20 ng/mL, and vitamin D insufficiency was defined as a 25(OH)VitD₃ level less than 20–30 ng/mL[14].

Health-related QOL survey

All patients completed three questionnaires at the time of enrollment. The International Physical Activity Questionnaire Short Form (IPAQ-SF) consisted of 7 questions, 6 of which asked about the weekly frequency and activity duration of vigorous physical activity, moderate physical activity and walking, and the last question asked about the time spent sitting. Based on the latest expert opinion, the metabolic equivalent (MET) (in minutes) for walking in the IPAQ-SF was 3.3, the MET for moderate physical activity was 4.0, and the MET for vigorous physical activity was 8.0[15]. According to the Chinese IPAQ Guidelines, for the IPAQ-SF, an individual's weekly physical activity level at any intensity was calculated as follows: the weekly frequency of physical activity per MET category (day/week)* the daily duration (min/day). The results were divided into low, medium and high groups according to the standards [16].

The 16-item Assessment of Health-Related Quality of Life in Osteoporosis (ECOS-16) is a short questionnaire, that was first proposed by Badia *et al* and has been used to evaluate the QOL of osteoporosis patients [17]. The ECOS-16 includes 16 items and is divided into four dimensions: pain, physical functioning, fear of illness, and psychological functioning. Pain and physical functioning constituted the physical summary score, and fear of illness and psychological functioning constituted the mental summary score. Each item has 5 responses on a scale ranging from 1 to 5, and a high score means a worse QOL[17, 18].

The Short-Form 36-item Questionnaire (SF-36) has been widely used to assess QOL in patients with osteoporosis and contains a total of 36 items, divided into 8 domains, with scores from 0-100 in each domain. The physical component summary scale (PCS) and the mental component summary scale (MCS) are the average scores of the first four domains and the last four domains, respectively, indicating the degree of physiological and mental impairment [20]. A lower score on the SF-36 indicates a worse QOL.

Statistical analysis

The variables are presented as the means $\pm$ SDs or percentages. Two-sample t-tests, nonparametric tests, and χ^2 tests were used to compare the differences in variables between patients with normal BMD values and low BMD values, and analysis of variance (ANOVA) was used to analyze differences in QOL among normal controls, patients with osteopenia and patients with osteoporosis. Spearman's correlation was used to evaluate the relationships between osteoporosis and variables. Linear regression was used to identify the factors affecting BMD, and the variables with a *P* value < 0.1 in the univariate regression were included in the multivariate model. All statistical analyses were performed using IBM SPSS statistics version 24.

Results

Characteristics of patients

Of the original 212 eligible patients, 30 refused to undergo the DXA examination, and 3 did not complete questionnaires; 179 patients were eventually included in this study (Fig. 1). The average age of all enrolled patients was 62.98 ± 9.90 years old, 86 (48%) were male, and 93 (52%) were female. In this study, 137 patients had IIPs, 34 patients had connective tissue disease-associated interstitial lung diseases (CTD-ILD) and 8 patients had other types. The patients with IIPs were 9 with idiopathic pulmonary fibrosis (IPF), 2 with idiopathic nonspecific interstitial pneumonia (NSIP), 17 with interstitial pneumonia with autoimmune features (IPAF), 7 with cryptogenic histologic pneumonia (COP), 1 with lymphatic carcinoma, and 101 patients with un-classified subtypes. Six patients with pulmonary sarcoidosis and 2 patients with hypersensitivity pneumonitis (HP) were included in the other subtype. The baseline characteristics of the patients are shown in Table 1 and Table 2.

