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ORIGINAL ARTICLE

Factors associated with osteoporosis in patients with chronic obstructive pulmonary disease—a nationwide retrospective study

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Abstract

Summary The present study aimed to identify the factors associated with osteoporosis in patients with chronic obstructive pulmonary disease in Taiwan. The study found that female sex, old age, and use of a high dose of oral corticosteroids were significantly associated with osteoporosis in these patients.

Introduction Chronic obstructive pulmonary disease (COPD) is becoming an increasingly serious and prevalent issue worldwide. The treatment of COPD with long-term steroid use may cause osteoporosis and have significant influences on disability and mortality. However, few studies have evaluated the association between steroid use and osteoporosis in patients with COPD. The present study aimed to identify the factors, including demographic characteristics and steroid use (oral corticosteroids [OCSs], inhaled corticosteroids, and injected steroids), associated with osteoporosis in patients with COPD in Taiwan.

Methods This was a retrospective case-control study. Data were obtained from the National Health Insurance Research Database from 1997 to 2009. Cox proportional hazard regression models were used to identify the factors associated with osteoporosis.

Results The incidence of osteoporosis in the patients with COPD was 1343.0 per 100,000 person-years, the majority of patients were women (63.6 %), and the mean age of the patients was 72.5 years. In multivariate regression analysis, female sex, old age, and use of a high OCS dose with a defined daily dose (DDD) >56 (hazard ratio 1.85, 95 % confidence interval 1.52–2.26, $P < .0001$) exhibited significant independent associations with osteoporosis.

Conclusions Female sex, old age, and use of a high OCS dose with a cumulative DDD >56 are associated with osteoporosis in patients with COPD. Additionally, female patients >50 years old and male patients >70 years old have a higher risk of osteoporosis. Medical personnel should actively

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provide health education for the prevention of osteoporosis in these patients.

Keywords Age · Chronic respiratory disease · Retrospective case-control study · Sex · Steroid use

Introduction

In 2011, the World Health Organization reported that chronic obstructive pulmonary disease (COPD) was the fourth leading cause of death worldwide [1], and in 2012, with the increased size of the aging population, COPD was considered the third leading cause of death worldwide [2]. According to statistical data and the codes of the International Classification of Diseases, Ninth Revision (ICD-9), COPD was the eighth leading cause of death in Taiwan in 2009, and the mortality rate associated with COPD was 18.1 per 100,000 people [3].

Patients with COPD have been shown to be at high risk for the development of osteoporosis [4]. In a previous cross-sectional study of 95 outpatients with COPD in Brazil, 40 (42 %) of the outpatients were diagnosed with osteoporosis and osteopenia [5]. Another study in Italy investigated the lung function, biochemical data, and bone mineral density of 82 male individuals aged >65 years and found that the incidence of osteoporosis was higher in patients with COPD than in healthy subjects [6]. Moreover, Gratte-Verboom et al. [7] performed a systematic literature review and reported that the mean prevalence of osteoporosis was 32 % in patients with COPD and 11 % in healthy control subjects ($P < .001$). Furthermore, the US Department of Veterans Affairs performed a retrospective cohort study with 87,360 male patients who were newly diagnosed with COPD (aged >50 years) from 1997 to 2003 and found that the fracture incidence was 3.99 and 1.31 ‰ in the hip and wrist joints, respectively [8].

Studies have shown that the risk of osteoporosis is associated with the severity of COPD and the use of steroids [7, 9]. Moreover, age, smoking history, lack of exercise, systemic inflammation related to COPD, vitamin D deficiency, and systemic corticosteroid use have been demonstrated to negatively affect bone mineral density [10]. The side effects of long-term use of steroids include not only osteoporosis but also damage to the nervous and endocrine systems, calcium metabolism, and muscle cells. Additionally, steroid use may cause myopathies and myasthenia gravis indirectly. In patients with COPD and long-term use of oral systemic corticosteroids, the abovementioned symptoms are relatively common and are associated with a high risk of falls and fractures [10].

