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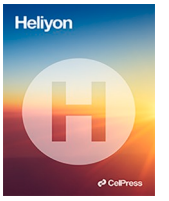

Smoking index and COPD duration as potential risk factors for development of osteoporosis in patients with non-small cell lung cancer – A retrospective case control study evaluated by CT Hounsfield unit

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ABSTRACT

Objective: To investigate the effect of smoking index (calculated as number of cigarettes per day × smoking years) and chronic obstructive pulmonary disease (COPD) duration on osteoporosis (OP) evaluated by opportunistic chest CT in patients with non-small cell lung cancer (NSCLC).

Methods: A total of 101 patients diagnosed with NSCLC were included in our cohort study. Among them, 50 patients with a history of smoking and COPD were assigned to the experimental group, while 51 patients without a history of smoking and COPD were assigned to the control group. Hounsfield unit (HU) value was measured by conventional chest CT to investigate the bone mineral density; and the mean values of axial HU value in the upper, middle and lower parts of T4, T7, T10 and L1 vertebral bodies were measured as the study variables.

Results: There were no significant differences in gender, age, body mass index, type of lung cancer, clinical stage of lung cancer and comorbidities between the two groups ($P = 0.938$, $P = 0.158$, $P = 0.722$,$P = 0.596$,$P = 0.813$,$P = 0.655$). The overall mean HU values of T4, T7, T10, L1 in the experimental group were 116.60 ± 30.67, 110.56 ± 30.03, 109.18 (96.85–122.95), 94.63 (85.20–104.12) and 106.86 ± 22.26, respectively, which were significantly lower than those in the control group (189.55 ± 34.57, 174.54 ± 35.30, 172.73 (156.33–199.50), 158.20 (141.60–179.40) and 177.50 ± 33.49) ($P < 0.05$). And in the experimental group, smoking index and COPD duration were significantly and negatively correlated with HU values ($r = -0.627$, -0.542, $P < 0.05$, respectively).

Conclusion: Patients with NSCLC who have a history of smoking and COPD exhibit a notably lower HU value compared to the control groups. Additionally, it has been observed that the smoking index and duration of COPD may be influential factors affecting bone mineral density in NSCLC patients.

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1. Introduction

Osteoporosis (OP) is a systemic skeletal disorder distinguished by diminished bone mass and compromised bone microarchitecture, leading to heightened susceptibility to bone fractures. Its prevalence has escalated considerably, imposing substantial burdens on healthcare expenditure, morbidity rates, and mortality rates. Given the escalating aging population, advancements in medical services, and prolonged human lifespan, OP has emerged as a critical public health concern jeopardizing human well-being [1]. Lung cancer, with a prevalence of 11.6 % among all cancer cases, stands as the foremost cause of cancer-related mortality, claiming over 1.7 million lives globally in 2018. A significant proportion of individuals affected by this disease receive a diagnosis during advanced stages, which frequently entails severe systemic complications. For instance, certain lung cancers may exhibit calmodulin secretion, leading to diminished serum calcium levels and subsequent development of OP. Elevated serum levels of calmodulin, accompanied by hypocalcemia, bony pain, fractures, and other manifestations, can be observed in these patients. Therefore, it is imperative to consider the bone mass of lung cancer patients, as it can significantly impact the 5-year survival rate of patients [2,3]. A large number of scientific studies have also demonstrated that smoking plays an important role in the development of OP. One of the seven primary fracture risk factors endorsed by the World Health Organization Fracture Risk Assessment Tool (FRAX) encompasses age, sex, personal fracture history, family history of fracture, smoking, exercise, and mental factors, with smoking being among them (Fig. 1). [4–6]. Simultaneously, OP can significantly impact patients with COPD, leading to diminished activity levels and a decline in quality of life. The confluence of compromised pulmonary function, reduced physical activity, and the presence of OP substantially heightens the susceptibility to falls and fractures [4,7]. Therefore, patients with both a history of smoking and COPD should be followed up for bone mineral density to prevent OP-related complications in advance. Bone mineral density can be measured by a variety of current examination techniques, dual energy X-ray absorptiometry (DXA) and quantitative computed tomography (QCT) are more commonly used in clinical practice. Furthermore, DXA is recommended by the World Health Organization as the gold standard for the diagnosis of OP [8,9]; however, the above two devices have a narrow scope of application and only exist in large tertiary general hospitals or physical examination centers, also it is difficult to be popularized in general primary hospitals. Therefore, how to simply and accurately understand bone mineral density, timely prevent and treat osteoporosis, and prevent serious complications caused by OP (such as osteoporotic fractures) is essential; at present, a large number of studies have recommended HU value as an important tool for screening OP [10–13]. Groch et al. [14], for example, identified the HU values at L4, L5, and S1 by lumber vertebrate CT of 50 patients,

