

Prevalence, risk factors, and health-related quality of life of osteoporosis in patients with COPD at a community hospital in Taiwan

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Background: Data regarding osteoporosis in COPD patients in Taiwan remain limited. The primary end point of this study was to evaluate the prevalence and risk factors of osteoporosis in COPD patients in Taiwan. The secondary end point was to examine the association between osteoporosis and health-related quality of life (HRQL) in COPD patients.

Materials and methods: This prospective cross-sectional study enrolled 125 COPD patients (mean age 73.6 years, forced expiratory volume in 1 second [FEV₁] 1.19±0.43 L) who had bone mineral-density measurements performed consecutively. Demographic data, lung function, and HRQL including modified Medical Research Council dyspnea scale, St George's Respiratory Questionnaire, oxygen-cost diagram, Center for Epidemiologic Studies – depression scale, and COPD Assessment Test scores were recorded.

Results: A total of 50 (40%) participants were diagnosed as having osteoporosis. In a multivariate logistic regression model including age, smoking amount (pack-year), body mass index (BMI), and FEV₁, only BMI (odds ratio 0.824, 95% confidence interval 0.73–0.93; *P*=0.002) and FEV₁ (odds ratio 0.360, 95% confidence interval 0.13–0.98; *P*=0.046) were negatively associated with an increased risk of osteoporosis in COPD patients. In addition, COPD patients with osteoporosis had significantly higher modified Medical Research Council dyspnea scale scores (1.7±0.8 vs 1.4±0.8, *P*=0.046), St George's Respiratory Questionnaire scores (36.6 vs 28.0, *P*=0.01), and COPD Assessment Test scores (14.7±8 vs 11.5±7, *P*=0.019), and lower oxygen-cost diagram score (4.8±1.8 vs 5.4±1.6, *P*=0.045) than patients without osteoporosis.

Conclusion: The prevalence of osteoporosis in COPD patients was high at a community hospital in Taiwan. BMI and FEV₁ were the independent risk factors for osteoporosis in COPD. In addition, COPD patients with osteoporosis had worse HRQL than those without osteoporosis.

Keywords: osteoporosis, chronic obstructive pulmonary disease, bone density

Introduction

COPD is characterized by persistent airflow limitation caused by an enhanced chronic inflammatory response in the airways and the lungs.^{1–3} It is not only a pulmonary disease but is also being recognized a systemic disease with widespread comorbidities, such as cardiovascular diseases, psychological disorders, and osteoporosis.^{4–6} COPD is the fourth-leading cause of death in the world, and the economic burden related to this disease is projected to increase in coming decades because of continued exposure to COPD risk factors and aging of the general population.^{7,8}

Osteoporosis has been recognized as a major comorbidity in COPD, but it is often underdiagnosed and associated with poor health status and prognosis.⁹ The etiology of osteoporosis in COPD is complex, and various risk factors may contribute to its

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pathogenesis, such as older age, tobacco smoking,¹⁰ systemic inflammation, vitamin D deficiency, and the use of oral or inhaled corticosteroids (ICS).¹¹ The reported prevalence of osteoporosis in COPD patients ranges widely from 23% to ~50% as diagnosed by bone mineral density (BMD), and from 24% to ~80% as diagnosed by BMD or vertebral compression fracture.^{10,12–20} However, there are currently no studies regarding the prevalence and risk factors of osteoporosis in patients with COPD in Taiwan. In addition, few studies have reported an association between health-related quality of life (HRQL) and osteoporosis in patients with COPD.²¹

The primary end point of this study was to investigate the prevalence and risk factors of osteoporosis in COPD among Taiwanese patients. The secondary end point was to examine the association between HRQL and osteoporosis in patients with COPD.

Materials and methods

Study setting

In this cross-sectional study, we examined the data (collected from March 2011 to December 2012) of participants enrolled in the CMPICO study.²² In brief, part of the CMPICO study was designed to investigate relevant comorbidities in patients with COPD, such as osteoporosis, cardiovascular diseases, and psychological diseases. The study was carried out at the outpatient department of the Division of Pulmonary and Critical Care Medicine, Ditmanson Medical Foundation, Chia-Yi Christian Hospital, which is a 1,000-bed community-based teaching hospital in Chiayi, Taiwan. The Institutional Review Board of Ditmanson Medical Foundation approved this study (100001), and also approved the consent procedure outlined as follows. The majority of the enrolled individuals provided written informed consent; however, there were a few illiterate subjects enrolled. Our team explained the study design thoroughly to all of these illiterate subjects, and if they agreed to participate, they signed consent forms using fingerprints in lieu of a written signature. A total of 189 COPD patients at outpatient departments were recruited in the CMPICO study during the period, and 125 (66%) patients were willing to undergo BMD examination and X-ray survey.