McEvoy et al. [11] analyzed the associations of the use of two types of steroids with fracture risk in male patients with COPD. The authors found that the incidence of spinal fracture was 1.35 and 1.8 times higher with the use of inhaled corticosteroids (ICSs) and oral corticosteroids (OCSs), respectively, than without the use of steroids. In another study, the risk of spinal fracture and osteoporosis was two and nine times higher, respectively, in patients with COPD and chronic high-dose OCS use than in those without chronic high-dose OCS use [12].

The risk and severity of osteoporosis have been hypothesized to increase in patients with COPD treated with long-term steroids; however, few studies have evaluated the association between steroid use and osteoporosis in patients with COPD in Taiwan. The present study aimed to identify the factors, including demographic characteristics and steroid use (OCSs, ICSs, and injected steroids), associated with osteoporosis among patients with COPD in Taiwan.

Methods

Data source

This was a retrospective case-control study. Data were obtained from the National Health Insurance Research Database (NHIRD) from 1997 to 2009. This study was approved by the ethics review boards of Chang-Gung Memorial Hospital and the National Health Research Institutes, Taiwan.

In Taiwan, registration for the National Health Insurance (NHI) program is compulsory according to the law. At the end of December 2011, the total number of people registered for the NHI program was 23,198,644 and the registration rate was over 99 %, which almost met the goal of registering all Taiwanese people [13]. Data of patients who are treated under the NHI program are entered in the NHIRD. This database includes the overall data of visits since the beginning of the health insurance and allows researchers to connect the basic characteristics of patient visits, physicians, hospitals, and clinics. The NHI Administration shares data from the NHIRD after obtaining assurances for personal privacy and data safety. In 2000, the National Health Research Institutes was authorized to publish the NHIRD.

Study cohort

In this study, the longitudinal cohort was based on data obtained from the NHIRD. Patients aged <40 years and those with incomplete NHI claims, unclear sex, or missing/unreasonable age (>120 years) were excluded. Furthermore, patients with liver diseases, intestinal diseases, autoimmune diseases, kidney diseases, anorexia, hyperparathyroidism, diabetes mellitus, gonad diseases, and depression (ICD-9 codes

571.2, 571.3, 571.5, 571.9, 558.9, 263.9, 714.0, 710.0, 588.8, 255.0, 585, 586, 250.01, 626.0, and 311) were excluded [14–17]. Only patients who were newly diagnosed with COPD and osteoporosis and who had two clinic visits and/or one or more hospital admissions in a year were included. A study flowchart of the sample selection process is presented in Fig. 1.

COPD status

According to a previous study [18] and clinical experiences, the present study selected patients with the following conditions: chronic bronchitis (ICD-9 code 491), emphysema (ICD-9 code 492), and chronic airway obstruction, not elsewhere classified (ICD-9 code 496), using the medical records of ambulatory care expenditures at visits and inpatient expenditures after admission. To reduce the risk of misclassification, we used the definition of chronic status presented by Wolff et al. [19], and patients with two clinic visits and/or one or more hospital admissions in a year, with physician diagnosis of the abovementioned conditions related to COPD, were diagnosed with COPD.

Osteoporosis status

The definition of osteoporosis was based on that presented in the study by Shih et al. [20]. The following conditions were considered: osteoporosis (ICD-9 code 733.0), osteoporosis, unspecified (ICD-9 code 733.00), senile osteoporosis (ICD-9 code 733.01), idiopathic osteoporosis (ICD-9 code 733.02), disuse osteoporosis (ICD-9 code 733.03), and other osteoporosis (ICD-9 code 733.09). Considering the definition of chronic status, patients with two clinic visits and/or one or more hospital admissions in a year, with physician diagnosis of the abovementioned conditions related to osteoporosis, were diagnosed with osteoporosis.