Table 1
The general characteristics of the patients by BMD result

Variable	Normal BMD N = 59	Low BMD N = 120
	Mean $\pm$ SD or proportion	Mean $\pm$ SD or proportion
Age, (years)	60.81 $\pm$ 11.56	64.04 $\pm$ 8.82**
Sex, Female	12(20.3%)	81(67.5%) ***
Height, (cm)	168.36 $\pm$ 7.91	160.03 $\pm$ 7.90 ***
Weight, (Kg)	72.84 $\pm$ 12.58	64.05 $\pm$ 9.90 ***
BMI, (Kg/m ²)	25.62 $\pm$ 3.41	25.02 $\pm$ 3.50
Duration, (month)	15.73 $\pm$ 19.01	20.15 $\pm$ 30.52
Fracture	1 (1.7%)	3 (2.5%)
Education *		
Primary and below	14 (23.7%)	47 (39.2%)
Junior high school	19 (32.2%)	31 (25.8%)
High school	16 (27.1%)	31 (25.8%)
University and above	10 (16.9%)	11 (9.2%)
Economic, (yuan/month)		
0-3000	23 (39.0%)	47 (39.2%)
3000–6000	26 (44.1%)	63 (52.5%)
6000–9000	5 (8.5%)	6 (5.0%)
>9000	5 (8.5%)	4 (3.3%)
Smoking **		
Never smoker	23 (39.0%)	76 (63.3%)
Previous smoker	29 (49.2%)	33 (27.5%)
Smoker	7 (11.9%)	11 (9.2%)
ILD subtypes		

Results are given as mean $\pm$ SD or number (%); *=*P* value between normal and low BMD measurements. *, *P* $\leq$ 0.05; **, *P* $\leq$ 0.01; ***, *P* $\leq$ 0.001.

BMI, body mass index; ILD, interstitial lung disease; IIPs, idiopathic interstitial pneumonias; CTD-ILD, connective tissue disease-associated interstitial lung diseases.

Variable	Normal BMD N = 59	Low BMD N = 120
IIPs	50 (84.7%)	87 (72.5%)
CTD-ILD	6 (10.2%)	28 (23.3%)
Others	3 (5.1%)	5 (4.2%)
Physical activity		
Low	31 (52.5%)	80 (66.7%)
Medium	24 (40.7%)	34 (28.3%)
High	4 (6.8%)	6 (5.0%)
Results are given as mean $\pm$ SD or number (%); *= <i>P</i> value between normal and low BMD measurements. *, $P \leq 0.05$; **, $P \leq 0.01$; ***, $P \leq 0.001$.		
BMI, body mass index; ILD, interstitial lung disease; IIPs, idiopathic interstitial pneumonias; CTD-ILD, connective tissue disease-associated interstitial lung diseases.		

Table 2
The clinical characteristics of patients by BMD results

Variable	Normal BMD		Low BMD	
	N	Mean $\pm$ SD or proportion	N	Mean $\pm$ SD or proportion
Pulmonary function test				
FVC (L)	56	2.96 $\pm$ 0.93 ***	112	2.44 $\pm$ 0.72
FVC (% of predicted)	56	82.13 $\pm$ 18.36 **	112	93.68 $\pm$ 23.46
FEV ₁ (L)	56	2.37 $\pm$ 0.72 ***	112	1.94 $\pm$ 0.55
FEV ₁ (% of predicted)	56	82.59 $\pm$ 8.44**	112	91.42 $\pm$ 20.90
FEV ₁ /FVC (%)	56	94.37 $\pm$ 10.55	112	95.12 $\pm$ 8.51
DLco (mmol/min/kPa)	56	5.10 $\pm$ 2.14	111	4.65 $\pm$ 1.54
DLco (% of predicted)	56	59.68 $\pm$ 21.83	111	64.68 $\pm$ 20.14
TLC (L)	56	4.54 $\pm$ 1.20 ***	112	3.89 $\pm$ 0.97
TLC (% of predicted)	56	74.98 $\pm$ 15.59	112	79.88 $\pm$ 16.83
HRCT score	56		105	
Ground-glass score		4.26 $\pm$ 2.75**		3.34 $\pm$ 2.65
Fibrosis score		3.27 $\pm$ 2.49		2.57 $\pm$ 1.95
25(OH)VitD ₃ , (ng/ml)	56	21.62 $\pm$ 10.47***	109	16.12 $\pm$ 8.85
PTH, (pg/ml)	53	39.14 $\pm$ 21.21*	107	48.57 $\pm$ 22.93
ILD-GAP	59	2.44 $\pm$ 1.67*	120	1.73 $\pm$ 1.87
Data are given as mean $\pm$ SD; *= <i>P</i> value between normal and low BMD measurements. *, <i>P</i> $\leq$ 0.05; **, <i>P</i> $\leq$ 0.01; ***, <i>P</i> $\leq$ 0.001.				
FVC, forced vital capacity; FEV ₁ , forced expiratory volume in 1 second; DLco: diffusing capacity of the lung for carbon monoxide; TLC, total lung capacity; HRCT, high-resolution computed tomography; 25(OH)VitD ₃ , 25-hydroxyvitamin D ₃ ; PTH: intact parathyroid hormone; ILD-GAP, ILD-gender, age, physiology Index; BMD: bone mineral density.				