Subjects

A total of 125 COPD patients who had undergone measurement for BMD and spinal X-rays were enrolled in the current study. The diagnosis of COPD was based on the GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines.²³ Eligible patients were 47–90 years

of age with a postbronchodilator forced expiratory volume in 1 second (FEV₁) to forced vital capacity (FVC) ratio of less than 0.7.¹⁹ Patients with a history of bronchial asthma and other structural lung diseases (such as lung cancer, bronchiectasis, and fibrotic lung) were excluded. A chest physician carefully reviewed the chest radiographs of all the patients. A total of 125 patients (98% male) with a mean age of 73.6±7.69 years met the inclusion criteria and were enrolled.

Diagnosis of osteoporosis

BMD was measured by performing a dual-energy X-ray absorptiometry scan of the lumbar spine and bilateral femoral neck. Bone with artificial implantation was excluded in this study. *T*-scores were calculated based on the results of BMD, as described by Brunader and Shelton.²⁴ Osteoporosis is defined as a systemic skeletal disease characterized by low-bone density and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility.²⁵ Notably, vertebral fracture has been demonstrated to have a strong relationship with microarchitectural deterioration.²⁶ Vertebral fracture was evaluated from a lateral chest X-ray and lumbosacral spine X-ray by an orthopedic surgeon. Fracture was defined as >20% reduction in anterior, middle, or posterior height using the semiquantitative method, as described by Genant et al.²⁷ As a result, patients with low BMD (*T*-score ≤−2.5) or vertebral fracture were diagnosed as having osteoporosis in our study. Otherwise, patients with a *T*-score >−2.5 and no vertebral fracture were classified into the nonosteoporosis group (Figure 1).

Health-related quality of life and depression

Questionnaire tools included the modified Medical Research Council (mMRC) dyspnea scale,²⁸ St George's Respiratory Questionnaire (SGRQ),²⁹ COPD Assessment Test (CAT),³⁰ oxygen-cost diagram (OCD),³¹ and Center for Epidemiologic Studies – depression (CES-D) scale,³² and scores were obtained to evaluate each patient's life quality and the severity of depression.

Data collection

Interviews were conducted by a trained staff member in charge of COPD case management who used a well-established questionnaire to collect demographic information of the study participants, including date of birth, sex, smoking status, and personal medical history. Body weight, height, and blood pressure were measured for each participant.

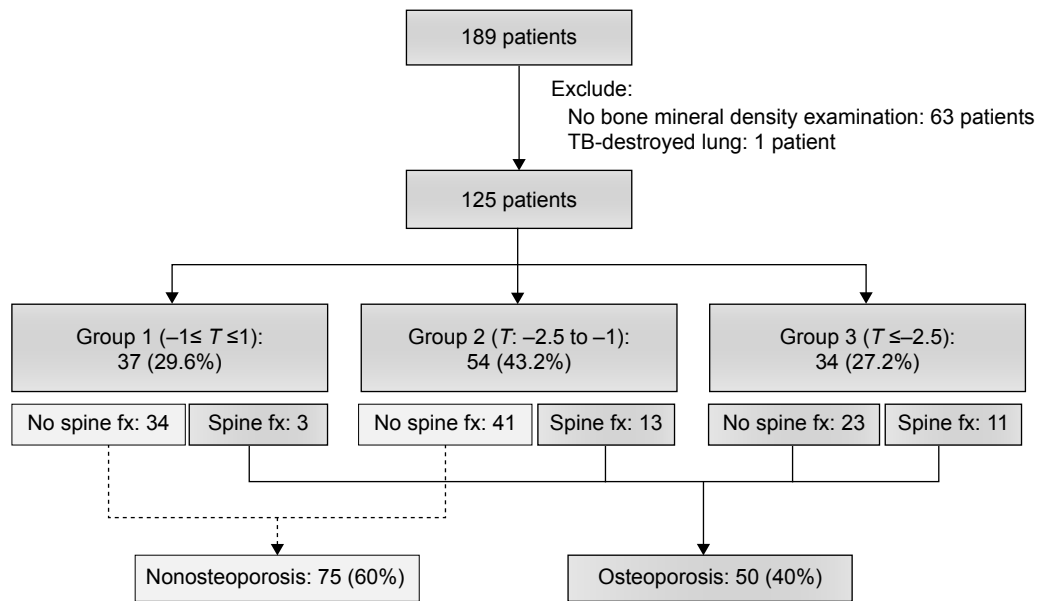


Figure 1 Algorithm of the study.