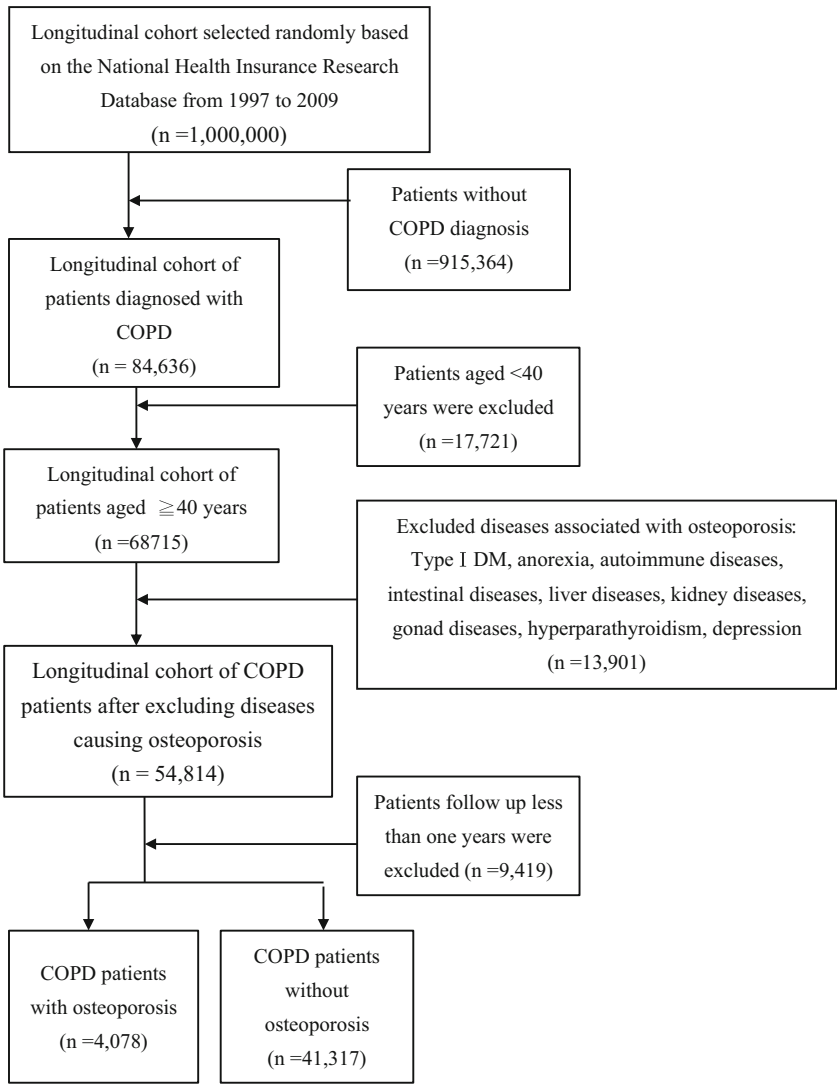

Fig. 1 Flowchart of the sample selection of chronic obstructive pulmonary disease (COPD) patients with or without osteoporosis

Steroid use

We identified patients who received steroid prescriptions (OCSs, ICSs, and injected steroids) using medical records including admissions and outpatient visits from the date of COPD diagnosis to the end of follow-up. The defined daily dose (DDD) is the assumed average daily maintenance dose of a drug taken for its main indication in adults, as recommended by the World Health Organization [21]. The formula is as follows: (total amount of drug) / (amount of drug in a DDD) = number of DDDs. By using the DDD, we were able to compare all steroids using the same standard. The cumulative DDD (cDDD), which indicates the duration of exposure, was estimated as the sum of the dispensed DDD of any steroid to compare its use to the risk of osteoporosis. To examine the dose–effect relationship, we categorized the steroid into three groups (cDDD <28, cDDD 28–56, and cDDD >56). In Taiwan, physicians give patients with chronic illnesses a refill prescription if their condition is stable. Refill prescriptions must be renewed at least every 3 months; therefore, we strictly defined medication usage for more than 8 weeks (cDDD >56) as long-term steroid use.