Table 3
Unadjusted analysis of factors associated with osteoporosis

Variable	Osteoporosis	
	Correlation Coefficient	P-Value
Sex	0.516	0.000
Age	0.155	0.038
Height	-0.481	0.000
Weight	-0.381	0.000
Education	-0.187	0.012
Smoking	-0.278	0.000
ILD subtypes	0.185	0.013
FVC (L)	-0.291	0.000
FVC (% of predicted)	0.305	0.000
FEV ₁ (L)	-0.325	0.000
FEV ₁ (% of predicted)	0.233	0.002
TLC (L)	-0.289	0.000
TLC (% of predicted)	0.179	0.020
Ground-glass score	-0.156	0.047
25(OH)VitD ₃ , (ng/ml)	-0.305	0.000
ILD-GAP	-0.209	0.005
Physical Activity Level	-0.145	0.052
BMI, body mass index; ILD, interstitial lung disease; FVC, forced vital capacity; FEV ₁ , forced expiratory volume in 1 second; DLco: diffusing capacity of the lung for carbon monoxide; TLC, total lung capacity; 25(OH)VitD ₃ , 25-hydroxyvitamin D ₃ ; PTH: intact parathyroid hormone; ILD-GAP, ILD-gender, age, physiology Index; BMD: bone mineral density.		

The BMD value and factors influencing decreased BMD

Of our 179 enrolled Chinese ILD patients, 59 (33%) had normal BMD, and 120 (67%) had low BMD. The mean LS-BMD, FN-BMD and TH-BMD of patients with low BMD (1.26 ± 0.15 , 1.05 ± 0.14 , 1.09 ± 0.12) were significantly lower than those of patients with normal BMD (0.97 ± 0.13 , 0.81 ± 0.10 , 0.86 ± 0.11). Among the patients with low BMD, 76 patients met the diagnostic criteria for osteopenia, and 44 patients met the diagnostic criteria for osteoporosis. There were significant differences in age, sex, height, weight,

education, smoking, pulmonary function, HRCT findings, and the levels of vitamin D and PTH between the two groups.

Thirty-nine (41.9%) female patients had osteoporosis, while 5 (5.8%) male patients had osteoporosis. Female patients had lower BMD values at all sites than male patients and were more prone to osteoporosis. The average age of patients with low BMD was older than that of patients with normal BMD, and patients with low BMD also had lower average values for height, weight, and BMI. In multiple regression analysis, sex, height and weight had a significant effect on BMD (Table 6). More than half of the previous and current smokers were in the normal BMD group, while 63.3% of the patients in the low BMD group had never smoked; smoking was significantly associated with osteoporosis and had a lower BMD at any site. Compared to the low BMD group, the normal BMD group had a higher proportion of patients with higher education (Table 1, Table 4, Table 5).

