International Journal of General Medicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Potential Predictive of Thoracic CT Value and Bone Mineral Density T-Value in COPD Complicated with Osteoporosis

Tinghua Hu[1,*], Shanshan Dai[2,*], Lan Yang[1], Bo Zhu[1]

[1]Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, 710000, People's Republic of China; [2]Department of Respiratory and Critical Care Medicine, Xi'an No. 9 Hospital, Xi'an, Shaanxi, People's Republic of China

*These authors contributed equally to this work

Correspondence: Bo Zhu, Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, 277 Yanta West Road, Xi'an, Shaanxi, 710061, People's Republic of China, Email zhubo685689@163.com

Background: COPD, combined with Osteoporosis, has a high incidence and potential for great harm. Choosing an optimal diagnostic method to achieve bone mineral density (BMD) screening is crucial for COPD patients. Studies on COPD patients with BMD reduction are lacking.

Purpose: To identify the risk factors of BMD reduction and osteoporosis in COPD patients.

Patients and Methods: We included a total of 81 patients with AECOPD, who were admitted to the hospital from July 1, 2019, to January 31, 2020. Patients were grouped into BMD normal group, BMD reduced group and OP group. The areas under ROC curve were used to explore the value of CT values in the diagnosis of bone abnormality, and clinical indicators were collected.

Results: The CT value of the vertebral cancellous bone is highly correlated with the T value of BMD ($R > 5.5$, $P < 0.0001$). Using multivariate Logistic regression analysis, we showed that COPD duration, BMI, 25-hydroxyvitamin D3, and long-term inhaled glucocorticoid were independent factors affecting different BMD levels in COPD patients. No significant difference in bone formation indexes between groups. β-crossL was negatively correlated with serum IL-6 ($r=-0.254$, $P=0.022$), and ALP was positively correlated with serum TNF-α ($r=0.284$, $P=0.023$).

Conclusion: Thoracolumbar vertebral cancellous bone CT has potential value in the diagnosis of bone abnormality. COPD duration, BMI, 25-hydroxyvitamin D3, and long-term inhaled glucocorticoid may contribute to the BMD reduction in COPD patients, and serum IL-6 and TNF-α regulate bone metabolism in COPD patients.

Keywords: chronic obstructive pulmonary disease, osteoporosis, bone mineral density, chest CT

Introduction

COPD is a common clinical disease that causes secondary osteoporosis (OP). Prior studies have repeatedly confirmed that the prevalence of OP in COPD patients is considerably higher than in the general population.[1] In a study involving 91 COPD patients, the overall prevalence of vertebral or femoral neck fractures was 4.7 times higher in the COPD group than in the control group.[2] Vertebral fractures, in particular, were more common in the COPD group than in the control group (25.9% vs 6.5%, P =0.01). Moreover, the prevalence of OP, as defined by bone mineral density (BMD), was 2.6 times higher in the general population than in the COPD group. A meta-analysis of 58 studies, published by Chen et al, revealed that the global incidence of OP in COPD patients was as high as 38% (95% confidence interval, 34% to 43%, OR=2.83).[3] In another study that examined the association between COPD and OP in male smokers, OP was significantly increased in the femoral neck (48.6% vs 16.7%, P< 0.001) and lumbar vertebrae (68.9% vs 37.9%, P< 0.01) of COPD patients. In addition, COPD increased the probability of OP in male smokers.[4,5] Similarly, Ryan et al retrospectively analyzed the clinical data of 234 male patients with OP and found that COPD is a major cause of

Received: 28 February 2024
Accepted: 20 June 2024
Published: 10 July 2024

secondary OP. In addition, OP-related fractures worsened lung function and impaired daily living activities of patients with COPD.[6] As a result, the two diseases form a vicious cycle that imposes a heavy burden on patients.[7] GOLD 2019 also suggested that comorbidities in patients with COPD are independent risk factors for hospitalization and death,[8] and suggested that patients diagnosed with COPD should be actively screened for comorbidities and be treated accordingly.

Previous studies have shown that various hormones, cytokines and growth factors in human body can regulate the formation process of osteoclasts by acting on osteoblasts, including IL-1β, IL-6, IL-7, IL-17 and TNF-α.[9–11] Other studies have shown that airway irritants such as cigarette smoke activate airway epithelial cells in COPD patients to produce inflammatory mediators including TNF-α, IL-6, IL-8, IL-1β, and GM-CSF.[12] A clinical study[13] included 59 male patients with COPD, 32 smokers with normal lung function and 25 healthy non-smokers as controls. The results showed that plasma levels of IL-1β, IL-6 and IL-8 were elevated in COPD patients and correlated with the expression of RANKL. The level of RANKL in the blood of patients with COPD was significantly higher than that of smokers and healthy controls. The level of RANKL in patients with low bone mineral density was higher than that in the normal control group, and RANKL was negatively correlated with bone mineral density. The study of Ugay et al[14] also confirmed that COPD patients had higher levels of RANKL and lower levels of OPG compared with healthy controls. In conclusion, the imbalance mechanism of OPG/RANKL/RANK axis in COPD patients with osteoporosis is largely related to the mechanism of systemic inflammation.

COPD and OP exhibit a high prevalence and potential for significant adverse effects. The interplay between COPD and OP creates a detrimental cycle that leads to a substantial increase in disease burden and economic costs for patients, as well as a marked decline in quality of life during advanced stages of the conditions.[14] The 2017 Guidelines for the diagnosis and treatment of primary OP in China advocate for OP screening in individuals aged 50 years and older, particularly men and postmenopausal women. Furthermore, the guidelines recommend the use of Dual-energy X-ray Absorptiometry (DXA) to measure bone mineral density (BMD) in patients with underlying medical conditions or a history of certain medications. Early screening for OP in patients with COPD is essential. However, DXA is not commonly utilized for OP screening in COPD patients in clinical settings. DXA scans for OP screening are typically reserved for patients with endocrine or metabolic disorders or those who have experienced fragility fractures, while COPD patients are often overlooked for DXA testing by respiratory physicians. Therefore, selecting an appropriate and accessible diagnostic approach for BMD screening is imperative for individuals with COPD.

Chest computed tomography (CT) plays a crucial role in the diagnosis and treatment of pulmonary disease in patients with COPD. During acute exacerbations of COPD necessitating hospital admission, patients commonly undergo chest CT scans to evaluate the extent of emphysema and lung infections. The standard protocol for a routine chest CT scan typically encompasses the thoracic inlet to the inferior border of the lungs. Additionally, due to the anatomical features of the chest, the first lumbar vertebra and upper thoracic vertebra are frequently included in the scan field.