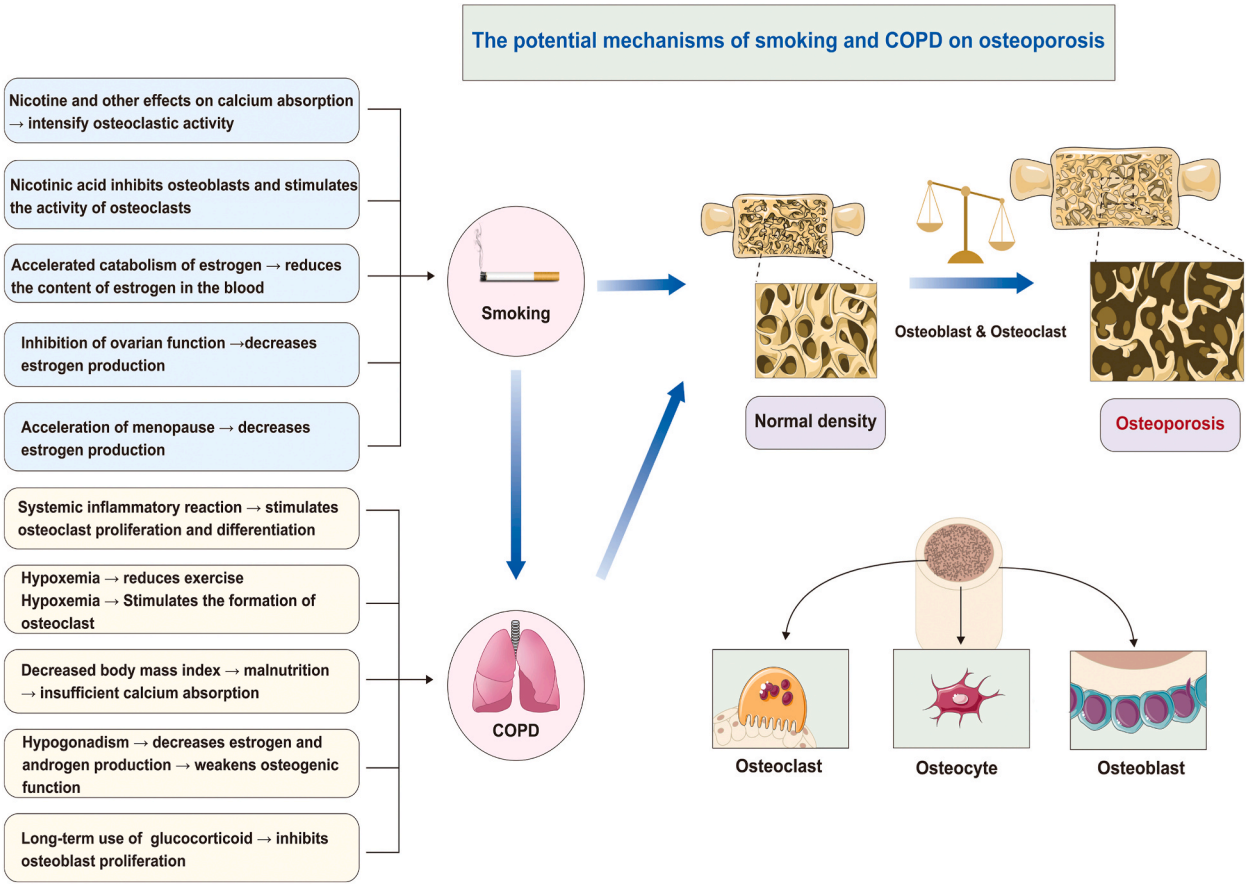

Fig. 1. The potential mechanisms of smoking and COPD on osteoporosis.

demonstrating that identified the HU values at L4, L5, and S1 by lumber vertebrate CT of 50 patients, demonstrating that the HU value is a rapid and cost-effective method that does not involve additional radiation exposure, allowing for the acquisition of supplementary information regarding bone health; Kim et al. [15], conducted measurements of HU values on chest CT scans of 232 patients, specifically focusing on the T4, T7, T10, and L1 vertebral bodies. These measurements were then subjected to quantitative analysis using dual-energy X-ray absorptiometry. The researchers determined that the optimal threshold for detecting the mean bone mineral density associated with OP in men was 136.2 HU, with a sensitivity of 95.0. specificity 77.6, while in women was 137.9 HU. with a sensitivity of 96.0, specificity 64.4. The above studies showed that, HU value obtained by opportunistic CT scans has been shown to be a feasible tool with good sensitivity to additionally assess patients' bone quality compared with the gold standard DXA. Therefore, the aim of this paper is to observe the correlation between smoking index, COPD duration (interval between the patient's initial diagnosis of COPD and their subsequent enrollment in the study.) and HU values in patients with NSCLC, so as to determine the effect of smoking index and COPD duration on bone mineral density and provide a reliable basis for early prevention and treatment of OP in this population.

2. Materials and methods

2.1. General data

A retrospective, non-randomized collection was conducted on a cohort of 101 patients diagnosed with non-metastatic NSCLC in the Department of Respiratory Medicine at Guizhou Provincial People's Hospital between October 2021 and October 2022, who had not received chemoradiotherapy prior to the study. The inclusion of these patients in the study was subject to review and approval by the Ethics Committee of Guizhou Provincial People's Hospital (NO.KY 2022-133); among them, 50 lung cancer patients with history of smoking and COPD were included in the experimental group, with an average age of (63.46 $\pm$ 7.05) years, while 51 lung cancer patients without smoking history and COPD at this time period were selected and included in the control group, with an average age of (62.10 $\pm$ 7.76) years. The lung cancer types in the two groups were compiled based on the pathological biopsy results, in accordance with the 8th edition of the International Society for the Study of Lung Cancer TNM staging criteria for lung cancer [16] , The clinical staging of lung cancer was assessed in both the experimental and control groups of this study, and the comorbidities between these groups were subjected to statistical analysis.

2.2. Research methods

2.2.1. Medical history collection

A unified inquiry process was used, and the inquiry doctors were composed of attending doctors who had been specially trained, information including general data, past history (COPD history), medication history, family history, and living habits (smoking and drinking) were obtained.

2.2.2. Physical examination

The height and weight of the subjects were recorded, and the body mass index (BMI) was calculated. BMI = weight (kg)/height (m^2).

2.2.3. HU value measurement

The chest CT utilized in this study refers to the CT image acquired during the patient's initial diagnosis of lung cancer at our hospital. Additionally, the HU value was measured based on the chest CT obtained during the patient's initial lung cancer diagnosis. The HU value of chest CT (Siemens, dual-source computed tomography, defined tube voltage 120 kV) was measured by two professional doctors including T4, T7, T10, and L1 vertebral bodies of the patients, (Fig. 2). Finally, the mean values of each vertebra between the two groups were compared. Measurement method: first, the above four targeted vertebral bodies were located from the sagittal and axial chest position (Fig. 2A and B), and then 3 axial planes of targeted locations were selected from the sagittal view of each vertebral body (Fig. 2C–a): was located below the upper endplate (Fig. 2C–b), was located in the middle of the vertebral body, and (Fig. 2C–c) was located above the lower endplate. Finally, the average HU value of each vertebra was calculated by marked ellipses of the above three axial planes (Fig. 2D–G). The overall total mean HU values were then calculated from the mean HU values of the four vertebral bodies.

2.2.4. Calculation of smoking amount

This study utilized multiple measures, such as the smoking index, cumulative smoking index, and other indicators, to quantitatively assess the prevalence of smoking among the patients. The smoking index was determined by multiplying the number of cigarettes smoked per day by the number of years of smoking, and it was categorized into three levels: mild smoking (smoking index $\leq$200), moderate smoking (200 $<$ smoking index $<$400), and severe smoking (smoking index $\leq$400). According to a study, there was a notable elevation in the likelihood of developing cancer when the smoking index reached or surpassed a value of 400 [17]; Based on the prevailing consensus among experts, it can be considered a substantial risk factor for the onset of lung cancer when an individual's cumulative smoking index reaches or surpasses 20 packs. This index is determined by multiplying the number of packs smoked per day (20 cigarettes per pack) by the total number of years of smoking [18]. The mean cumulative smoking index among the smoking patients in this study was 50.20 pack years, indicating a high risk for lung cancer (Fig. 3). Notably, all smoking patients in the experimental group exclusively smoked cigarettes, which contains 20 cigarettes per pack. Due to potential exposure to secondhand