Statistical analysis

Descriptive statistics are used to report the results, and the data are presented as frequencies, means ± standard deviations, and/or proportions. The factors associated with osteoporosis in the patients with COPD were determined. Inferential statistics were used to control for demographic characteristics and steroid use, and Cox proportional hazard models were used to analyze the hazard ratios (HRs) and 95 % confidence intervals (CIs). All statistical analyses were performed using SAS for Windows version 9.3 (SAS Institute, Cary, NC).

Results

Patient demographic characteristics and incidence of osteoporosis

From 1998 to 2009, 45,395 patients were diagnosed with COPD, and of these patients, 4078 (8.98 %) were diagnosed with osteoporosis. The demographic characteristics of the study subjects are presented in Table 1. The mean age of all the patients with COPD was 64.6 years (standard deviation, ±13.4). The majority of patients were men (n = 28,171, 62.1 %), and the most common age was 71–80 years (n = 11,690, 25.8 %). The main type of steroids used was OCSs (n = 21,647, 47.7 %), followed by injected corticosteroids (n = 1683, 41.2 %). Among the patients with COPD and osteoporosis, the proportion of male patients was lower and female patients was higher, mean age was higher, and OCS use was less common than in those without osteoporosis (male patients 36.4 vs. 64.6 %; female patients 63.6 vs. 35.4 %; age 72.5 ± 10.7 vs. 63.8 ± 11.3 years; OCS use 44.0 vs. 48.1 %, respectively; all P < .0001).

The number of patients with COPD and osteoporosis was 4078, and the incidence was 1343.0 per 100,000 person-years. The number of male patients with COPD and osteoporosis was 1483, and the incidence was 776.0 per 100,000 person-years. The number of female patients with COPD and osteoporosis was 2595, and the incidence was 2305.5 per 100,000 person-years (Table 2).

Factors associated with osteoporosis in patients with COPD

Univariate and multivariate regression analyses were used to identify the factors, including demographic characteristics and steroid use, associated with osteoporosis in patients with COPD (Table 3). In the univariate regression analysis, the risk of osteoporosis was found to be low in male patients and increased with age. Although the use of a moderate-to-high ICS dose with a cDDD >28 had a significant influence on the risk of osteoporosis, the hazardous effect was not higher with a moderate-to-high dose than with a low dose. A high OCS dose with a cDDD >56 was significantly associated with osteoporosis risk, while injected corticosteroid use was not significantly associated with osteoporosis risk (Table 3).

In the multivariate regression analysis, female sex, old age, and use of a high ICS or OCS dose with a cDDD >56 (HR 0.70, 95 % CI 0.59–0.83, P < .0001; HR 1.85, 95 % CI 1.52–2.26, P < .0001, respectively) exhibited significant independent associations with osteoporosis risk (Table 3).

Discussion

Although osteoporosis is theoretically a common health problem in patients with COPD, limited data are available on the association between osteoporosis and COPD. The present study found that female sex, old age, and use of a high OCS dose with a cDDD >56 were significantly associated with osteoporosis in patients with COPD. To our knowledge, this is the first cohort study in Taiwan to use the NHIRD and follow over 45,000 individuals for 12 years.

In the present study, the incidence of osteoporosis was 8.98 %. Previous studies from Europe and the USA have reported incidences ranging from 32 to 46 % [5–7, 12]. Therefore, the incidence identified in Taiwan in the present study is much lower than that identified in Europe and the

Table 1 Demographic characteristics of chronic obstructive pulmonary disease (COPD) patients with or without osteoporosis ($N = 45,395$)