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Table 4
Stratified pulmonary function by sex and height between normal and low BMD groups

Variable		Normal BMD		Low BMD	
		N	Mean $\pm$ SD or proportion	N	Mean $\pm$ SD
FVC (% of pred)					
Height $\leq$ 160cm	Female	31	92.11 $\pm$ 23.95	29	99.42 $\pm$ 24.44
160 $\leq$ Height $\leq$ 170cm	Male	12	82.73 $\pm$ 15.89	22	94.41 $\pm$ 19.36
	Female	8	83.20 $\pm$ 24.16	21	92.98 $\pm$ 21.87
170cm $\leq$ Height	Male	28	83.67 $\pm$ 19.09	17	77.74 $\pm$ 23.13
FEV ₁ (% of pred)					
Height $\leq$ 160cm	Female	31	88.54 $\pm$ 21.55	29	93.83 $\pm$ 20.13
160 $\leq$ Height $\leq$ 170cm	Male	12	86.79 $\pm$ 16.15	22	95.11 $\pm$ 18.29
	Female	8	82.70 $\pm$ 21.72	21	91.14 $\pm$ 22.74
170cm $\leq$ Height	Male	28	83.40 $\pm$ 19.38	17	79.64 $\pm$ 20.67
FEV ₁ /FVC (%)					
Height $\leq$ 160cm	Female	31	94.10 $\pm$ 7.52	29	93.49 $\pm$ 9.07
160 $\leq$ Height $\leq$ 170cm	Male	12	99.15 $\pm$ 7.96	22	97.48 $\pm$ 6.66
	Female	8	96.39 $\pm$ 8.31	21	96.32 $\pm$ 7.52

Data are given as mean $\pm$ SD; *=*P* value between normal and low BMD measurements. *, *P* $\leq$ 0.05; **, *P* $\leq$ 0.01; ***, *P* $\leq$ 0.001.

FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; DLco: diffusing capacity of the lung for carbon monoxide; TLC, total lung capacity.

Variable			Normal BMD	Low BMD
			NMean ± SD or proportion	NMean ± SD or proportion
170cm ≤ Height	Male	28	91.91 ± 12.28	17 94.60 ± 11.50
DLco (% of pred)				
Height ≤ 160cm	Female	31	61.97 ± 19.92	29 67.26 ± 19.66
160 ≤ Height ≤ 170cm	Male	12	64.74 ± 22.45	22 64.95 ± 17.56
	Female	8	60.38 ± 27.72	21 67.24 ± 23.93
170cm ≤ Height	Male	28	60.83 ± 21.91	17 53.70 ± 17.60
TLC (% of pred)				
Height ≤ 160cm	Female	31	79.09 ± 17.57	29 82.75 ± 18.06
160 ≤ Height ≤ 170cm	Male*	12	70.75 ± 11.43	22 81.36 ± 11.89
	Female	8	76.49 ± 18.08	21 81.59 ± 19.46
170cm ≤ Height	Male	28	75.98 ± 15.76	17 70.72 ± 14.74
Data are given as mean ± SD; *=P value between normal and low BMD measurements. *, P ≤ 0.05; **, P ≤ 0.01; ***, P ≤ 0.001.				
FVC, forced vital capacity; FEV ₁ , forced expiratory volume in 1 second; DLco: diffusing capacity of the lung for carbon monoxide; TLC, total lung capacity.				