The thoracolumbar vertebral body is anatomically characterized by the presence of both cortex and cancellous bone, with the former being denser and enclosed within the latter. Previous studies have demonstrated that the BMD of the cancellous bone in the vertebrae is a more accurate indicator of load-bearing capacity and risk of vertebral compression fractures.[15] DXA is widely accepted as the gold standard for diagnosing osteoporosis, while thoracolumbar CT images have been shown to correlate with BMD measurements.[16,17]

Upon admission of patients, we conducted an evaluation to investigate the relationship between the CT value of cancellous bone in the thoracolumbar vertebra and the T-score obtained through DXA scanning. Our objective was to ascertain the potential inclusion of CT value in the screening criteria for individuals with both COPD and OP. Previous research has indicated a correlation between thoracolumbar vertebral CT values and bone mineral T scores. However, there is a paucity of similar studies focusing specifically on patients with COPD, despite the widespread use of chest CT scans in this population and their increased susceptibility to OP. This study investigated the correlation between thoracolumbar vertebral cancellous bone CT and BMDT values in patients with COPD, and further evaluated the diagnostic utility of thoracolumbar vertebral cancellous bone CT in detecting abnormal bone conditions such as reduced bone density and osteoporosis. The aim was to identify convenient and relatively accurate screening methods for assessing BMD.

Material and Methods

Data Collection

A total of 81 PATIENTS with COPD, who were admitted to the Respiratory Department of the First Affiliated Hospital of Xi'an Jiaotong University, from July 1, 2019, to January 31, 2020, and met our inclusion and exclusion criteria were recruited for our study. Blood gas analysis, blood coagulation function, liver function, and electrolyte check were completed without oxygen treatment. Moreover, serum interleukin-6, and bone metabolism check were completed on the second morning after admission. Pulmonary function tests were performed using MasterScreen Body (Jaeger, Wurzburg, Germany) and were performed by technicians at the pulmonary function laboratory. Forced expiratory volume in 1 s (FEV1), FEV1%, FVC, and FEV1/FVC ratio were included in the analysis. Chest CT, and BMD check were completed within 72 hours of admission. On the second day of admission, 3mL of whole blood was collected using a vacuum coagulant tube on an empty stomach for TNF-α testing.

Records of Patients Include

(1) general information: gender, age, height, weight, computed body mass index (BMI), smoking history (years of smoking, smoking counts, and daily smoking index calculation), continuous glucocorticoid usage (whether a continuous inhaled corticosteroids over a large period of time or more than 1 year), COPD disease history, number of exacerbations over the past year, other complications. (2) Questionnaire score: COPD assessment test Respiratory Questionnaire (CAT score) and modified British Medical Research Council Dyspnea Index (mMRC score) were completed upon admission. (3) Laboratory indicators: Blood gas analysis (PaO_2, $PaCO_2$, SaO_2), FIB, ALP, serum electrolyte (blood Ca, blood P), serum IL-6, human TNF-α, TPINP, V1TD-T, N-OST, β -crossL, and PTH. (4) Pulmonary function examination: FEV1, FEV1%, FVC, and FEV1/FVC. (5) BMD measurement: T-Score (including l1, L2, L3, L4, and l1-L4 mean T value). Normal BMD group (T value>-1). Reduced BMD group (−2.5<T value≤-1). OP group (T-score ≤ −2.5). (6) Chest CT: CT values of thoracolumbar vertebral cancellous bone (including T10, T11, T12, and L1).

Inclusion Criteria

1. All patients met the Global Initiative for Chronic Obstructive Pulmonary Disease 2019 diagnostic criteria for acute exacerbation of chronic obstructive pulmonary disease, were between 50 and 80 years of age, and female patients were also between 50 and 80 years of age and were postmenopausal;
2. In line with the diagnostic and classification criteria of secondary osteoporosis in China's Primary Osteoporosis Diagnosis and Treatment Guidelines 2017.

Exclusion Criteria

1. Suffering from other diseases of the respiratory system, such as bronchial asthma, lung cancer, pulmonary fibrosis, tuberculosis, etc.;
2. COPD patients combined with other diseases that can affect bone metabolism: such as endocrine metabolic diseases including hyperthyroidism, hyperparathyroidism, diabetes, gonadal dysfunctions, etc., rheumatic immune diseases including systemic lupus erythematosus, rheumatoid arthritis, etc., and gastrointestinal diseases or renal dysfunction;
3. Previous use of calcium, vitamin D preparations, and other drugs that can affect bone metabolism.

Statistical Method

Independent sample *t*-test or one-way ANOVA was used for data conforming to a normal distribution and homogeneous variance among groups. Statistical data were described by the component ratio (%), and the row × table $\chi 2$ test or its correction formula was used for comparison among the three groups or in pairs. For the correlation analysis, the Pearson correlation analysis method was selected to obtain the correlation coefficient R. Multivariate Logistic regression analysis was used for multi-factor analysis. When the significance of model fitting information met $P < 0.05$, the regression model was meaningful. The diagnostic value was evaluated by the MedCalc statistical software, using ROC curve analysis or

ROC curve comparative analysis. The remaining data analysis was processed by the SPSS 24.0 statistical software. The test level $P < 0.05$ was considered statistically significant.

Results

Grouping and General Data Analysis

In the BMD normal group, there were 22 patients (27.2%). Among them, 16 were males (72.7%), and 6 were females (27.3%). The mean age was 62.6+10.6 years. In terms of complications, 6 patients (27.3%) exhibited pulmonary hypertension, 4 patients (18.1%) exhibited coronary heart disease, and 11 patients (50.0%) exhibited with hypertension.

There were 22 patients (27.2%) in the BMD reduced group, including 16 males (72.7%) and 6 females (27.3%), with an average age of 66.1+11.3 years. 5 patients (22.7%) suffered from pulmonary hypertension, 5 patients (22.7%) from coronary heart disease, and 7 patients (31.8%) from hypertension.

There were 37 patients (45.7%) in the OP group, including 26 males (70.3%) and 11 females (29.7%), with an average age of 69.5+7.4 years. 8 patients (21.6%) suffered from pulmonary hypertension, 8 patients (21.6%) from coronary heart disease, and 14 patients (37.8%) from hypertension.