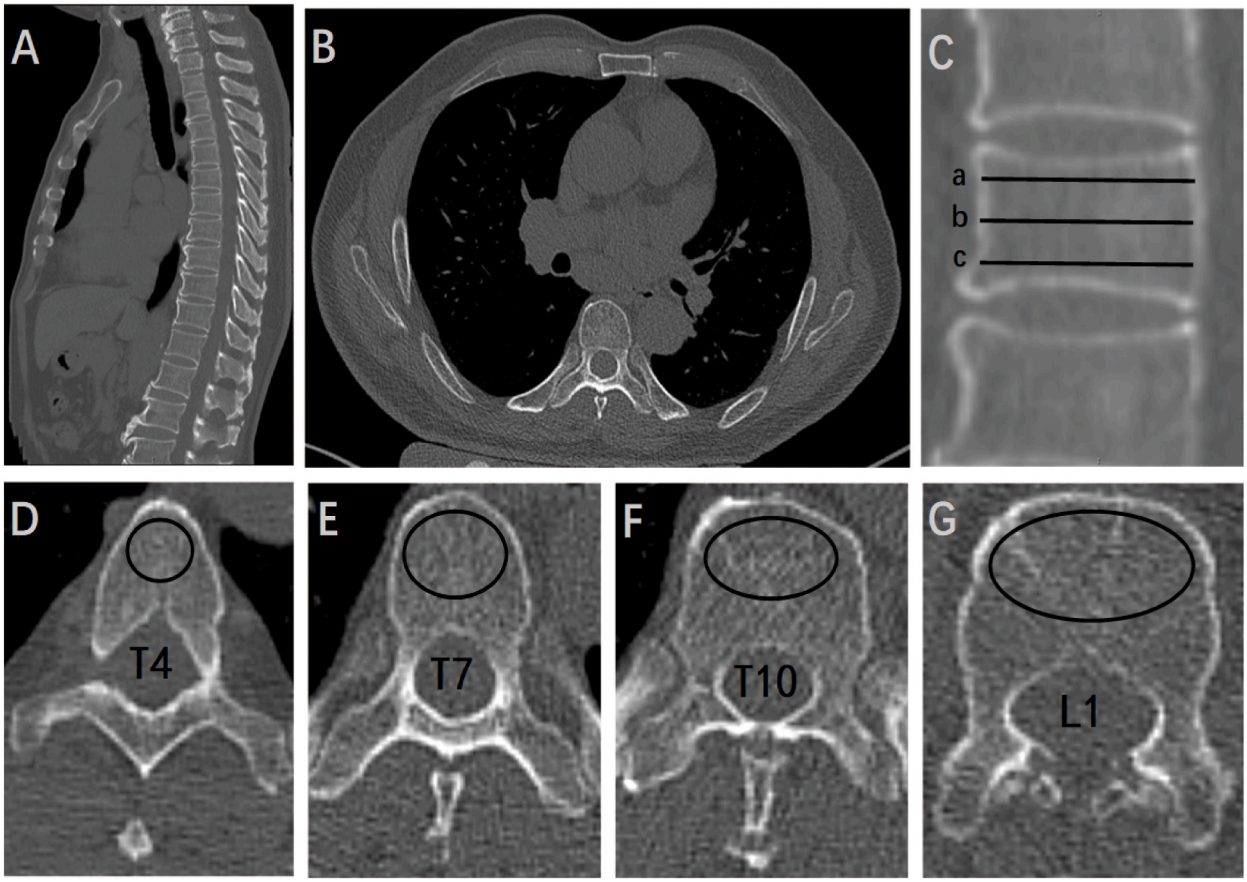

Fig. 2. Measurement of HU value by CT. A. sagittal CT view of the chest CT; B. axial CT view of the chest CT. C locations of the assessment (a. located below the upper endplate, b. located in the middle of the vertebral body, and c. located above the lower endplate.); D-G. axial locations of the assessment on T4,7,10 and L1.

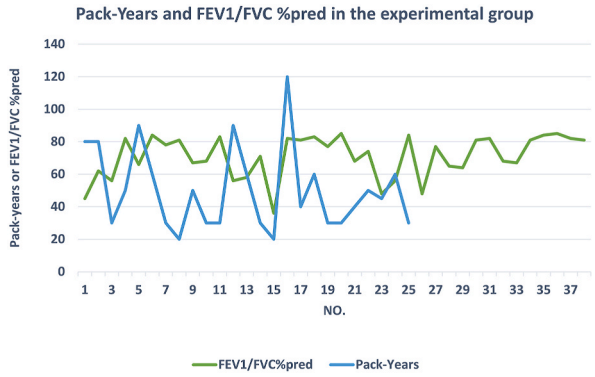

Fig. 3. Smoking status and COPD severity in the experimental group. Note: Cumulative smoking index: number of packs smoked per day (20 cigarettes/pack) * total years of smoking; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; FEV1/FVC%: FEV1/FVC.

smoke in both the experimental and control groups, the precise identification of secondhand smoke exposure was not feasible. Therefore, we solely recorded the smoking status of patients, considering those in the control group as nonsmokers and nonexposed to secondhand smoke.

2.2.5. Diagnostic criteria and measurement indicators of COPD

According to 2021 edition of Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease [19], the diagnostic criteria and measurement indicators of COPD diagnosis primarily relies on clinical data encompassing the assessment of risk

factor exposure history, symptoms, signs, pulmonary function tests, and the exclusion of other diseases that may present similar symptoms and persistent airflow limitation. Pulmonary function tests showing persistent airflow limitation are necessary for the diagnosis of COPD, and FEV1/FVC <70 % after inhalation of bronchodilators identifies the presence of persistent airflow limitation. Global initiative for chronic obstructive lung disease (GOLD) was graded according to the severity of irreversible airflow limitation in COPD according to the percentage of predicted FEV1 after diastole, which was divided into 4 grades: grade I (mild): FEVl/FVC <70 % but FEVl ≥80 % predicted; grade II (moderate): 50 % ≤ FEV1 < 80 % predicted; grade III (severe): 30 % ≤ FEV1 < 50 % predicted; and grade IV (very severe): FEV1 < 30 % predicted. In this study, all patients diagnosed with COPD were determined by FEV1 to FVC ratio (FEV1/FVC <70 %) measured by our spirometer (model: Master Screen SeS) after inhalation of bronchodilators, and FEV1% of predicted value was graded. The etiology of COPD may be related to factors such as smoking, air pollution, occupational exposure (occupational exposure to vapors, gases, dusts, and fumes), etc [20]. Siddharthan et al. [21] pooled data from five population-based studies in six countries and 13 regions of sub-Saharan Latin America and found that smoking accounted for approximately 20 % of the causes of COPD; According to Mehta et al. [22], air pollution accounts for approximately 56 % of the causes of COPD in a multicenter, population-based prospective cohort study of 9561 people randomly recruited in eight districts of Switzerland; In a Danish population-based cohort, occupational exposure to vapour, gas, dust, and fumes (predominantly organic dust) was associated with a more than threefold increased risk (LLN OR = 3.69 (95 % CI 1.36 to 10.04), with a population attributable fraction of 48 % (95 % CI 30 %–65 %) among never-smokers [23]. In our study, a total of 38 people in the experimental group had COPD, 16 patients in grade I, 18 patients in grade II, 4 patients in grade III, and no patients in grade IV (Fig. 3). 24 (63 %) of whom had a clear history of smoking, 5 (13 %) had a long history of polluted air exposure, and 9 (24 %) had a clear history of occupational exposure.

2.3. Inclusion and exclusion criteria

2.3.1. Inclusion criteria

(1) Patients who were initially diagnosed with non-metastatic NSCLC and had not yet undergone chemoradiotherapy; (2) All patients were over 45 years of age; (3) All patients in the experimental group met the diagnostic criteria for COPD in the Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease established in 2021; (4) Patients in the experimental group had no acute exacerbation of chronic obstructive pulmonary disease; (5) Patients who also had a history of smoking and had not quit smoking; (6) There were no other interfering factors that had an effect on bone mineral density recently.