Table 5
Univariate analysis of the influencing factors of bone mineral density

Variable	Bone Mineral Density		
	Lumbar Spine	Femoral neck	Total Hip
Sex	-0.189***	-0.170***	-0.184***
Age, (year)		-0.002(P = 0.097)	
Height, (cm)	0.011***	0.010***	0.010***
Weight, (Kg)	0.006***	0.006***	0.006***
Duration, (month)	-0.001	-0.001 (P = 0.056)	-0.001**
Education	0.042*	0.025*	0.030**
Economic	0.063**	0.045**	0.047**
Smoking	0.074**	0.03***	0.073***
ILD subtypes	-0.049	-0.053*	-0.056**
FVC (L)	0.074***	0.079***	0.081***
FEV ₁ (L)	0.100***	0.101***	0.103***
DLco(mmol/min/kPa)	0.021*	0.016*	0.021**
TLC (L)	0.057***	0.060***	0.064***
ILD-GAP	0.023**	0.020**	0.021**
25(OH)VitD ₃ , (ng/ml)	0.005**	0.005***	0.005***
PTH, (pg/ml)	-0.001	-0.002**	-0.001 (p = 0.052)
The correlation coefficients were presented in the table. * represents the <i>P</i> value of correlations between variables and BMD at lumbar spine, femoral neck, and total hip in the univariate linear regression analysis. *, $P \leq 0.05$; **, $P \leq 0.01$; ***, $P \leq 0.001$.			
ILD, interstitial lung disease; FVC, forced vital capacity; FEV ₁ , forced expiratory volume in 1 second; DLco: diffusing capacity of the lung for carbon monoxide; TLC, total lung capacity; ILD-GAP, ILD-gender, age, physiology Index; 25(OH)VitD ₃ , 25-hydroxyvitamin D ₃ ; PTH: intact parathyroid hormone.			

Patients with IIPs accounted for the majority in both groups, and the proportion of patients with CTD-ILD in the low BMD group (23.3%) was higher than that in the normal BMD group (10.2%). ILD subtypes were significantly correlated with osteoporosis, and the BMD values in patients with CTD-ILD, pulmonary sarcoidosis and HP were clearly reduced (Table 4, Table 5). In multivariate regression, ILD subtypes had a significant effect on FN-BMD and TH-BMD (Table 6).

ILD patients with normal BMD had better pulmonary function than those with low BMD. The actual measured values of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), carbon monoxide diffusion capacity (DLco) and total lung capacity (TLC) were significantly higher in patients with normal BMD, while the percentages of the predicted FVC, FEV₁, DLco and TLC were clearly lower in patients with normal BMD than in those with low BMD (Table 2). The actual measured values of FVC, FEV₁ and TLC were positively correlated with the formation of osteoporosis (Table 4). To elucidate this difference, we stratified pulmonary function by sex and height, and there was no significant difference in the percentages of the predicted FVC, FEV₁, DLco and TLC between normal and low BMD groups (Table 3). Regression analyses showed that the actual measured values of FVC, FEV₁, DLco and TLC were significantly associated with BMD at any site, while in multivariate analysis pulmonary function values showed no association with the BMD (Table 5, Table 6).

Patients with low BMD had lower ground-glass opacity scores and the average ground-glass opacity score was significantly different between the two groups, while there was no significant difference in the fibrosis score. The mean levels of vitamin D and PTH were significantly different between the two groups: normal BMD patients had lower vitamin D and higher PTH levels (Table 1, Table 2). The average vitamin D level was significantly correlated with osteoporosis and BMD at any site (Table 5). The level of vitamin D decreased markedly with a decrease in BMD (Fig. 4). The PTH level was obviously correlated with FN-BMD and TH-BMD in multivariate analysis, while vitamin D was not associated with BMD at any site (Table 6).

A total of 111 (62%) of the included patients had low physical activity levels, of whom 80 (44.7%) had low BMD. The group with osteoporosis had a higher proportion (70.5%) of patients with low activity levels than the proportion of the group with osteopenia (64.5%) and normal BMD (52.5%). A significantly lower proportion of patients with medium activity (27.3%) than the normal BMD group (40.7%) (Fig. 5). Compared with the other groups, the group with normal BMD had higher proportions of patients with medium and high physical activity levels (47.5% vs 33.3%). The mean physical activity level in the normal BMD group was higher than that in the group with osteoporosis ($P = 0.06$) (Fig. 3). The physical activity level was not significantly correlated with osteoporosis ($P = 0.052$), but the distribution was different among the three groups.