No statistical significance was observed in gender composition ratio, pulmonary hypertension, coronary heart disease, hypertension, and other complications among the three groups ($P > 0.05$), while there was a significant statistical significance in age ($P < 0.05$). In fact, with increasing age, we observed the gradual decline of BMD, as shown in Table 1.

Correlation Study of CT Value of Thoracolumbar and T Value of BMD in COPD Patients

CT Value of T10-L1 Vertebral Cancellous Bone in the Three Groups

As shown in Table 1, the CT value of cancellous bone gradually decreased with reduction in BMD in COPD patients. Moreover, the order of CT value was as follows: normal BMD group > reduced BMD group > OP group. The intra-group comparison showed that the T value of the vertebral body from T10 to L1 demonstrated a gradual decreasing trend, which may be related to the increasing bearing strength of the lower vertebral body on the body, and the difference was statistically significant, $P < 0.001$.

BMDT-Value in L1-L4 Vertebral Bodies of Patients in the Three Groups

As shown in Table 2, the BMD T value of the L1-L4 vertebral bodies in the three groups also showed a decreasing trend with the gradual decrease in BMD, and the difference was statistically significant ($P < 0.05$). The trend was: normal BMD group > reduced BMD group > OP group.

Statistical Correlation Analysis of CT Values of Cancellous Bone of Vertebral Bodies T10-T12 and L1

To evaluate the relationship between the CT values of thoracic and lumbar vertebral bodies, we collected the data of T10 to T12 and L1 vertebral bodies from chest CT. The Results indicated that the CT values of the thoracic vertebrae from

Table 1 General Data of Patients in the Three Groups

	BMD Normal	BMD Reduced	Osteoporosis	F/χ^2	*P*
Cases, n (%)	22 (27.2%)	22 (27.2%)	37 (45.6%)		
Gender, n (%)				0.06	0.971
Male	16 (72.7%)	16 (72.7%)	26 (70.3%)		
Female	6 (27.3%)	6 (27.3%)	11 (29.7%)		
Age (years)	62.6+10.6	66.1+11.3	69.5+7.4	3.773	0.027*
Pulmonary hypertension N, (%)	6 (27.3%)	5 (22.7%)	8 (21.6%)	0.254	0.881
Coronary heart disease N, (%)	4 (18.1%)	5 (22.7%)	8 (21.6%)	0.154	0.926
Hypertension, n (%)	11 (50.0%)	7 (31.8%)	14 (37.8%)	1.601	0.449

Notes: Data are mean ± SD or percentage. *$p<0.05$.
Abbreviation: BMD, bone mineral density.

Table 2 CT Value of Thoracolumbar Cancellous and Bone Mineral Density (BMD) T-Value in Three Groups

	BMD Normal		BMD Reduced		Osteoporosis		P
	Range	$\bar{x}+s$	Range	$\bar{x}+s$	Range	$\bar{x}+s$	
CT value							
T10	121~277	200.7±42.8	69~236	152.6±37.7	53~154	116.2±21.0	<0.001**
T11	107~282	190.7±48.0	70~214	134.4±35.6	40~146	100.6±24.5	<0.001**
T12	84~293	176.7±49.7	50~211	123.8±38.2	27~143	85.3±25.0	<0.001**
L1	65~270	167.8±48.1	45~200	113.1±39.7	18~123	81.7±21.9	<0.001**
Mean T10-T12	110~282	188.5±45.2	63~215	134.3±36.3	40~141	97.0±22.9	<0.001**
Mean T10-L1	106~279	183.0±45.6	59~210	129.1±36.9	34~136	91.7±22.7	<0.001**
BMD T-value							
L1	−1.4~4.1	0.9±1.7	−4.8~2.3	−1.2±1.6	−4.8~3.0	−2.2±1.6	<0.001**
L2	−1.4~4.7	0.7±1.5	−3.6~0.7	−1.4±0.9	−5.3~-0.9	−3.2±0.8	<0.001**
L3	−1.7~7.3	0.5±2.2	−2.7~-0.1	−1.7±0.7	−4.6~-0.5	−3.4±0.8	<0.001**
L4	−1.6~5.4	0.3±1.8	−2.8~0.5	−1.4±1.0	−6.0~4.0	−3.0±1.6	<0.001**
Mean L1-L2	−1.0~5.3	0.5±1.6	−2.4~-0.1	−1.4±0.7	−4.6~-0.3	−3.1±0.8	<0.001**

Note: **p<0.01.
Abbreviation: BMD, bone mineral density.

T10 to T12 were significantly and linearly correlated with lumbar vertebrae. Moreover, the correlation coefficients were all greater than 0.9, P < 0.001 (Table S1, Figure 1).

Therefore, although the T-value, measured by BMD, only relates to the lumbar spine, BMD alterations between the thoracolumbar spine may have a strong consistency. Hence, we speculated that the relationship between the CT value of the vertebral body and BMD may involve the level of the thoracic spine.

Correlation Analysis of CT Value of the Thoracolumbar Vertebral Body and Mean T Value of Bone Mineral Density

CT value of T10-L1 vertebral cancellous bone, mean CT value of T10-T12 vertebral cancellous bone, and mean CT value of T10-L1 vertebral cancellous bone were strongly correlated with the mean T value of the lumbar bone density. The corresponding R values were 0.632, 0.573, 0.553, 0.571, 0.597, and 0.593, respectively, and the results were statistically significant (p<0.001, Table S2).

The data were next drawn into a scatter plot, which showed that there was a close linear correlation between the CT and T values. Further linear regression analysis was conducted using equations: Y_{T10}=170+16.36X, Y_{T11}=158+14.74X, Y_{T12}=144+14.38X, Y_{L1}=135+14.49X, $Y_{T10\text{-}T12mean}$=157+15.16X, and $Y_{T10\text{-}L1mean}$=152+14.99X. The normalized residual distribution of each group of data was normal (Figure 2).

The Potential CT Value of the Thoracolumbar Vertebral Body in Predicting COPD with Abnormal Bone Mass

According to the T-score in BMD test results, 81 patients with COPD were divided into either a normal group, reduced group, or OP group. The reduced and OP groups were classified as abnormal bone mass groups, whereas the normal group was classified as the normal bone mass group.