2.3.2. Exclusion criteria

(1) Patients with liver and kidney dysfunction; (2) Patients with systemic immune diseases; (3) Patients with hyperparathyroidism or hypercortisolism; (4) Patients with primary or metastatic bone tumors in the spine and patients with foreign bodies caused by previous spinal surgery; (5) Patients with compression fractures; (6) Patients with small cell lung cancer; (7) Patients using anti-osteoporosis drugs, such as bisphosphonates, calcium or vitamin D, estrogen and estrogen receptor modulators.

2.3.3. Control factors

Due to the multitude of interconnected factors contributing to OP, the primary objective of this study is to investigate the impact of smoking index and COPD duration on HU values. To ensure the validity of our findings, we meticulously screened our patient cohort and eliminated any confounding variables that could potentially influence bone mineral density. Consequently, the participants included in this research were exclusively individuals who were initially diagnosed with non-metastatic NSCLC at our hospital and had not yet undergone chemoradiotherapy. The advantage of including such patients lies in the recent avoidance of high-dose hormone therapy, effectively eliminating the potential interference of glucocorticoids in this study. Additionally, given that age is an independent determinant of bone mineral density, we meticulously regulated the age of both patient groups to minimize any substantial age disparity.

2.4. Statistical analysis

SPSS 26 software was applied for statistical analysis. Measurement data conforming to normal distribution (body mass index, T4, T7 and overall total mean HU values) were expressed as $x \pm s$, the *t*-test was used for comparison between groups; measurement data not conforming to normal distribution (T10, L1 mean HU values) were expressed as median (interquartile spacing), and the Wilcoxon was used for comparison between groups. the categorical data (gender) were compared using χ^2 test. Pearson linear correlation test was used to analyze the correlation between smoking index, COPD duration and overall total mean HU values. $P < 0.05$ was considered statistically significant.

3. Results

3.1. General information

A total of 101 patients were investigated in this study, including 50 patients in the experimental group, 31 males (62 %) and 19 females (38 %); 51 patients in the control group, 32 males (63 %) and 19 females (37 %); there was no significant difference in gender between these two groups ($P = 0.938$). The age was ranged from 48 to 80 years, with an average age of (63.46 ± 7.05) years in the experimental group and (62.10 ± 7.76) years in the control group, there was no significant difference in the age between the two

Table 1
Comparison of demographic information between these two groups.

General information	Experimental group	Control group	*P*
no.	50	51	0.938
Male	31 (62 %)	32 (63 %)	
Female	19 (38 %)	19 (37 %)	
Age	63.46 ± 7.05	62.10 ± 7.76	0.158
BMI	22.57 ± 3.33	22.33 ± 3.47	0.722
Smoking index	900 (600–1200)	–	–
Pack-years	45 (30–60)	–	–
Type (n)			0.596
Adenocarcinoma	33 (66 %)	34 (67 %)	
Squamous cell carcinoma	17 (34 %)	16 (31 %)	
others	0 (0 %)	1 (2 %)	
Clinical staging(n)			0.813
IA	2 (4 %)	4 (8 %)	
IB	1 (2 %)	1 (2 %)	
IIA	1 (2 %)	0 (0 %)	
IIB	5 (10 %)	6 (12 %)	
IIIA	8 (16 %)	5 (10 %)	
IVA	21 (42 %)	25 (49 %)	
IVB	12 (24 %)	10 (20 %)	
Comorbidity			0.655
Diabetes mellitus	15 (30 %)	17 (33 %)	
Hypertension	18 (36 %)	20 (39 %)	
Hyperthyroidism	4 (8 %)	2 (4 %)	

Note: measures are expressed as number of patients (%) and mean ± standard deviation (x ± s).

groups (P = 0.158). BMI was ranged from 15.62 to 30.48 kg/m^2 with a mean BMI of (22.57 ± 3.33) in the experimental group and from 14.69 to 30.82 kg/m^2 with a mean BMI of (22.33 ± 3.47) in the control group, there was no significant difference in BMI between the two groups (P = 0.722). In experimental group, the smoking index was 900 (600–1200) , pack-years was 45 (30–60). Lung cancer types and clinical stages of lung cancer in the two groups: 33 cases of adenocarcinoma, 17 cases of squamous cell carcinoma and 0 case of other types of tumors in the experimental group, including 2 cases of stage IA, 1 case of stage IB, 1 case of stage IIA, 5 cases of stage IIB, 8 cases of stage IIIA, 21 cases of stage IVA and 12 cases of stage IVB; 34 cases of adenocarcinoma, 16 cases of squamous cell carcinoma and 1 case of other types of tumors (which is adenosquamous carcinoma) in the control group, including 4 cases of stage IA, 1 case of stage IB, 0 case of stage IIA, 6 cases of stage IIB, 5 cases of stage IIIA, 25 cases of stage IVA and 10 cases of stage IVB; there was no significant difference of lung cancer types and clinical stages between the two groups (P = 0.813, P = 0.655); There was also no statistical difference in comorbidities between the two groups (P = 0.655). The general information of the study subjects is shown in (Table 1**)**.

3.2. The comparisons of T4, T7, T10, L1 and total mean HU values between these two groups

After data processing of vertebral HU values in both group, the mean and standard deviation (or median and quartile) of T4, T7, T10, L1 and total mean HU values in the experimental group were 116.60 ± 30.67, 110.56 ± 30.03, 109.18 (96.85–122.95), 94.63 (85.20–104.12), and 106.86 ± 22.26, respectively; while in the control group, they were 189.55 ± 34.57, 174.54 ± 35.30, 172.73 (156.33–99.50), 158.20 (141.60–79.40), and 177.50 ± 33.49, respectively; it is showed that the mean HU values of each vertebral body in the experimental group were significantly lower than the control group (*P* < 0.05). The comparisons of T4, T7, T10, L1 and total mean HU values between these two groups are shown in **(Table 2).**

Table 2
Comparisons of average HU values between these two groups.

Groups	Average T4 HU value	Average T7 HU value	Average T10 HU value	Average L1 HU value	Total average HU value of (T4,7,10)	Total average HU value (T4,7,10 and L1)
Experimental group	116.60 ± 30.67	110.56 ± 30.03	109.18 (96.85–122.95)	94.63 (85.20–104.12)	110.98 ± 24.34	106.86 ± 22.26
Control group	189.55 ± 34.57	174.54 ± 35.30	172.73 (156.33–199.50)	158.20 (141.60–179.40)	181.90 ± 34.34	177.50 ± 33.49
P	< 0.05*	< 0.05*	< 0.05*	< 0.05*	< 0.05*	< 0.05*

Note: measures are expressed as mean ± standard deviation (x ± s); median (interquartile spacing) * with statistical significance.

3.3. Linear correlation analysis between smoking index, COPD index and HU value

It is showed that the overall mean HU values of the vertebral body in the experimental group was (106.86 ± 22.26), which showed a significant negative linear correlation with smoking index (Fig. 4A) ($r = -0.627$, $P < 0.05$); and a significant negative linear correlation with COPD duration (Fig. 4B) ($r = -0.542$, $P < 0.05$). Our study revealed a significant and inverse correlation between smoking index and COPD duration with HU value. Moreover, a higher smoking index and longer COPD duration were associated with lower HU values, thereby increasing the likelihood of OP. The correlations between smoking index, COPD duration and overall mean HU values are shown in (Table 3).