Impact of osteoporosis on the QOL in ILD patients

The physical score and mental score of the ECOS-16 were significantly higher in the osteoporosis group than in the other groups ($P < 0.01$). The difference in the ECOS-16 score between osteopenia group and normal BMD group was not statistically significant. Compared with the osteopenia group and the normal group, the osteoporosis group had a significantly lower PCS score on the SF-36. The PCS score on the SF-36 was significantly different between the osteoporosis group and the other two groups ($P < 0.01$). Although the MCS score on the SF-36 was lower in patients with osteoporosis than in patients with osteopenia and normal BMD, the differences were not significant (Table 7).

Table 6
Multiple regression analysis of the influencing factors of bone mineral density

Variables	Bone Mineral Density		
	Lumbar Spine	Femoral neck	Total Hip
Sex		0.127**	0.157***
Height, (cm)		0.008**	
Weight, (Kg)	0.004**		0.002*
ILD subtypes		-0.065*	-0.117*
PTH, (pg/ml)		-0.002***	-0.001*
The correlation coefficients in multivariate linear regression were presented in the table, and *represents the <i>P</i> value of correlations between variables and BMD at lumbar spine, femoral neck, and total hip.			
*, $P \leq 0.05$; **, $P \leq 0.01$; ***, $P \leq 0.001$.			
ILD, interstitial lung disease; PTH: intact parathyroid hormone.			

Table 7
The impact of osteoporosis on the quality of life

Variable	Normal N = 59	Osteopenia N = 76	Osteoporosis N = 44
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Physical score, ECOS-16	14.83 $\pm$ 5.59	14.42 $\pm$ 4.59	18.00 $\pm$ 7.44**
Mental score, ECOS-16	10.90 $\pm$ 4.76	10.34 $\pm$ 4.14	13.27 $\pm$ 4.77**
PCS, SF-36	61.48 $\pm$ 24.46	63.05 $\pm$ 21.23	50.20 $\pm$ 22.75**
MCS, SF-36	73.55 $\pm$ 25.69	79.63 $\pm$ 24.44	68.28 $\pm$ 24.49
Data are given as mean $\pm$ SD; * indicates the difference in variables between osteoporosis and normal and osteopenia. *, $P \leq 0.05$, **, $P \leq 0.01$ ***, $P \leq 0.001$.			
ECOS-16: 16-item Assessment of Health-Related Quality of Life in Osteoporosis; SF-36: 36-Item Short-Form Health Survey; PCS: physical component summary scale; MCS: mental component summary scale.			

Discussion

The current study found that osteoporosis was very common in ILD patients (24.6% of those with osteoporosis, 42.5% of those with osteopenia). The occurrence of osteoporosis was associated with multiple factors, among which sex, age, height, weight, smoking, the measured values of FVC, FEV₁, TLC, vitamin D deficiency and osteoporosis were significantly correlated. In multivariate analysis sex, height,

weight, ILD subtypes and PTH level were the most important factors influencing BMD. A reduced BMD leading to osteoporosis had a significant impact on the QOL of ILD patients.

The prevalence of osteoporosis in the general population is clearly lower than that in ILD patients, with values of 9.7% in France, 14% in Germany and 13.2% in China[19–21]. Our studies showed that the prevalence of osteoporosis in ILD patients was 24.6%, which was similar to a previous study. The mechanism underlying the development of osteoporosis in ILD patients remains unclear and may be associated with cytokines secreted by macrophages and fibroblasts in the pathogenesis of ILD[22, 23]. IPF patients have decreased autophagy and increased oxidative stress, which impair the function of osteoblasts, making patients more prone to osteoporosis [24–28].

Osteoporosis was more common in females than in males (88.6% vs 11.4%). Females have lower peak bone mass than males, and postmenopausal females have decreased estrogen secretion, which induces bone resorption rather than bone formation [29]. The risk of osteoporosis increases with age, and the average age of our enrolled patients was 62.98 years. Advanced age contributes to a high prevalence of osteoporosis in ILD patients, which is partly attributable to enhanced oxidative stress and reduced autophagy. Sex hormone deficiency and decreased immune system function mediate osteoclast activation, and the inhibition of osteoblasts can also partially explain the decrease in BMD [30, 31].