As shown in Figure 3, the areas under each ROC curve were AUCT10=0.913, AUCT11=0.887, AUCT12=0.863, AUCL1=0.860, AUCT10-T12 mean=0.894, and AUCT10-L1 mean=0.890, respectively. All test levels were P < 0.001, which suggested that the CT values had potential value in the diagnosis of bone abnormality. The area under the ROC curve of each vertebral body, the sensitivity, and specificity corresponding to the maximum index under the ROC curve, along with the CT values of the corresponding vertebral cancellous were summarized, and the results are illustrated in Table S3.

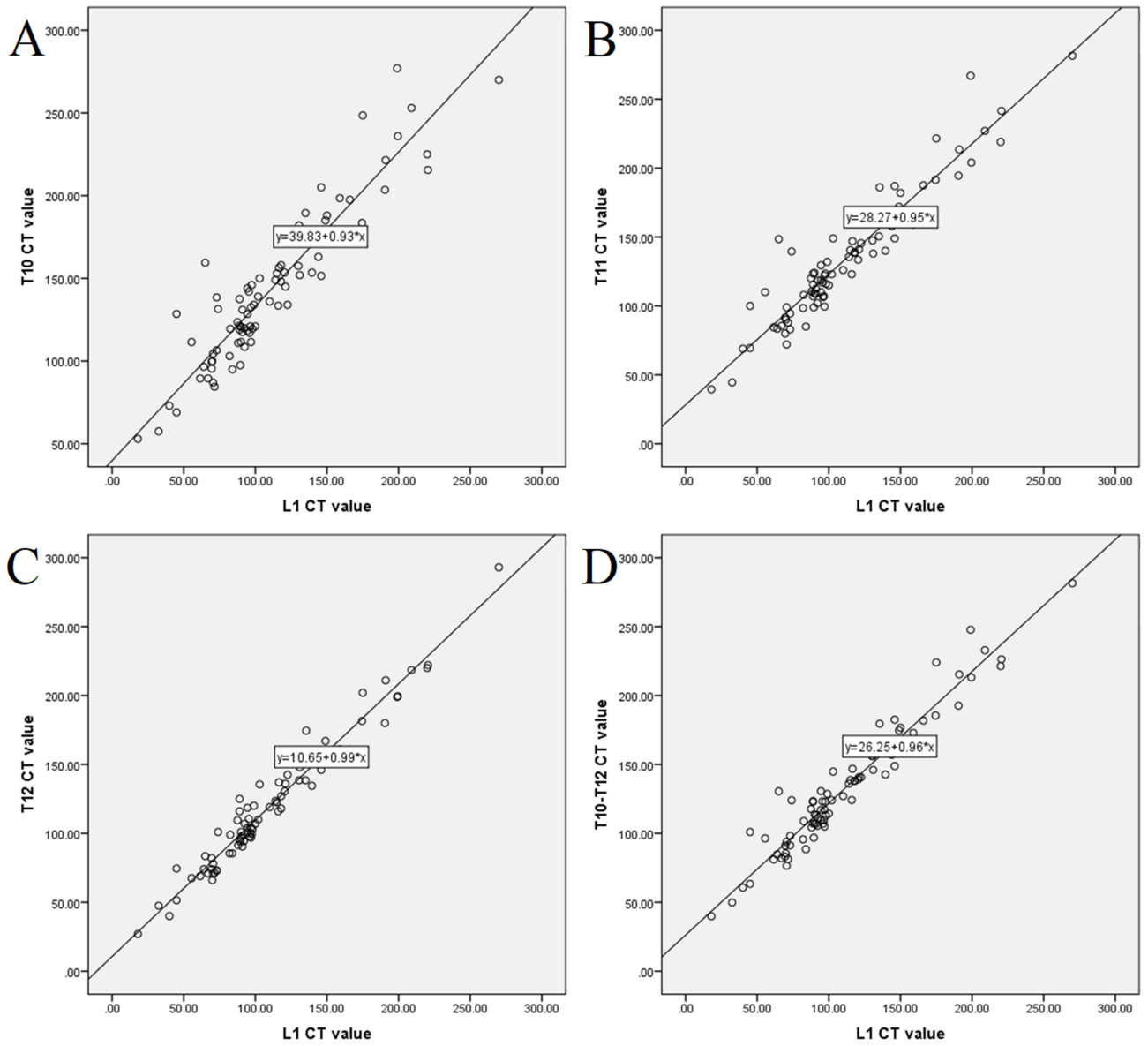

Figure 1 Correlation analysis of CT values of cancellous bone of vertebral bodies T10-T12 and L1. Statistics scatter diagrams and fitting lines of correlation analysis of CT values between (**A**) T10 vs L1, (**B**) T11 vs L1, (**C**) T12 vs L1, (**D**) T10-T12 mean value vs L1.

As shown in Figure 3, under the ROC curve area, the CT value of T10 was the largest (0.913), and, therefore, holds the largest significance in diagnosis of bone mass abnormality. The CT value corresponding to the maximum approximate Deng index was 150HU. In addition, the sensitivity and specificity were 86.4% and 90.9%, respectively (Table S4). DXA was used as the primary diagnostic standard of bone mass, the value of CT in the diagnosis of bone mass abnormality was evaluated compared with DXA.

The positive predictive value = 50/59×100% = 84.7%, and the negative predictive value = 19/22×100% = 86.4%. Based on this, the CT value was an excellent diagnostic marker for bone mass abnormality. In clinical settings, COPD patients with T10 CT value less than 150HU are strongly recommended to conduct dual-energy X-ray BMD to further evaluate bone mass. This is to determine the presence of bone loss or OP, so that the appropriate treatment measures can be taken as soon as possible.