4. Discussion

OP is a prevalent age-related degenerative ailment, impacting a substantial population of around 200 million individuals globally. A considerable proportion of OP patients are prone to developing osteoporotic fractures, which significantly contribute to disability and mortality rates among the elderly. Moreover, these fractures impose a substantial economic burden on society, families, and individuals. However, early detection of OP patients, effective management of risk factors, timely implementation of intervention treatment, and subsequent delay in bone mineral density decline can collectively contribute to a reduction in the incidence of

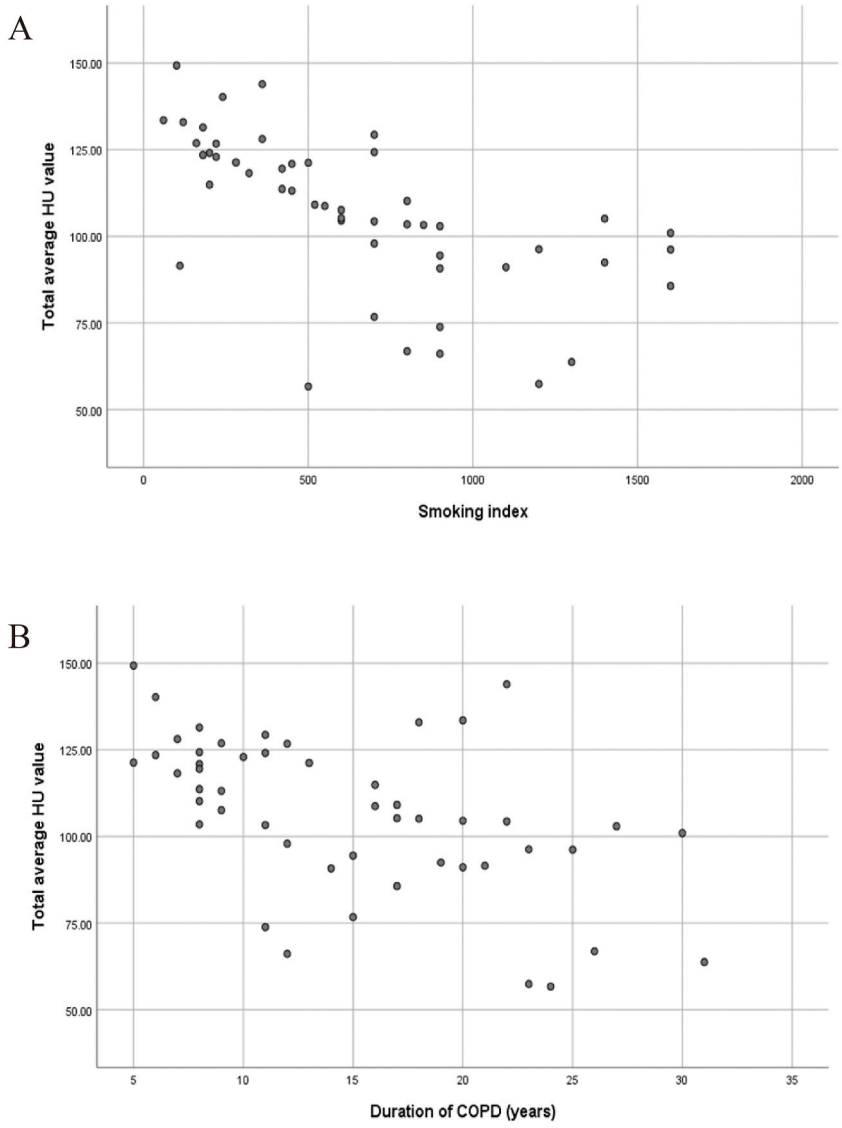

Fig. 4. Correlations of smoking index, COPD index and HU value. A. correlation between smoking index and total average HU value; B. correlation between COPD duration and total average HU value.

Table 3
Correlations between smoking index, COPD duration and total average HU value.

Relevance	Smoking index & total average HU value	COPD duration & total average HU value
Pearson correlation	−0.627	−0.542
P	< 0.05*	< 0.05*

* with statistical significance.

osteoporotic fractures [24,25]. At present, there are many known factors affecting OP, such as race, age, gender, weight, exercise, living habits and drugs abuse, which will have an impact on the bone mineral density [26,27]. Currently, many studies have confirmed that smoking index and COPD duration are related factors of OP, but mostly, based on the patient 's DXA bone mineral density examination [28,29]. Although DXA has been recommended by the World Health Organization as the gold standard for the diagnosis of OP, due to the need to produce additional rays and costs, only a considerable number of people in China have received bone mineral density examination, which is not easy to promote in clinical practice; on the contrary, chest CT, as a common imaging examination is more commonly used in general population, so the use of HU value measured by chest CT can simply and quickly understand the bone mineral density of patients, and it has been confirmed

by a number of studies [30–32]; It is widely recognized that OP is a prevalent complication among individuals with COPD, leading to a direct impact on patient mobility and a decline in their overall quality of life, particularly when spontaneous osteoporotic fractures occur. Conversely, COPD patients already experience compromised pulmonary function and reduced mobility, and when combined with OP, the risk of falls and fractures is significantly amplified [33]. Therefore, patients receiving chemoradiotherapy should prevent OP in advance. By measuring HU values from existing chest CT data of patients, we reminded respiratory physicians to pay attention to the bone mineral density of NSCLC patients, and it is especially important to prevent osteoporosis-related complications during late chemoradiotherapy in patients with both smoking history and COPD.