Current and former smokers are more likely to develop osteoporosis. The possible mechanism underlying the decrease in BMD in smokers is mainly the damaging effect of nicotine on osteoblasts, disrupting osteoblastic differentiation and collagen synthesis and increasing oxidative stress, which leads to increased bone resorption and decreased BMD [32]. The reason there were more nonsmokers in the low BMD group in the current study was because there were more female patients. In China, smoking is more common among males than females (66% vs 3.1%), and the correlation coefficient of sex with low BMD is higher than that of smoking (0.516 vs. 0.278)[33].

Weight is important for maintaining BMD, because both nutritional status and muscle strength can affect BMD. The loss of height is an indicator of the risk of vertebral fracture and a reduction in BMD, and it may be a predictor of osteoporosis[2, 34]. Patients who had lower education levels had a higher prevalence of osteoporosis; the relationship is complex and involves many socioeconomic factors, including lifestyle [35].

ILD patients with CTD are more likely to have osteoporosis. BMD values were lower in patients with rheumatoid arthritis, systemic sclerosis, and systemic lupus erythematosus than that the control group, possibly due to the pathogenesis of CTD, which involves bone tissue and inflammation [36–39]. Inflammation is crucial to the onset and development of CTD, and proinflammatory cytokines can induce osteoclast differentiation and activation, reducing the number and function of osteoblasts and weakening their antagonistic effect on osteoclasts resulting in reduced BMD[24, 25, 40–43]. Vitamin D insufficiency and deficiency are very common in ILD patients and are important for maintaining BMD and bone formation. This association may result in lower vitamin D levels accompanied by a more serious degree of inflammation. The PTH level was positively correlated with osteoporosis, which was similar to

previous results; PTH can increase the number of osteoblasts and promote bone formation[8, 29]. PTH may be a therapeutic target for ILD patients with osteoporosis in the future.

The severity of disease affected BMD, and there was a relatively greater risk of osteoporosis in severe ILD patients with worse pulmonary function. Impairment of pulmonary ventilation and diffusion, which result in hypoxia; changes in the lifestyle factors; reduced food intake; and reduced sunlight exposure are not conducive to the maintenance of BMD. Hypoxia can inhibit the generation and differentiation of osteoblasts and stimulate osteoclasts, leading to bone resorption.

Most ILD patients seek medical attention because of the development and aggravation of cough or dyspnea, which are often accompanied by pulmonary inflammation. Ground-glass opacities indicate the presence of inflammation in the alveoli, and the finding of extensive ground-glass opacities in the group with normal BMD in our study may be because inflammation in the short term has little effect on BMD.

Physical activity also has an effect on osteoporosis in ILD patients. ILD patients reduced their exercise duration and intensity due to dyspnea, resulting in decreased muscle strength, which promotes the loss of BMD. Reduced mechanical movement increases sclerosing protein levels, which suppress the Wnt signaling pathway and inhibit bone formation [44]. A mechanical load of a certain weight is essential to maintain BMD and bone integrity, and weight-bearing and resistance exercises are beneficial for increasing bone and muscle strength, maintaining bone strength and reducing the risk of fracture [5, 45, 46].

Osteoporosis seriously impaired both physical and mental QOL in ILD patients, although the effect was especially pronounced with regard to the physical aspects, which was similar to the results of previous studies[47–50]. The treatment of ILDs is difficult, the prognosis is poor; therefore, it is considered relatively more important to improve the QOL of patients with ILDs. QOL was generally impaired in ILD patients, and the QOL of ILD patients with osteoporosis was the most significantly impaired. Therefore, regular monitoring of BMD should be performed. Appropriate preventive measures and timely interventions to delay the progression of osteopenia to osteoporosis will be conducive to improving the QOL of patients.