As shown in Table S5, areas under the ROC were different between the T10 and T12, and the difference was statistically significant. The other groups showed no statistical difference. These results demonstrated the potential

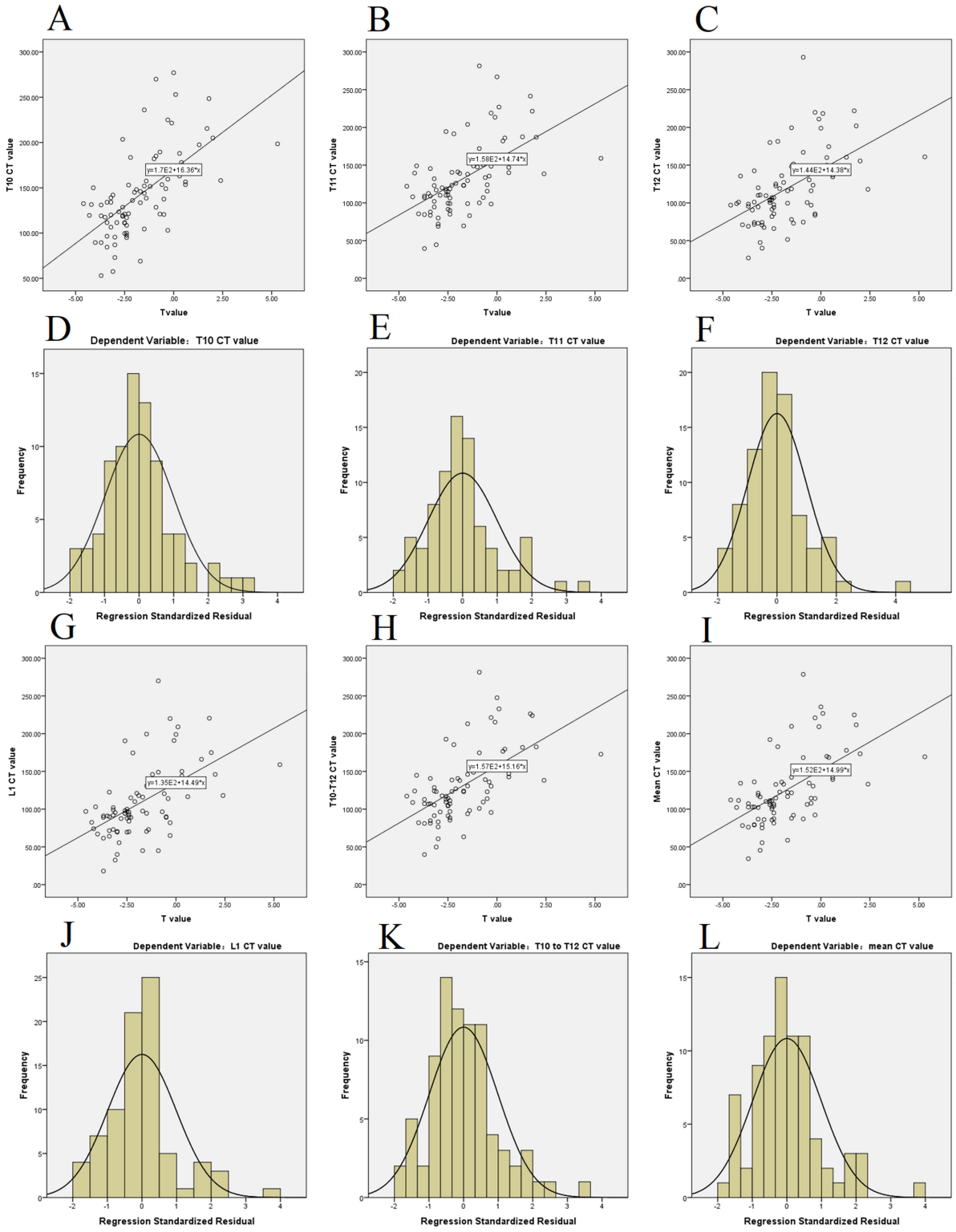

Figure 2 Correlation analysis of CT values of cancellous bone of vertebral bodies and T value of bone mineral density. (**A**) Statistics scatter diagrams and fitting lines of correlation analysis between CT values and T values of T10. (**B**) Statistics scatter diagrams and fitting lines of correlation analysis between CT values and T values of T11. (**C**) Statistics scatter diagrams and fitting lines of correlation analysis between CT values and T values of T12. (**D**) histogram and curve of mean CT values of cancellous bone of vertebral bodies of T10. (**E**) histogram and curve of mean CT values of cancellous bone of vertebral bodies of T11. (**F**) histogram and curve of mean CT values of cancellous bone of vertebral bodies of T12. (**G**) Statistics scatter diagrams and fitting lines of correlation analysis between CT values and T values of L1, (**H**) Statistics scatter diagrams and fitting lines of correlation analysis between mean CT values and mean T values of T10-T12. (**I**) Statistics scatter diagrams and fitting lines of correlation analysis between mean CT values and mean T values of T10-L1. (**J**) histogram and curve of mean CT values of cancellous bone of vertebral bodies of L1. (**K**) histogram and curve of mean CT values of cancellous bone of vertebral bodies of T10-T12. (**L**) histogram and curve of mean CT values of cancellous bone of vertebral bodies of T10-L1.

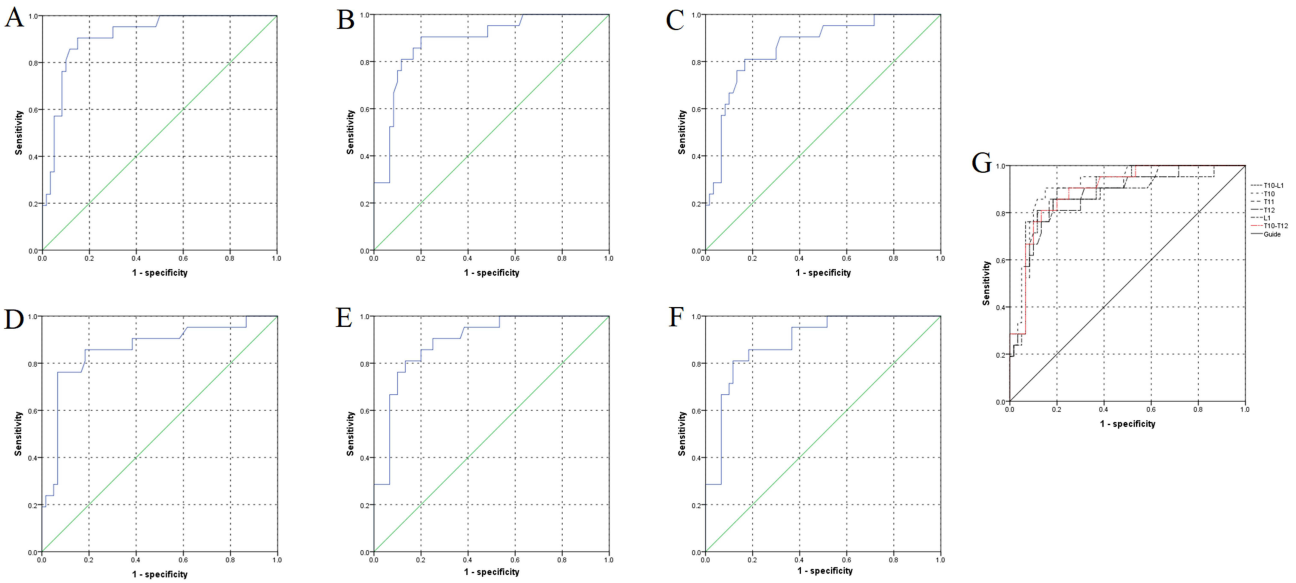

Figure 3 ROC curve analysis of CT value of vertebral cancellous bone in diagnosing abnormal bone mass. Sensitivity and specificity of CT value of (**A**) T10, (**B**) T11, (**C**) T12, (**D**) L1, (**E**) T10-T12, (**F**) T10-L1 (**G**) all vertebral cancellous bones in prediction of bone density.