Variable	Total number of patients ($n = 45,395$)		COPD patients with osteoporosis ($n = 4078$)		COPD patients without osteoporosis ($n = 41,317$)		*P* value
	Number	Percentage	Number	Percentage	Number	Percentage	
Sex							
Male	28,171	62.1	1483	36.4	26,688	64.6	<.0001[b]
Female	17,224	37.9	2595	63.6	14,629	35.4	
Age							
Mean ± SD	64.6 ± 13.4		72.5 ± 10.7		63.8 ± 13.4		
40–50	8110	17.9	129	3.2	7981	19.3	<.0001[b]
51–60	9701	21.4	464	11.4	9237	22.4	
61–70	9736	21.5	889	21.8	8847	21.4	
71–80	11,690	25.8	1516	37.2	10,174	24.6	
81–90	5471	12.1	969	23.8	4502	10.9	
> 91	687	1.5	111	2.7	7981	19.3	
Monthly income (NT$)							
0	7312	16.1	1003	24.6	6309	15.3	<.0001[b]
<15,840	8131	17.9	788	19.3	7343	17.8	
15,841–25,000	20,932	46.1	1898	46.5	19,034	46.1	
>25,000	9020	19.9	389	9.5	8631	20.9	
Degree of urbanization							
High	12,425	27.4	977	24.0	11,448	27.7	<.0001[b]
Medium	20,026	44.1	1740	42.7	18,286	44.3	
Emerging	8115	17.9	818	20.1	7297	17.7	
General	4829	10.6	543	13.3	4286	10.4	
COPD severity							
AE < =1	44,085	97.1	3980	97.6	40,105	97.07	0.0536[b]
AE > =2	1310	2.9	98	2.4	1212	2.93	
Steroid drugs[a]							
Inhaled	9991	22.0	609	14.9	9382	22.7	<.0001[b]
Oral	21,647	47.7	1794	44.0	19,853	48.1	<.0001[b]
Injected	18,683	41.2	1776	43.6	16,907	40.9	.0011[b]
Length of hospital stay (days) ± SD	42.2 ± 157.5		50.0 ± 122.5		41.4 ± 160.5		<.0001[c]
Number of hospital visits ± SD	348.9 ± 226.7		481.5 ± 256.3		335.8 ± 219.2		<.0001[c]

[a] Steroid drugs with a defined daily dose >28 were included in the analysis

[b] Chi-squared test for the difference between COPD patients with osteoporosis and without osteoporosis

[c] *t* Test for the difference between COPD patients with osteoporosis and without osteoporosis

USA in these previous studies. Of note, most of the abovementioned previous studies investigated patients with COPD and osteoporosis at a single institution. Moreover, in these previous studies, the total number of patients with COPD was low. Furthermore, some of the studies only included male patients aged >65 years and did not exclude patients with diseases related to osteoporosis, such as kidney diseases, diabetes mellitus, and autoimmune diseases. These factors may have resulted in the high incidence of osteoporosis in the previous studies. The present study used strict definitions of COPD and osteoporosis and excluded patients with other comorbidities related to osteoporosis and fracture risk, even those without an osteoporosis diagnosis.

The present study found that the number of male patients with COPD was higher than the number of female patients, whereas the majority of patients with COPD and osteoporosis were female. The incidence of osteoporosis in patients with COPD was found to increase with age, and the ratio of female to male patients with COPD and osteoporosis reduced gradually with age, from 7.02:1 to 1.88:1. Although female patients with COPD aged >50 years were at the highest risk of osteoporosis, the number of male patients aged >70 years with

Table 2 Incidence of osteoporosis in chronic obstructive pulmonary disease (COPD) patients classified by sex and age

Variable	Total number of COPD patients					Total number of male patients with COPD					Total number of female patients with COPD				
	Total number	Number of person-years	Number of osteoporosis	Incidence (100,000 person-years)	95 % CI	Total number	Number of person-years	Number of osteoporosis	Incidence (100,000 person-years)	95 % CI	Total number	Number of person-years	Number of osteoporosis	Incidence (100,000 person-years)	95 % CI
Total number	45,395	303,657.1	4078	1343.0	1302.4–1384.8										
Gender															
Male	28,171	191,098.8	1483	776.0	737.5–816.6	28,171	191,098.8	1483	776.0	737.5–816.6					
Female	17,224	112,558.4	2595	2305.5	2218.4–2395.9						17,224	112,558.4	2595	2305.5	2218.4–2395.9
Age															
40–50	8110	54,494.2	129	236.7	199.2–281.3	4614	30,673.5	20	65.2	42.1–101.1	3496	23,820.7	109	457.6	379.3–552.1
51–60	9701	64,335.7	464	721.2	658.5–789.9	5638	37,456.6	76	202.9	62.0–254.1	4063	26,879.1	388	1443.5	1306.8–1594.5
61–70	9736	65,004.0	889	1367.6	1280.6–1460.5	5906	39,902.7	242	606.5	534.7–687.9	3830	25,101.3	647	2577.6	2386.4–2784.0
71–80	11,690	79,668.3	1516	1902.9	1809.5–2001.1	7949	55,643.8	644	1157.4	1071.3–1250.3	3741	24,024.6	872	3629.6	3396.5–3878.7
81–90	5471	36,081.7	969	2685.6	2521.7–2860.1	3691	25,132.3	456	1814.4	1655.3–1988.8	1780	10,949.3	513	4685.2	4296.8–5108.7
>91	687	4073.3	111	2725.1	2262.5–3282.2	373	2290.0	45	1965.1	1467.2–2631.9	314	1783.3	66	3701.0	2907.7–4710.9