Limitations

There are some limitations of present study. First, our study was a cross-sectional study with no follow-up observations, thus impact of changes in the disease on osteoporosis could not be evaluated. Second, this study was an observational study, and no therapeutic interventions were conducted. Third, most patients enrolled in the current study had been newly diagnosed with ILD and had no history of glucocorticoid use. Therefore, it is difficult to analyze the effect of glucocorticoid use on osteoporosis in ILD patients.

Conclusion

In conclusion, our study demonstrated that osteoporosis and osteopenia were very common in Chinese ILD patients. Sex, height, weight, ILD subtypes, and the PTH level were significantly associated with the decline of BMD. Osteoporosis seriously affects Chinese ILD patients' QOL, especially their physical QOL, and monitoring BMD and providing correct and timely interventions to prevent osteoporosis may be crucial in the management of ILD patients. The mechanism underlying the susceptibility of ILD patients to osteoporosis is still unclear, and further research is needed to clarify whether controlling osteoporosis affects the severity and prognosis of Chinese ILD.

Abbreviations

ILD

Interstitial lung disease

QOL

quality of life

BMD

bone mineral density

PTH

parathyroid hormone

HRCT

high-resolution computed tomography

BMI

body mass index

DXA

dual energy X-ray absorptiometry

WHO

World Health Organization

LS

lumbar spine

FN

femoral neck

TH

total hip

IPAQ-SF

the International Physical Activity Questionnaire Short Form

25(OH)VitD₃

25-hydroxyvitaminD₃

MET

metabolic equivalent

ECOS-16

the 16-item Assessment of Health-Related Quality of Life in Osteoporosis

SF-36
the Short-Form 36-item Questionnaire
PCS
the physical component summary scale
MCS
the mental component summary scale
ANOVA
analysis of variance
CTD-ILD
connective tissue disease-associated interstitial lung diseases
IPF
idiopathic pulmonary fibrosis
NSIP
idiopathic nonspecific interstitial pneumonia
IPAF
interstitial pneumonia with autoimmune features
COP
cryptogenic histologic pneumonia
HP
hypersensitivity pneumonitis
FVC
forced vital capacity
FEV₁
forced expiratory volume in 1 second
DLco
carbon monoxide diffusion capacity
TLC
total lung capacity

Declarations

Ethics approval and consent to participate This study was approved by the Institutional Review Board and Ethics Committee of Beijing Chaoyang Hospital, Capital Medical University (2018-science-318). Patients enrolled in this study passed the ethics review, signed the informed consent form upon enrollment in the study and were treated following routine clinical practice without any interventions.

Consent for publication Not applicable

Availability of data and materials All data generated or analysed during this study are included in this published article.

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Authors' contributions: Ai Cui the conception and design of the work; Hui Zhang and Xiao-Wen Sheng, contributed to the acquisition, interpretation of data, as well as significant contributions to the drafting and revision of the manuscript; Fan Zhang, Li-Ru Huang, Yu-Qi Hu, Xue-Yan Yuan contributed to the acquisition and analysis of data. All authors read and approved the final manuscript.

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Figures

Figure 1

Flow Chart of the Study DXA: dual energy X-ray absorptiometry

Figure 2

Number of Osteoporosis Patients by Sex *=P value between the normal, osteopenia and osteoporosis groups by sex. **, $P \leq 0.01$; ***, $P \leq 0.001$.

Figure 3

Pulmonary Function by BMD Level (a): The mean actual measured values of FVC and FEV1 in the three groups. FVC, forced vital capacity, (L); FEV1, forced expiratory volume in 1 second, (L). b The mean actual measured value of DLco in the three groups: diffusing capacity of the lung for carbon monoxide, (mmol/min/kPa). Fig3b is not available with this version

Figure 4

Level of Vitamin D by BMD Level The mean level of vitamin D in the normal, osteopenia and osteoporosis groups. *, $P \leq 0.05$; **, $P \leq 0.01$.

Figure 5

Physical Activity Level Distribution Low, medium and high represent the distribution of low, medium and high physical activity levels in different BMD groups, respectively.