Abbreviations: TB, tuberculosis; T, T-score.

Body mass index (BMI) was calculated as weight (kilograms) divided by the square of the height (meters). The subjects self-reported their medical history, including hypertension, hyperlipidemia, and diabetes mellitus, for which the diagnostic definitions are detailed in our previous study.²² Smoking status was also evaluated by a self-reported questionnaire.

Statistical analysis

Data were analyzed by SPSS statistical software for Windows version 22 (IBM Corporation, Armonk, NY, USA). Relationships between two continuous parameters were evaluated by independent Student's *t*-test. Relationships between two discrete parameters were evaluated by cross-table χ^2 test. Continuous data are expressed as means \pm standard deviation. Variables with significant difference between the osteoporosis and nonosteoporosis groups were analyzed using a multivariate logistic regression model.

Results

Of the 125 participants, 50 (40%) were diagnosed as having osteoporosis. The most common comorbidity observed was hypertension ($n=63$, 50.4%), followed by diabetes mellitus ($n=16$, 12.8%), and hyperlipidemia ($n=13$, 10.4%). A total of 118 (94.4%) had a history of smoking (at least 10 pack-years), including current ($n=53$, 42.4%) and former ($n=65$, 52%) smokers. Mean pack-years of smoking was 47.22.

As shown in Table 1, there were no significant differences in clinical characteristics between the COPD patients with and without osteoporosis with the exception of BMI,

which showed that COPD patients with osteoporosis had a lower BMI than patients without osteoporosis (21.75 ± 3.4 vs 23.93 ± 3.3 , $P=0.001$). Certainly, COPD patients with osteoporosis had lower values with regard to the parameters of lumbar spine, left femoral neck, right femoral neck, and *T*-score in terms of BMD than COPD patients without osteoporosis.

Severity of COPD had been classified in stages (I–IV) previously and groups (A–D) currently according to the GOLD guidelines. Comparing the GOLD stages (I–IV) between the COPD patients with and without osteoporosis, there was no significant difference between the two groups. However, if patients were classified by current GOLD groups (A–D), there was a significant difference between the two groups ($P=0.024$, Table 2). However, COPD patients with osteoporosis had significantly lower FEV_1 (1.07 ± 0.37 vs 1.28 ± 0.45 L, $P=0.007$), and FEV_1/FVC (52.79 ± 11.0 vs 58.43 ± 8.9 , $P=0.002$) than those without osteoporosis.

Using a multivariate logistic regression model that included age, smoking amount (pack-year), BMI, and FEV_1 , only BMI (odds ratio [OR] 0.824, 95% confidence interval 0.73–0.93; $P=0.002$) and FEV_1 (OR 0.360, 95% confidence interval 0.13–0.98; $P=0.046$) were significantly associated with an increased risk of osteoporosis in COPD patients (Table 3).

To evaluate the HRQL in all enrolled patients, various questionnaires were obtained and analyzed (Table 4). COPD patients with osteoporosis had significantly higher mMRC

Table 1 Clinical characteristics of COPD patient with and without osteoporosis

	Nonosteoporosis n=75	Osteoporosis n=50	P-value
Age, years, mean \pm SD	71.7 \pm 7.2	73.6 \pm 7.7	0.173
Sex, male, n (%)	74 (98.7)	49 (98.0)	1.000
BMI, kg/m ² , mean \pm SD	23.9 \pm 3.3	21.8 \pm 3.4	0.001
Smoking, n (%)			
Never	3 (4.0)	4 (8.0)	0.414
Quit	37 (49.3)	28 (56.0)	
Current	35 (46.7)	18 (36.0)	
Smoking amount, pack-years, mean \pm SD	45.8 \pm 27.0	49.4 \pm 30.6	0.490
BMD, mean \pm SD			
LS	1.11 \pm 0.14	0.905 \pm 0.159	<0.001
LFK	0.86 \pm 0.17	0.682 \pm 0.120	<0.001
RFK	0.87 \pm 0.16	0.689 \pm 0.121	<0.001
T-score	-1.169 \pm 0.81	-2.48 \pm 0.89	<0.001
Underlying disease, n (%)			
DM	10 (13.3)	6 (12)	0.827
HTN	43 (57.3)	20 (40)	0.058
Hyperlipidemia	11 (14.7)	2 (4)	0.074
Alcohol	24 (32)	9 (18)	0.082
CAD	3 (4)	4 (8)	0.436
CHF	2 (2.7)	6 (12)	0.059
CKD	5 (6.7)	1 (2)	0.400
CLD	9 (12)	2 (4)	0.197
Education, n (%)			0.612
Illiterate	17 (22.7)	11 (22)	
Elementary	33 (44)	29 (58)	
Junior	5 (6.7)	3 (6)	
Senior	11 (14.7)	5 (10)	
College	7 (9.3)	2 (4)	