Table 3 Influencing factors associated with osteoporosis in chronic obstructive pulmonary disease (COPD) patients

Variable	Univariate regression coefficient			Multivariate regression coefficient								
	HR	95 % CI	*P* value	HR	95 % CI	*P* value	HR	95 % CI	*P* value	HR	95 % CI	*P* value
Gender												
Male	0.34	0.32–0.36	<.0001	0.29	0.27–0.31	<.0001	Male					
Female	Reference			Reference						Female		
Age												
40–50 years	Reference			Reference			Reference			Reference		
51–60 years	3.05	2.51–3.71	<.0001	3.14	2.58–3.82	<.0001	3.17	1.94–5.19	<.0001	3.16	2.55–3.90	<.0001
61–70 years	5.79	4.81–6.96	<.0001	6.17	5.12–7.42	<.0001	9.46	5.99–14.93	<.0001	5.63	4.60–6.91	<.0001
71–80 years	8.05	6.72–9.63	<.0001	9.32	7.77–11.19	<.0001	16.45	10.50–25.75	<.0001	7.90	6.44–9.69	<.0001
81–90 years	11.37	9.46–13.66	<.0001	13.02	10.79–15.71	<.0001	24.79	15.75–39.03	<.0001	10.17	8.22–12.59	<.0001
>91 years	11.66	9.05–15.03	<.0001	11.25	8.70–14.55	<.0001	27.87	16.37–47.45	<.0001	8.01	5.87–10.93	<.0001
Steroid use												
Inhaled												
<28 cDDDs	Reference			Reference			Reference			Reference		
28–56 cDDDs	0.74	0.60–0.91	0.0048	0.83	0.67–1.03	0.0852	0.82	0.61–1.10	0.1809	0.81	0.60–1.10	0.1838
>56 cDDDs	0.65	0.55–0.77	<.0001	0.70	0.59–0.83	<.0001	0.60	0.46–0.77	<.0001	0.81	0.63–1.03	0.0877
Oral												
<28 cDDDs	Reference			Reference			Reference			Reference		
28–56 cDDDs	1.12	0.97–1.46	0.1035	1.16	0.94–1.43	0.1793	1.19	0.88–1.61	0.2556	1.13	0.84–1.52	0.4392
>56 cDDDs	1.62	1.34–1.95	<.0001	1.85	1.52–2.26	<.0001	1.91	1.46–2.50	<.0001	1.78	1.32–2.40	0.0002
Injected												
<28 cDDDs	Reference			Reference			Reference			Reference		
28–56 cDDDs	0.83	0.65–1.05	0.1118	0.68	0.54–0.87	0.0016	0.64	0.46–0.89	0.0084	0.71	0.50–1.00	0.0491
>56 cDDDs	1.11	0.89–1.39	0.3637	0.89	0.70–1.12	0.3164	0.79	0.56–1.11	0.1713	0.98	0.71–1.36	0.9146

$n = 4078$. The HR for COPD patients with osteoporosis was adjusted for income, degree of urbanization, length of hospital stay, number of hospital visits and COPD severity

HR hazard ratios, *CI* confidence interval, *cDDD* cumulative defined daily dose

COPD and osteoporosis was high as well (Table 2). Thus, medical personnel should carefully assess the risk of osteoporosis in female patients aged >50 years and male patients aged >70 years.