clinical significance of the T11 and L1 CT value, but not the T12 CT value, in diagnosing COPD-associated OP, especially when T10 CT value is difficult to measure, due to vertebral surgery or trauma.

Analysis of Influencing Factors of Different BMD Levels in COPD Patients

Univariate Analysis of Different BMD Levels in COPD

As shown in Table 3, there were significant differences in the mean age, medical history, long-term hormone inhalation, mMRC dyspnea grade, body weight, and BMI among the three groups ($P < 0.05$), whereas, there were no significant differences in smoking index SI, number of acute exacerbations (≥2 times in the past 1 year), and CAT score ($P > 0.05$). These results suggest that the age, COPD duration, long-term inhaled corticosteroids, mMRC dyspnea grade, body weight, and BMI may contribute to BMD loss in patients with COPD.

Furthermore, blood gas analysis revealed statistically significant differences in oxygen partial pressure and blood oxygen saturation among the three groups ($P < 0.05$), while there was no significant difference in carbon dioxide partial pressure among the three groups ($P > 0.05$). The oxygen partial pressure and blood oxygen saturation gradually decreased

Table 3 Univariate Analysis of Different BMD Levels in COPD

	BMD Normal	BMD Reduced	Osteoporosis	F/χ2	P
General data					
Age (years)	62.6±10.6	66.1±11.3	69.5±7.4	3.773	0.027*
History (years)	5.5±4.3	11.8±14.6	14.5±12.3	10.091	0.006**
Long-term inhaled corticosteroids, n (%)	8 (36.4%)	12 (54.5%)	26 (70.3%)	6.526	0.038*
SI	452.3±698.4	516.4±524.6	676.0±757.4	1.971	0.373
Acute exacerbation ≥2 per year, n (%)	16 (72.7%)	15 (68.2%)	20 (54.1%)	2.416	0.299
CAT	16.9±6.1	18.0±5.8	17.9±6.6	0.323	0.815
mMRC	0.9±0.8	1.5±0.9	1.9±0.9	10.259	0.006**
Weight (kg)	71±13.4	63.5±11.7	58.4±9.63	8.565	0.001**
BMI (kg/m^2)	24.9±3.4	22.7±3.8	21.2±3.6	13.055	0.001**

(*Continued*)

Table 3 (Continued).

	BMD Normal	BMD Reduced	Osteoporosis	F/χ2	P
Blood analysis					
PaO_2 (mmHg)	73.4±10.1	68.5±7.7	65.8±11.1	3.647	0.031*
$PaCO_2$ (mmHg)	42.7±5.6	40.6±8.1	44.3±8.2	5.067	0.079
SaO_2 (%)	94.4±2.0	93.4±2.5	92.0±3.9	7.821	0.020*
Ca (mmol/L)	2.37±0.08	2.26±0.29	2.24±0.13	13.934	0.001**
P (mmol/L)	0.95±0.21	0.92±0.24	0.84±0.23	1.851	0.396
Fibrinogen (mmol/L)	3.89±1.14	4.31±1.53	4.04±1.33	0.548	0.580
IL-6 (pg/mL)	4.97±5.40	6.38±7.32	10.25±12.31	2.269	0.322
TNF-α (pg/mL)	96.33±73.07	75.79±102.45	110.46±293.84	4.296	0.117
25-hydroxyvitamin D3 (ng/mL)	17.26±8.54	15.06±7.76	11.88±6.03	7.001	0.030*
PTH (pg/mL)	62.77±24.46	55.08±24.13	63.88±33.8	2.841	0.242
Pulmonary function					
FEV_1 (L)	1.31±0.58	1.04±0.47	0.90±0.39	8.256	0.016*
FEV_1% (%)	47.34±19.72	41.64±19.64	34.68±13.08	6.385	0.041*
FVC (L)	2.27±0.59	2.01±0.68	1.87±0.71	6.462	0.040*
FEV_1/FVC (%)	56.68±15.43	52.09±15.61	50.06±10.88	1.653	0.438
Bone metabolic index					
ALP (U/L)	83.18±21.21	80.55±23.79	83.27±26.29	0.443	0.801
TPINP (ng/mL)	35.81±15.72	40.84±48.87	34.40±17.93	0.369	0.832
N-OST (ng/mL)	11.80±4.85	9.60±4.62	12.58±8.52	3.180	0.204
β-crossL (pg/mL)	456.00±204.48	519.83±265.44	670.42±294.58	5.082	0.008**

Notes: **p<0.01, *p<0.05.
Abbreviations: BMD, bone mineral density; COPD, Chronic Obstructive Pulmonary Disease; SI, smoking index; CAT, COPD assessment test; mMRC, modified British medical research council; BMI, body mass index.

between the normal BMD and OP groups, suggesting that the decrease of oxygen partial pressure may be a risk factor that negatively affects BMD in COPD patients (Table 3).

As shown in Table 3, there were statistically significant differences in other blood indexes like serum calcium and 25-hydroxyvitamin D3 among the three groups, while there were no statistically significant differences in serum phosphorus, serum fibrinogen, interleukin-6, and parathyroid hormone. In addition, from the normal BMD group to the OP group, the blood calcium and 25-hydroxyvitamin D3 levels decreased gradually, suggesting that the lack of above indicators may contribute to BMD abnormality in COPD patients.

The differences in FEV1, FEV1%, and FVC among the three groups were statistically significant as well ($P < 0.05$), while FEV1/FVC remained the same among the three groups. Moreover, FEV1, FEV1%, and FVC in COPD patients with normal BMD were higher than those in the decreased BMD and OP groups, suggesting that a decrease in the above indexes in lung function may be a risk factor for decreased BMD or OP in COPD patients (Table 3).