Note: Education represents the highest academic degree of patient.

Abbreviations: BMI, body mass index; BMD, body mineral density; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease mellitus; CLD, chronic liver disease; DM, diabetes mellitus; HTN, hypertension; LFK, left femoral neck; LS, lumbar spine; RFK, right femoral neck; SD, standard deviation.

scores (1.7 \pm 0.8 vs 1.4 \pm 0.8, $P=0.046$), higher SGRQ scores (36.6 vs 28.0, $P=0.01$), lower OCD scores (4.8 \pm 1.8 vs 5.4 \pm 1.6, $P=0.045$), and higher CAT scores (14.7 \pm 8 vs 11.5 \pm 7, $P=0.019$) than patients without osteoporosis. However, there was no significant difference in CES-D scores between the two groups.

Discussion

To the best of our knowledge, this is the first study to highlight the prevalence and risk factors of osteoporosis in patients with COPD at a community hospital in Taiwan. Our study showed that the prevalence of osteoporosis was 40% in patients with COPD. COPD patients with osteoporosis had lower BMI, FEV₁, and FEV₁/FVC than COPD patients without osteoporosis. In a multivariate logistic regression model, only BMI and FEV₁ were significantly associated with an increased risk of osteoporosis in COPD patients. When comparing the HRQL between the two

groups, COPD patients with osteoporosis had significantly higher mMRC scores, SGRQ scores, CAT scores, and lower OCD scores than those without osteoporosis, indicating that osteoporosis patients had worse quality of life and exercise performance.

Osteoporosis has been recognized as an emerging issue in the care of COPD, since osteoporosis would increase the difficulty and complexity in the management of COPD. It has also been identified as most at risk for the experiencing of severe exacerbations requiring hospitalization.³³ As shown in Table 5, there have been a number of studies investigating the prevalence and related risk factors worldwide over the past decade.^{12,15,17–20} Based on different definitions, the prevalence of osteoporosis ranges from 23% to 42% diagnosed only by BMD and from 47% to 83.7% diagnosed by both BMD and vertebral compression fracture.^{12,17–20} The wide range with regard to osteoporosis-prevalence rates in the world may be in part be related to the methodological differences of

Table 2 GOLD stage and pulmonary function in COPD patients with and without osteoporosis

	Nonosteoporosis n=75	Osteoporosis n=50	P-value
GOLD, n (%)			0.255
Stage I	8 (11)	5 (10)	
Stage II	40 (53)	19 (38)	
Stage III	24 (32)	21 (42)	
Stage IV	3 (4)	5 (10)	
GOLD, n (%)			0.024
Group A	30 (40)	13 (26)	
Group B	12 (16)	8 (16)	
Group C	17 (22.7)	6 (12)	
Group D	16 (21)	23 (46)	
Systolic BP, mmHg, mean ± SD	137±16	133±16	0.155
Diastolic BP (mmHg), mean ± SD	82±12	79±12	0.283
Heart rate/minute, mean ± SD	84±15	84±15	0.850
SpO ₂ , %, mean ± SD	95±2	95±3	0.212
Pulmonary function			
FVC, liters, mean ± SD	2.15±0.59	1.99±0.45	0.111
FVC, predicted %, mean ± SD	63.6±17	58.7±14	0.096
FEV ₁ , liters, mean ± SD	1.28±0.45	1.07±0.37	0.007
FEV ₁ , predicted %, mean ± SD	58.4±18	48.5±19	0.080
FEV ₁ /FVC, mean ± SD	58.43±8.9	52.79±11.0	0.002
BD response, n (%)	13 (17.3)	9 (18)	0.924
MMEF, liters, mean ± SD	0.66±0.38	1.61±7.86	0.399

Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease; BP, blood pressure; SD, standard deviation; SpO₂, oximetric oxygen saturation; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; BD, bronchodilator; MMEF, maximum midexpiratory flow.

osteoporosis diagnosis and the enrollment criteria of patient populations, such as age and severity of COPD.