Mechanism of smoking-induced OP: 1.Smoking can inhibit intestinal absorption of calcium and vitamin D, which may be an important factor in bone loss; the main site of intestinal absorption of calcium ions is usually in the upper small intestine, particularly the upper duodenum and jejunum as the most effective absorption site; and the main site of intestinal absorption of vitamin D is also located in the jejunum and ileum; some components of cigarette smoking have been demonstrated in animal studies to directly harm the intestinal villi, while nicotine has the effect of compressing the intestinal microvessels, resulting in a decrease in the intestinal absorption rate of calcium and vitamin D [34,35]. 2.Nicotine in tobacco enhances osteoclast activity and raises blood and urine calcium concentrations, resulting in OP [36,37]. 3.Marinucci et al. [38] discovered that nicotine produces significant intracellular H_2O_2 buildup, which stimulates MG-H1 accumulation/release by inhibiting Glo1. MG-H1 then causes additional H_2O_2 overproduction via RAGE and, in parallel, an apoptotic mitochondrial pathway by inducing TG2 downregulation-dependent NF-kB desensitization, introducing the antiglycation enzyme defense Glo1 and MG-H1 as molecular events involved in osteoblast apoptosis, a critical event in smoker-related osteoporosis. 4.Nicotine reduces estrogen synthesis, promotes estrogen dissociation and metabolism, and dysregulates calcium-regulated hormones, thereby affecting bone mineral density [39]. 5.Smoking can inhibit ovarian function, lead to premature menopause in female patients, reduce estrogen secretion, leading to OP [40,41]. 6.Ernster et al. [42] found that smoking is an important factor leading to skin aging; and skin synthesis is the main source of vitamin D in the human body, so the synthesis of vitamin D will be affected by skin aging, smoking will accelerate skin aging and affect the synthesis of vitamin D in the human body, thus affecting the transport of calcium in the human body, leading to reduced calcium deposition in the bones, thereby reducing bone mass. 7.Smoking has been shown to influence the expression of cytokines and inflammatory mediators. In the study by Tsutakawa et al., nicotine (0.3 mg kg-1 day-1) significantly increased the protein expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), increased the release of pro–inflammatory mediators, hampered or prevented the healing of skin and blood vessels, disrupted the body's ability to make vitamin D and calcium, and therefore decreased bone mass [43]. 8.Smokers have higher serum levels of ionized calcium, and small changes in ionized calcium levels cause rapid changes in parathyroid hormone secretion and synthesis, demonstrating that smoking can affect parathyroid hormone secretion and synthesis, which leads to increased osteolysis and causes osteoporosis [44,45]. 9.Vitamin D3 produced by the skin and vitamin D2 taken from food circulating in the body are hydroxylated in the liver before being hydroxylated in the kidneys by the 1 hy-droxylase CYP27B1 to make active vitamin D, 1,25(OH) 2D3. Tobacco plants contain heavy metals such as lead and cadmium, and long-term smoking can lead to heavy metal accumulation in the body, with the kidneys being the primary site of accumulation. Indeed, an increase in lead and cadmium in the body can harm tubular and glomerular function, interfering with the proper biotransformation of vitamin D in the body and resulting in calcium absorption issues and decreased bone mass [46–49].

Mechanism of OP caused by COPD: 1.systemic inflammatory response caused by COPD can lead to osteoclast proliferation and differentiation, resulting in bone loss; 2.COPD patients frequently experience long-term hypoxemia, which primarily results in reduced patient activity and an increased risk of osteoporosis. Additionally, hypoxemia directly stimulates osteoclastogenesis; 3.Long-term COPD patients can lead to cachexia, leading to malnutrition, thus affecting the absorption of calcium; 4.COPD patients with long-term malnutrition, leading to hypogonadism, causing decreased estrogen and androgen production, and further weakening osteogenic activity. 5.A significant proportion of individuals diagnosed with COPD require prolonged corticosteroid therapy for the successful management and alleviation of symptoms, consequently establishing a direct correlation with bone demineralization [50–53].

Smoking, including secondhand smoking or passive smoking, is the first important cause of COPD. And the longer the duration of smoking, the greater the amount of smoking, the higher the prevalence; the pathogenesis of COPD caused by smoking is as follows: 1. Zhou et al. [17] concluded that smoking activates MMP-12, degrades elastin into elastin peptides, and activates immune cells to release

inflammatory factors, resulting in the occurrence of airway inflammation, and the excessive production of airway mucus, will causes long-term lung damage and eventually leads to the onset and progression of COPD. 2.Amatngalim et al. [54] found that smoking can harm the respiratory tract and epithelial cells, resulting in epithelial barrier disruption and cell death which further cause the onset or worsening of COPD. 3.Barnes et al. [55] found that chronic exposure to cigarette smoking activates reactive oxygen species (ROS), inflammation-oxidative stress, and apoptosis, resulting in enlarged alveolar spaces and causing the development of COPD. 4.Maremanda et al. [56] found that cigarette smoking has also been shown to alter the structure and function of mitochondria, and mitochondrial dysfunction is a key event in the pathogenesis of chronic lung diseases such as COPD and idiopathic pulmonary fibrosis (IPF). 5.Barnes et al. [57] found that cigarette smoking can activate alveolar macrophages to release elastase, which can lead to emphysema in combination with cytotoxic T cells, while promoting small airway fibrosis, resulting in COPD. It has also been shown that smoking cessation is essential in reducing COPD incidence and improving clinical symptoms. By observing 181 patients, Pezzuto et al. [58] found that smoking cessation and was effective in improving symptoms and respiratory function after 3 months of smoking abstinence. Pezzuto et al. [59] also retrospectively analyzed 45 patients with severe COPD in 2016 and found that lung function decline was closely related to smoking, which resulted in deterioration of symptoms, while smoking cessation was effective in increasing FEV1 and improving their symptoms. Second, exhaled carbon monoxide in quitters can return to normal within a few hours. Smoking cessation also relieves symptoms of chronic cough and sputum in the short term and reduces other symptoms such as shortness of breath and wheezing [60].

There is a large number of clinical literatures have demonstrated that HU value can be used as an important tool for the diagnosis of OP; for example, Kim et al. [15] evaluated the application of low-dose chest computed tomography (LDCT) in detecting OP and demonstrated that LDCT has a good correlation with bone mineral density measured based on dual-energy X-ray. The results of this study demonstrate that low-dose chest computed tomography can provide comprehensive information on the bone status without the need of additional examinations or exposure to radiation or contrast agents. Marinova et al. [61] also proved that Hu values from abdominal and particularly thoracic CT scans can sensibly be applied toward determining BMD, detecting OP and identifying persons at high fracture risk. It is showed that Hu value is superiorly to DXA, fragility fractures can be easily detected by it without additional imaging or radiation exposure, which can initiate early adequate treatment. It is therefore feasible to use HU values from chest CT to assess bone mineral density in patients. Furthermore, there is a considerable body of literature that provides thresholds for HU values corresponding to T scores from DXA, for example, Zaidi et al. [62] identified that L1 HU threshold for detecting OP is 110 HU and 135 HU for detecting osteopenia, with a specificity of 90 %. Zou et al. [63] recommended the following criteria for the diagnosis of OP: L1 $\leq$ 110 HU or L2 $\leq$ 100 HU or L3 $\leq$ 85 HU or L4 $\leq$ 80 HU. Based on previous research, it has been determined that patients diagnosed with NSCLC and exhibiting HU values below 110 in the L1 vertebral body or T4, T7, T10, L1 vertebral bodies, along with an overall mean HU value below 138, should undergo additional Dual-energy X-ray Absorptiometry (DXA) testing to validate the presence of OP and enable early intervention.

5. Limitations

First, only 101 patients are included in this study, so it is still necessary to verify the accuracy of the conclusions with larger prospective randomized trials; second, this paper only included NSCLC patients, so that the study results may have selective deviation; third, due to potential exposure to secondhand smoke in control group, the precise identification of secondhand smoke exposure was not feasible, which might cause biased results; fourth, the paper did not verify the correlation and accuracy between HU values and DXA, making it impossible to use HU values to determine whether patients have OP; lastly, in this experiment, the correlations between smoking, COPD and Hu value were investigated using univariate analysis, for further confirmation, a larger sample size and multi-center study are needed to control for potential confounding factors.

6. Conclusions

The study found that NSCLC patients with a smoking history and COPD had significantly lower HU values compared to those without such histories, suggesting a potential impact of smoking and COPD on bone mineral density. The use of HU values obtained from chest CT scans was found to be a simple and efficient method for predicting OP in NSCLC patients. Therefore, clinicians should consider utilizing HU values measured by chest CT scans to assess bone mineral density, particularly in patients with a history of smoking and COPD, as this approach may help reduce the occurrence of complications related to OP.