Pairwise Comparative Analysis Among the Three Groups

We observed statistically significant differences among the three groups in terms of age, COPD duration, long-term inhalation of glucocorticoids, mMRC dyspnea grade, body weight, BMI, oxygen partial pressure, oxygen saturation, blood calcium, total blood 25-hydroxyvitamin D3, FEV1, FEV1%, FVC, and other indicators, using univariate analysis (Table S7). Indicators with statistically significant differences were compared and analyzed in pairs among the three groups. The results are summarized in Tables S6–S8.

Logistic Regression Analysis

The differing BMD levels in COPD patients were used as dependent variables, and the statistically significant indicators from univariate analysis results were used as independent variables in regression analysis. Because the normal BMD group, the decreased BMD group, and the OP group belonged to multiple level classification variables, and there was an

Table 4 Logistic Regression Analysis

Factor	B value	SE	Wald value	DOF	*P*	OR value	95% CI
COPD history	0.06	0.026	5.333	1	0.021*	1.06	1.01~1.12
BMI	−0.422	0.183	5.317	1	0.021*	0.66	0.46~0.94
25-hydroxyvitamin D3	−0.112	0.043	6.866	1	0.009**	0.89	0.82~0.97
Inhaled corticosteroids	1.365	0.576	5.625	1	0.018*	3.92	1.27~12.10

Note: **p<0.01, *p<0.05.
Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; BMI, body mass index.

obvious sequential relationship between the levels, the ordered multiple classification Logistic regression method was selected for subsequent analysis (Table S9).

The assigned variables and corresponding data were then imported into the SPSS statistical software for ordered multi-classification Logistic regression analysis. The results met the parallel line test (P=0.988), and the value of the regression model was statistically significant (P < 0.05). The results are presented in Table 4. The COPD duration, BMI, serum 25-hydroxyvitamin D3, and inhaled glucocorticoids were the influential factors that predicted different BMD levels in COPD patients.

Bone Metabolic Indexes Under Different BMD Levels

There were no significant differences in the ALP, TPINP, and N-OST among the three groups (P > 0.05), but there was significant difference in β -crossL (P < 0.05) (Table 3). We next conducted the pair-wise comparative analysis of β -CrossL. The results showed statistically significant differences between the normal BMD and OP groups (P=0.004), and between the decreased BMD and OP groups (P=0.038), while there was no statistically significant difference between the normal BMD and decreased BMD groups (P > 0.05).

Correlation Between SERUM IL-6, TNF-α, and Various Bone Metabolic Indices

Correlation analysis was conducted between IL-6 and various bone metabolism indicators within the three groups. The results showed that β-CrossL, representing bone resorption index, was negatively correlated with serum IL-6 (r=−0.254, P=0.022, Table S10), while ALP, TPINP, and N-OST, that represented the bone formation index, showed no correlation with IL-6.

Correlation analysis between TNF-α and various bone metabolism indexes in all three groups showed a low positive correlation between serum TNF-α and ALP, which represents bone formation index (r=0.284, P=0.023, Table S11), whereas, TPINP and N-OST, which represent bone formation index, showed no correlation with TNF-α. There was also no correlation between TNF-α and serum β-crossL, which represents bone resorption index.

Discussion

OP is a common complication for COPD patients, leading to vertebral compression fractures, reduced thoracic activity, restricted lung ventilation, and increased hypoxemia and hypercapnia.[7] Lack of oxygen can worsen bone loss and imbalance in bone formation.[18] This can increase the risk of peripheral bone fractures[19] and potentially lead to venous thrombosis or pulmonary embolism dependent mortality in COPD patients. Prolonged bed rest can decrease sun exposure, leading to inadequate vitamin D3 synthesis and weakened absorption of calcium and phosphorus, which can worsen bone mineral density damage in patients with COPD and osteoporosis. This coexistence of diseases can greatly impact patient quality of life and increase mortality.[20,21] Hence, it is imperative to recognize the high incidence of OP in individuals with COPD and promptly implement appropriate diagnostic interventions. Timely identification of risk factors can effectively halt the advancement of osteoporosis in COPD patients.

Patients with COPD often experience complications such as pulmonary infection during acute exacerbation, necessitating a routine chest CT examination upon admission. This study investigated the relationship between CT values and T values of the vertebra. Our findings demonstrated a significant correlation between the CT value of vertebral cancellous

bone and the T value of bone mineral density ($R > 5.5$, $P < 0.001$). Utilizing scatter plots and linear regression analysis, we established a linear association between these variables. Furthermore, the CT value of vertebral cancellous bone mineral density at the T10 level exhibited the highest correlation to T value. CT is effective for diagnosing abnormal bone mass, including osteoporosis. Patients with COPD can have their T10-L1 vertebral bone measured via chest CT for screening. A value lower than 150HU suggests the need for further evaluation and treatment.

Through univariate analysis, we identified several potential risk factors, including age, disease duration, long-term inhalation of glucocorticoids, mMRC level, body weight, BMI, PaO2, SaO2, blood calcium, total 25-hydroxyvitamin D3, FEV1, FEV%, and FVC, that may impact BMD in patients with COPD. Subsequently, utilizing multivariate logistic regression analysis, we determined that COPD duration, BMI, 25-hydroxyvitamin D3 levels, and long-term use of inhaled glucocorticoids were independent factors associated with varying BMD levels in COPD patients.

There were no statistically significant differences in bone formation indexes (ALP, TPINP, N-OST) observed among the normal BMD group, decreased BMD group, and OP group. However, the bone resorption index, β-CrossL, exhibited a significant difference across all three groups. This finding suggests that osteoporosis in patients with COPD may be primarily characterized by bone resorption. In the context of osteoporosis, inflammatory markers such as TNF-α and IL-6 are believed to play a crucial role in osteoclast-mediated bone resorption. In this investigation, we explored the association between IL-6, TNF-α, and bone metabolic markers. Our findings indicate a negative correlation between serum IL-6 and β-crossL, a marker of bone resorption ($r=-0.254$, $P=0.022$), as well as a positive correlation between serum TNF-α and ALP, a marker of bone formation ($r=0.284$, $P=0.023$). These results suggest a regulatory role of serum IL-6 and TNF-α in bone metabolism among individuals with COPD. Due to the multifaceted nature of bone metabolism, which encompasses both bone formation and resorption processes, an imbalance between these processes can trigger a complex cascade leading to OP. A superficial examination of the relationship between inflammatory markers such as IL-6, TNF-α, and bone metabolic indicators may not provide a comprehensive understanding of the inflammatory mechanisms underlying OP in patients with COPD. Therefore, thorough assessments are imperative to elucidate the inflammatory mechanisms contributing to OP in COPD patients.