Malnutrition, indicated by lower BMI, is a possible cause of bone loss and fractures, frequently associated with inflammation and hormonal change.³⁴ Several studies have confirmed that BMI is positively associated with BMD in a variety of patient populations.^{35–38} Not surprisingly, this is consistent in patients with COPD based on previous studies^{12,13,15,16,19} and also as seen in our findings, which all showed that BMI was an independent risk factor for osteoporosis.

Similarly to previous reports,^{12,13,15,16,19} our data showed that pulmonary function, like FEV₁ or FVC, was the independent risk factor for osteoporosis. A South Korean study that enrolled 456 premenopausal women who had never smoked showed that FVC and FEV₁ were correlated with

BMD.³⁹ This is consistent with our findings showing that FEV₁ is an independent risk factor regardless of smoking history.

The related literature has been inconsistent as to whether oral steroid use is a risk factor for osteoporosis in COPD.^{13,15,17,40} The TORCH study demonstrated that ICS use was not associated with BMD.¹⁸ Other studies likewise have shown that oral steroid use was not correlated with osteoporosis in patients with COPD.^{15,17} On the contrary, ICS use was associated with a modest but statistically significant increase (>20%) in the risk of fractures in patients with COPD from a meta-analysis of randomized controlled trials (16 trials) and observational studies (seven trials).⁴¹ Another large case–control study showed that current use of high-dose ICS (more than 700 µg/day) was associated with an increased

Table 3 Multivariate logistic regression analysis of factors for osteoporosis in COPD patients

Variables	B	SE	Odds ratio	95% CI for Odds ratio		P-value
				Lower	Upper	
Smoking amount (pack-years)	0.008	0.007	1.008	0.995	1.022	0.229
Age (years)	0.020	0.028	1.020	0.965	1.078	0.476
BMI (kg/m ²)	−0.194	0.064	0.824	0.727	0.933	0.002
FEV ₁ (L/s)	−1.021	0.511	0.360	0.132	0.981	0.046
Constant	3.332	2.679	27.988			0.214

Abbreviations: CI, confidence interval; SE, standard error; BMI, body mass index; FEV₁, forced expiratory volume in 1 second.

Table 4 Health-related quality of life in COPD patients with and without osteoporosis

	Nonosteoporosis n=75	Osteoporosis n=50	P-value
mMRC, mean \pm SD	1.4 \pm 0.8	1.7 \pm 0.8	0.046
mMRC grades			0.156
Grade 0, n (%)	5 (7)	2 (4)	
Grade 1, n (%)	42 (56)	18 (38)	
Grade 2, n (%)	22 (29)	21 (44)	
Grade 3, n (%)	5 (7)	7 (15)	
Grade 4, n (%)	1 (1)	0	
mMRC \geq 2, n (%)	28 (37.3)	28 (56)	0.045
SGRQ, mean \pm SD	28.0 \pm 17.3	36.6 \pm 18.6	0.010
OCD, mean \pm SD	5.4 \pm 1.6	4.8 \pm 1.8	0.045
CES-D, mean \pm SD	11.7 \pm 8.0	13.6 \pm 8.6	0.434
CAT, mean \pm SD	11.5 \pm 7	14.7 \pm 8	0.019

Notes: Two mMRC score data and one CES-D score data in osteoporosis patients were missing.

Abbreviations: mMRC, modified Medical Research Council; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire; OCD, oxygen-cost diagram; CES-D, Center for Epidemiologic Studies – depression; CAT, COPD Assessment Test.

risk of nonvertebral fractures compared with patients with no ICS exposure (adjusted OR 1.68). Therefore, the impact of ICS should be further verified by studies in the future.