Statements & declarations

Ethic statements and patients' consent

This study was approved by the Medical Ethics Committee of Guizhou Provincial People's Hospital (NO.KY 2022-133). All patients selected for inclusion in the group signed the informed consent form for the trial.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Yue Zhou: Data curation, Investigation, Software, Writing – original draft. **Yunxiang Hu:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Xixi Yan:** Formal analysis, Investigation, Software. **Yueyue Zheng:** Investigation, Software, Writing – original draft, Writing – review & editing. **Sanmao Liu:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Writing – original draft, Writing – review & editing. **Hongmei Yao:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Hu Y, Han J, Ding S, Liu S, Wang H. Identification of ferroptosis-associated biomarkers for the potential diagnosis and treatment of postmenopausal osteoporosis. Front Endocrinol (Lausanne).13:986384.
[2] The L. Lung cancer: some progress, but still a lot more to do. Lancet.394(10212):1880.
[3] Hatlen P, Langhammer A, Forsmo S, Carlsen SM, Amundsen T. Bone mass density, fracture history, self-reported osteoporosis as pro xy variables for estrogen and the risk of non-small-cell lung cancer– a population based cohort study, the HUNT study: are proxy variables f riends or faults? Lung Cancer.81(1):39-46.
[4] Inoue D, Watanabe R, Okazaki R. COPD and osteoporosis: links, risks, and treatment challenges. Int J Chron Obstruct Pulmon Dis.11:637-648.
[5] Raisz LG, Prestwood KM. Epidemiology and pathogenesis of osteoporosis. Clin. Cornerstone.2(6):1-10.
[6] Sheu Y, Cauley JA, Patrick AL, Wheeler VW, Bunker CH, Zmuda JM. Risk factors for fracture in middle-age and older-age men of African d escent. J. Bone Miner. Res..29(1):234-241.
[7] 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.156(6):1092-1110.
[8] Löffler MT, Jacob A, Valentinitsch A, Rienmüller A, Zimmer C, Ryang Y-M, et al. Improved prediction of incident vertebral fractures using opportunisti c QCT compared to DXA. Eur. Radiol..29(9):4980-4989.
[9] Cheng X, Zhao K, Zha X, Du X, Li Y, Chen S, et al. Opportunistic screening using low-dose CT and the prevalence of osteop orosis in China: a nationwide, multicenter study. J. Bone Miner. Res..36(3):427-435.
[10] Hocaoglu E, Inci E, Vural M. Could computed tomography hounsfield unit values of lumbar vertebrae D etect osteoporosis? Curr Med Imaging.17(8):988-995.
[11] Yaprak G, Gemici C, Seseogullari OO, Karabag IS, Cini N. CT derived hounsfield unit: an easy way to determine osteoporosis and radiation related fracture risk in irradiated patients. Front. Oncol..10:742.
[12] Ahern DP, McDonnell JM, Riffault M, Evans S, Wagner SC, Vaccaro AR, et al. A meta-analysis of the diagnostic accuracy of Hounsfield units on comp uted topography relative to dual-energy X-ray absorptiometry for the d iagnosis of osteoporosis in the spine surgery population. Spine J..21(10):1738-1749.
[13] Amin MFM, Zakaria WMW, Yahya N. Correlation between Hounsfield unit derived from head, thorax, abdomen , spine and pelvis CT and t-scores from DXA. Skeletal Radiol..50(12):2525-2535.
[14] Berger-Groch J, Thiesen DM, Ntalos D, Hennes F, Hartel MJ. Assessment of bone quality at the lumbar and sacral spine using CT sca ns: a retrospective feasibility study in 50 comparing CT and DXA data. Eur. Spine J..29(5):1098-1104.
[15] Kim YW, Kim JH, Yoon SH, Lee JH, Lee CH, Shin CS, et al. Vertebral bone attenuation on low-dose chest CT: quantitative volumetr ic analysis for bone fragility assessment. Osteoporos. Int..28(1):329-338.
[16] Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WEE, et al. The IASLC lung cancer staging project: proposals for revision of the T. J. Thorac. Oncol..11(1):39-51.
[17] Zhou J-S, Li Z-Y, Xu X-C, Zhao Y, Wang Y, Chen H-P, et al. Cigarette smoke-initiated autoimmunity facilitates sensitisation to el astin-induced COPD-like pathologies in mice. Eur. Respir. J..56(3):2000404.
[18] Pleasants RA, Rivera MP, Tilley SL, Bhatt SP. Both duration and pack-years of tobacco smoking should Be used for cli nical practice and research. Ann Am Thorac Soc.17(7):804-806.
19 Global strategy for the diagnosis management and prevention of chronic obstructive pulmonary disease 2021 REPORT EB OL 2020-11-17.
[20] Yang IA, Jenkins CR, Salvi SS. Chronic obstructive pulmonary disease in never-smokers: risk factors, pathogenesis, and implications for prevention and treatment. Lancet Respir. Med..10(5):497-511.
[21] Siddharthan T, Grigsby MR, Goodman D, Chowdhury M, Rubinstein A, Irazola V, et al. Association between household air pollution exposure and chronic obstr uctive pulmonary disease outcomes in 13 low- and middle-income country settings. Am. J. Respir. Crit. Care Med..197(5):611-620.
[22] Mehta AJ, Miedinger D, Keidel D, Bettschart R, Bircher A, Bridevaux P-O, et al. Occupational exposure to dusts, gases, and fumes and incidence of chro nic obstructive pulmonary disease in the Swiss Cohort Study on Air Pol lution and Lung and Heart Diseases in Adults. Am. J. Respir. Crit. Care Med..185(12):1292-1300.
[23] Würtz ET, Schlünssen V, Malling TH, Hansen JG, Omland Ø. Occupational COPD among Danish never-smokers: a population-based study. Occup. Environ. Med..72(6):456-459.
[24] Kanis JA, Cooper C, Rizzoli R, Reginster JY, Scientific Advisory Board of the European Society for C, Eco nomic Aspects of O, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos. Int..30(1):3-44.
[25] Vilaca T, Eastell R, Schini M. Osteoporosis in men. Lancet Diabetes Endocrinol..10(4):273-283.
[26] Srivastava M, Deal C. Osteoporosis in elderly: prevention and treatment. Clin. Geriatr. Med..18(3):529-555.
[27] Vescini F, Chiodini I, Falchetti A, Palermo A, Salcuni AS, Bonadonna S, et al. Management of osteoporosis in men: a narrative review. Int. J. Mol. Sci..22(24): 13640.
[28] Høiberg MP, Rubin KH, Gram J, Hermann AP, Brixen K, Haugeberg G. Risk factors for osteoporosis and factors related to the use of DXA in Norway. Arch Osteoporos.10:16.
[29] González J, Rodríguez-Fraile M, Rivera P, Restituto P, Colina I, Calleja MdLD, et al. Trabecular bone score in active or former smokers with and without COP D. PLoS One.14(2):e0209777.
[30] Pan Y, Shi D, Wang H, Chen T, Cui D, Cheng X, et al. Automatic opportunistic osteoporosis screening using low-dose chest co mputed tomography scans obtained for lung cancer screening. Eur. Radiol..30(7):4107-4116.
[31] Sebro R, De la Garza-Ramos C. Machine learning for the prediction of osteopenia/osteoporosis using t he CT attenuation of multiple osseous sites from chest CT. Eur. J. Radiol..155:110474.
[32] Yang J, Liao M, Wang Y, Chen L, He L, Ji Y, et al. Opportunistic osteoporosis screening using chest CT with artificial in telligence. Osteoporos. Int..33(12):2547-2561.
[33] Xing L, Ebetino FH, Boeckman RK, Jr., Srinivasan V, Tao J, Sawyer TK, et al. Targeting anti-cancer agents to bone using bisphosphonates. Bone.138:115492.
[34] Krall EA, Dawson-Hughes B. Smoking increases bone loss and decreases intestinal calcium absorptio n. J. Bone Miner. Res..14(2):215-220.