Data Sharing Statement

We declared that materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality.

Ethics Approval and Informed Consent

This project was approved by the ethics committee of the First Affiliated Hospital, Medical College, Xi'an Jiaotong University for clinical research, and all specimens were obtained from patients with informed consent. All procedures involving the patients complied with the ethical standards of the institutional and national research committees and with the Declaration of Helsinki and its later amendments.

Consent for Publication

All authors have reviewed the final version of the manuscript and approved it for publication.

Funding

This study was supported by the Research and development Project of First Affiliated Hospital of Xi'an Jiaotong University (No. 2022MS-15); Shaanxi Provincial Key Research and Development Program (No. 2021KW-51, No. 2014JM2-8185).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Barker K, Eickmeyer S. Therapeutic exercise. *Med Clin North Am*. 2020;104(2):189–198. doi:10.1016/j.mcna.2019.10.003
2. Adas-Okuma MG, Maeda SS, Gazzotti MR, et al. COPD as an independent risk factor for osteoporosis and fractures. *Osteoporos Int*. 2020;31(4):687–697. doi:10.1007/s00198-019-05235-9
3. Chen Y-W, Ramsook AH, Coxson HO, Bon J, Reid WD. Prevalence and risk factors for osteoporosis in individuals with COPD: a systematic review and meta-analysis. *Chest*. 2019;156(6):1092–1110. doi:10.1016/j.chest.2019.06.036
4. Bari MZJ, Patwary I, Hussain D, Islam SAHMM, Rasker JJ. Association of COPD with osteoporosis in male smokers: a case control study in a tertiary medical college hospital in Bangladesh. *J Back Musculoskelet Rehabil*. 2020;33(1):119–125. doi:10.3233/BMR-181303
5. Pezzuto A, Ricci A, D'Ascanio M, et al. Short-term benefits of smoking cessation improve respiratory function and metabolism in smokers. *Int J Chron Obstruct Pulmon Dis*. 2023;18:2861–2865. doi:10.2147/COPD.S423148
6. Ryan CS, Petkov VI, Adler RA. Osteoporosis in men: the value of laboratory testing. *Osteoporos Int*. 2011;22(6):1845–1853. doi:10.1007/s00198-010-1421-0
7. Inoue D, Watanabe R, Okazaki R. COPD and osteoporosis: links, risks, and treatment challenges. *Int J Chron Obstruct Pulmon Dis*. 2016;11:637–648. doi:10.2147/COPD.S79638
8. Zhang X-J, Cui Z-H, Dong Y, et al. GPNMB contributes to a vicious circle for chronic obstructive pulmonary disease. *Biosci Rep*. 2020;40(6):BSR20194459.
9. Trouvin A-P, Goëb V. Receptor activator of nuclear factor-κB ligand and osteoprotegerin: maintaining the balance to prevent bone loss. *Clin Interv Aging*. 2010;5:345–354. doi:10.2147/CIA.S10153
10. Sarkar M, Bhardwaj R, Madabhavi I, Khatana J. Osteoporosis in chronic obstructive pulmonary disease. *Clin Med Insights Circ Respir Pulm Med*. 2015;9:CCRPM.S22803. doi:10.4137/CCRPM.S22803
11. Briot K, Geusens P, Em Bultink I, Lems WF, Roux C. Inflammatory diseases and bone fragility. *Osteoporos Int*. 2017;28(12):3301–3314. doi:10.1007/s00198-017-4189-7
12. Gao W, Li L, Wang Y, et al. Bronchial epithelial cells: the key effector cells in the pathogenesis of chronic obstructive pulmonary disease? *Respirology*. 2015;20(5):722–729. doi:10.1111/resp.12542
13. Hu X, Sun Y, Xu W, Lin T, Zeng H. Expression of RANKL by peripheral neutrophils and its association with bone mineral density in COPD. *Respirology*. 2017;22(1):126–132. doi:10.1111/resp.12878
14. Ugay L, Kochetkova E, Nevzorova V, Maistrovskaia Y. Role of osteoprotegerin and receptor activator of nuclear factor-κB ligand in bone loss related to advanced chronic obstructive pulmonary disease. *Chin Med J*. 2016;129(14):1696–1703. doi:10.4103/0366-6999.185857
15. Eswaran SK, Gupta A, Adams MF, Keaveny TM. Cortical and trabecular load sharing in the human vertebral body. *J Bone Miner Res*. 2006;21(2):307–314. doi:10.1359/jbmr.2006.21.2.307
16. Papadakis AE, Karantanas AH, Papadokostakis G, Damilakis J. Assessment of the morpho-densitometric parameters of the lumbar pedicles in osteoporotic and control women undergoing routine abdominal MDCT examinations. *J Bone Miner Metab*. 2011;29(3):352–358. doi:10.1007/s00774-010-0227-7
17. Emohare O, Cagan A, Morgan R, et al. The use of computed tomography attenuation to evaluate osteoporosis following acute fractures of the thoracic and lumbar vertebra. *Geriatr Orthop Surg Rehabil*. 2014;5(2):50–55. doi:10.1177/2151458514525042
18. Manolagas SC. From estrogen-centric to aging and oxidative stress: a revised perspective of the pathogenesis of osteoporosis. *Endocr Rev*. 2010;31(3):266–300. doi:10.1210/er.2009-0024
19. Biskobing DM. COPD and osteoporosis. *Chest*. 2002;121(2):609–620. doi:10.1378/chest.121.2.609
20. Jones A, Fay JK, Burr M, Stone M, Hood K, Roberts G. Inhaled corticosteroid effects on bone metabolism in asthma and mild chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2002;2002(1):CD003537. doi:10.1002/14651858.CD003537
21. Gluck O, Colice G. Recognizing and treating glucocorticoid-induced osteoporosis in patients with pulmonary diseases. *Chest*. 2004;125(5):1859–1876. doi:10.1378/chest.125.5.1859