A study reported on an association between HRQL and osteoporosis in patients with COPD.²¹ This study showed that HRQL, which was assessed by mMRC scale, SGRQ, and CAT scores, was significantly worse in patients with osteoporosis than those without osteoporosis. The mMRC scale is based on the patient's perception of dyspnea in daily

activities,²⁸ and is a practical tool to assess the HRQL of patients with COPD.⁴² Notably, current GOLD guidelines combine a dyspnea scale (mMRC or CAT) and pulmonary function to classify the severity of COPD, which is compatible with our finding that the proportion of osteoporosis was more correlated with group classification than stage classification (pulmonary function alone). This study showed that osteoporosis was associated with higher mMRC dyspnea scores in patients with COPD, which is similar with results from previous studies.^{43,44} There is a paucity of data regarding the association between SGRQ and osteoporosis. To the best of our knowledge, this is the first study revealing that COPD patients with osteoporosis had higher SGRQ scores than those without osteoporosis. The CES-D scale is a short self-reporting scale designed to measure depressive symptomatology in the general population. This study showed that depression was not associated with osteoporosis in patients with COPD.

This study has a number of limitations that are worth noting. First, the sample size was small, and the majority of patients were male. A previous study has shown that the ratio of male to female smoking rates was 10.9 to 1 among adults in Taiwan.⁹ Since smoking is the major risk factor for COPD, it is reasonable that COPD patients are predominantly male in Taiwan. However, large studies are needed to verify our results. Second, information regarding possible risk factors

Table 5 Prevalence and related risk factors of osteoporosis in COPD patients for the past decade worldwide

Study	Country	n	Osteoporosis (%)	Associated factors
Watanabe et al ¹²	Japan	136	38.8% by BMD ^a , 79.4% by VCF 83.7% by BMD and VCF ^b	(+): FEV ₁ , FVC, smoking
Hattiholi and Gaude ¹³	India	102	66.6% by BMD	(+): COPD stage, low BMI, AEs >3, steroids
Li et al ¹⁴	USA	179	69% in African-Americans 65% in Caucasians by BMD	(+): FVC/predicted FVC (-): Sex, race
Silva et al ¹⁵	Brazil	95	42.1% by BMD	(+): Low BMI, activity, BODE, FVC, FRV, IC, D _{LCO} (-): Oral steroids, smoking, 6MWT
Rittayamai et al ¹⁶	Thailand	102	31.4% by BMD	(+): BMI <20.5 kg/m ² and hs-CRP >2.3 mg/L (-): COPD stage, age, smoking, and steroid use
Jørgensen et al ¹⁷	Denmark	62	24% by VCF 42% by BMD	(-): Steroids, FEV ₁ , FVC, smoking
Ferguson et al ¹⁸ TORCH		658	23% by BMD	(-): ICS, fluticasone
Graat-Verboom et al ¹⁹	the Netherlands	49	50% in GOLD-II by BMD and VCF ^b	(+): Low BMI, high RV/TLC
Graat-Verboom et al ²⁰	the Netherlands	90	47%–61% in 3 years by BMD and VCF ^b	(+): Low T-score in trochanter, vitamin D deficiency (-): Smoking

Notes: ^aosteoporosis is defined by the measure of bone mineral density (BMD); ^bosteoporosis is defined by both bone mineral density (BMD) and vertebral compression fracture (VCF). (+) A significant risk factor for osteoporosis and (-) not a significant risk factor for osteoporosis.

Abbreviations: BMD, bone mineral density; VCF, vertebral compression fracture; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; BMI, body mass index; AEs, acute exacerbation; BODE, BMI, obstruction (airflow), dyspnea (score), exercise (capacity); FRV, functional residual volume; IC, inspiratory capacity; D_{LCO}, diffusing capacity of the lungs for carbon monoxide; 6MWT, 6-minute walking test; hs-CRP, highly sensitive C-reactive protein; ICS, inhaled corticosteroids; TORCH, Towards a Revolution in COPD Health; GOLD, Global Initiative of Chronic Obstructive Lung Disease; TLC, total lung capacity.

like vitamin D deficiency and oral steroid use was unavailable during our study. However, most previous studies showed that oral steroids were not associated with increased risk of osteoporosis in patients with COPD.

In conclusion, the prevalence of osteoporosis in COPD patients was high in Taiwan. BMI and FEV₁ were the independent risk factors for osteoporosis in COPD. Therefore, measuring BMD in COPD patients with lower BMI or pulmonary function should be recommended. As a result, further study may be required to investigate whether the prevention of osteoporosis utilizing such strategies as increasing body weight, encouraging smoke cessation, and/or prescribing medications that can help prevent osteoporosis would improve the quality of life in patients with COPD.

Disclosure

The authors report no conflicts of interest in this work.

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