[35] Zhang XY, Leung FW. Cigarette smoke aggravates acid-induced duodenal mucosal injury in the rat. Role of mesenteric vasoconstriction. Scand. J. Gastroenterol..29(3):214-218.
[36] Law MR, Hackshaw AK. A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: recognition of a major effect. BMJ.315(7112):841-846.
[37] Weng W, Li H, Zhu S. An overlooked bone metabolic disorder: cigarette smoking-induced osteo porosis. Genes (Basel).13(5):806.
[38] Marinucci L, Balloni S, Fettucciari K, Bodo M, Talesa VN, Antognelli C. Nicotine induces apoptosis in human osteoblasts via a novel mechanism driven by H_2O_2 and entailing Glyoxalase 1-depend ent MG-H1 accumulation leading to TG2-mediated NF-kB desensitization: implication for smokers-related osteoporosis. Free Radic. Biol. Med..117:6-17.
[39] Papakitsou EF, Margioris AN, Dretakis KE, Trovas G, Zoras U, Lyritis G, et al. Body mass index (BMI) and parameters of bone formation and resorption in postmenopausal women. Maturitas.47(3):185-193.
[40] Tziomalos K, Charsoulis F. Endocrine effects of tobacco smoking. Clin. Endocrinol.61(6):664-674.
[41] Daniell HW. Osteoporosis and smoking. JAMA.221(5):509.
[42] Ernster VL, Grady D, Miike R, Black D, Selby J, Kerlikowske K. Facial wrinkling in men and women, by smoking status. Am J Public Health.85(1):78-82.
[43] Tsutakawa S, Kobayashi D, Kusama M, Moriya T, Nakahata N. Nicotine enhances skin necrosis and expression of inflammatory mediato rs in a rat pressure ulcer model. Br. J. Dermatol..161(5):1020-1027.
[44] Need AG, Kemp A, Giles N, Morris HA, Horowitz M, Nordin BEC. Relationships between intestinal calcium absorption, serum vitamin D m etabolites and smoking in postmenopausal women. Osteoporos. Int..13(1):83-88.
[45] Schwarz P, Sørensen HA, Transbøl I. Inter-relations between the calcium set-points of Parfitt and Brown in primary hyperparathyroidism: a sequential citrate and calcium clamp s tudy. Eur. J. Clin. Invest..24(8):553-558.
[46] Omdahl JL, Morris HA, May BK. Hydroxylase enzymes of the vitamin D pathway: expression, function, an d regulation. Annu. Rev. Nutr..22:139-166.
[47] Lugon-Moulin N, Martin F, Krauss MR, Ramey PB, Rossi L. Cadmium concentration in tobacco (Nicotiana tabacum L.) from different countries and its relationship with other elements. Chemosphere.63(7):1074-1086.
[48] Cooper RG. Effect of tobacco smoking on renal function. Indian J. Med. Res..124(3):261-268.
[49] Li H, Wallin M, Barregard L, Sallsten G, Lundh T, Ohlsson C, et al. Smoking-induced risk of osteoporosis is partly mediated by cadmium fro m tobacco smoke: the MrOS Sweden study. J. Bone Miner. Res..35(8):1424-1429.
[50] Biskobing DM. COPD and osteoporosis. Chest.121(2):609-620.
[51] Ozcakir S, Sigirli D, Ursavas A, Uzaslan E. COPD and osteoporosis: associated factors in patients treated with inh aled corticosteroids. Int J Chron Obstruct Pulmon Dis.15:2441-2448.
[52] Janson C, Lisspers K, Ställberg B, Johansson G, Gutzwiller FS, Mezzi K, et al. Osteoporosis and fracture risk associated with inhaled corticosteroid use among Swedish COPD patients: the ARCTIC study. Eur. Respir. J..57(2):2000515.
[53] Y. Li, H. Gao, L. Zhao, J. Wang, Osteoporosis in COPD patients: risk factors and pulmonary rehabilitation, Clin Respir J 16 (7) (2022) 487–496.
[54] G.D. Amatngalim, W. Broekman, N.M. Daniel, et al., Cigarette smoke modulates repair and innate immunity following injury to airway epithelial cells, PLoS One 11 (11) (2016), e0166255.
[55] P.J. Barnes, New concepts in chronic obstructive pulmonary disease, Annu. Rev. Med. 54 (2003) 113–129.
[56] K.P. Maremanda, I.K. Sundar, I. Rahman, Role of inner mitochondrial protein OPA1 in mitochondrial dysfunction by tobacco smoking and in the pathogenesis of COPD, Redox Biol. 45 (2021), 102055.
[57] P.J. Barnes, Inflammatory mechanisms in patients with chronic obstructive pulmonary disease, J. Allergy Clin. Immunol. 138 (1) (2016) 16–27.
[58] A. Pezzuto, C. Spoto, B. Vincenzi, G. Tonini, Short-term effectiveness of smoking-cessation treatment on respiratory function and CEA level, J Comp Eff Res 2 (3) (2013) 335–343.
[59] A. Pezzuto, G. Tonini, M. Ciccozzi, et al., Functional benefit of smoking cessation and triple inhaler in combustible cigarette smokers with severe COPD: a retrospective study, J. Clin. Med. 12 (1) (2022) 234.
[60] A. Pezzuto, M. D'Ascanio, A. Grieco, A. Ricci, Functional benefit of smoking cessation in severe COPD patients undergoing bronchial valve implantation, Eur. J. Intern. Med. 68 (2019) 55–59.
[61] Marinova M, Edon B, Wolter K, Katsimbari B, Schild HH, Strunk HM. Use of routine thoracic and abdominal computed tomography scans for as sessing bone mineral density and detecting osteoporosis. Curr. Med. Res. Opin..31(10):1871-1881.
[62] Q. Zaidi, O.A. Danisa, W. Cheng, Measurement techniques and utility of hounsfield unit values for asses sment of bone quality prior to spinal instrumentation: a review of cur rent literature, Spine (Phila Pa 44 (4) (1976) E239–E244.
[63] Zou D, Li W, Deng C, Du G, Xu N. The use of CT Hounsfield unit values to identify the undiagnosed spina l osteoporosis in patients with lumbar degenerative diseases. Eur. Spine J..28(8):1758-1766.