This study also found that the adverse effects of a high ICS dose on osteoporosis were lower with a cDDD >56 than a cDDD <28, which seems to indicate that a high ICS dose with a cDDD >56 has a protective effect for osteoporosis. However, subgroup analysis revealed that this effect of ICS on the HR of osteoporosis was not consistent in terms of sex, age, acute exacerbation (AE), or OCS (Table 4). Of interest was our finding that in the AE <1 group, a higher ICS dose corresponded with a lower HR of osteoporosis. Based on the literature

Table 4 Subgroup analysis of inhaled corticosteroids

Variable	Male	Female	<50 years	≥50 years	AE 0–1	AE ≥ 2	Oral steroid <28 cDDDs	Oral steroid ≥28 cDDDs
	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)
Inhaled corticosteroid								
<28 cDDDs	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
28–56 cDDDs	0.82 (0.61–1.10)	0.81 (0.60–1.10)	0.68 (0.17–2.75)	0.82 (0.66–1.01)	0.84 (0.68–1.04)	0.68 (0.27–1.77)	0.82 (0.65–1.04)	0.91 (0.53–1.56)
>56 cDDDs	0.60* (0.46–0.77)	0.81 (0.63–1.03)	0.53 (0.14–2.01)	0.68* (0.57–0.81)	0.67* (0.56–0.81)	1.16 (0.65–2.08)	0.67* (0.55–0.83)	0.81 (0.57–1.16)

HR hazard ratios, *CI* confidence interval, *cDDD* cumulative defined daily dose, *AE* acute exacerbation

*$p < .001$

[22–24], it is possible that patients with COPD on ICS had fewer exacerbations and may have used fewer systemic corticosteroids, and thus had a lower risk of osteoporosis. In addition, subgroup analysis revealed no protective effect with oral steroids ≥28 DDD, while there was a protective effect with oral steroids <28 DDD. These results indicate that ICS may have a protective effect only under certain circumstances, such as lower frequency of AE or less systemic corticosteroid use. However, this issue may need further exploration before it is fully understood.

This study found that OCSs were the most commonly used steroids in patients with COPD and that a high OCS dose with a cDDD >56 was associated with osteoporosis in patients with COPD. No significant associations were identified for ICSs or injected corticosteroids. These results differ from those of Dam et al. [25] and Bolton [12]. The study by Dam et al. [25] included 5541 non-Hispanic white American males aged >65 years with osteoporosis fractures. These authors reported that 714 patients had COPD or asthma, and of these 714 patients, 280 were using either ICSs or OCSs. Additionally, these authors reported that ICS use (odds ratio [OR] 1.91, 95 % CI 1.02–3.58) and OCS use (OR 1.71, 95 % CI 1.04–2.81) were associated with osteoporosis-related spinal fractures. The review article by Bolton [12] also found that OCS use and ICS use were associated with osteoporosis. In the present study, ICSs were seldom used in patients with COPD and this might be responsible for the finding of inconsistent association between ICS use and osteoporosis. A possible reason for the low use of ICSs in the present study is the inclusion of many elderly individuals. Considering that their sight, hearing, and hand-eye coordination were poor, ICSs might have been difficult to use. Therefore, OCSs might have been frequently prescribed. Additionally, oral and injected corticosteroids might have been used in severe, acute COPD attacks. Unfortunately, this information is not present in the NHIRD, and these associations need to be assessed in future clinical studies.

A previous study reported that the number of people using systemic steroids was higher in Taiwan than in other countries, with the most common underlying diseases being respiratory system diseases [26]. Furthermore, treatment and health education for the prevention of bone loss with steroid use are lacking [27]. Blalock et al. [28] performed a cross-sectional study with 277 patients treated with OCSs in the USA and reported that only 50 % of the patients had been informed of the risk of osteoporosis and that only 36.3 % of the patients had received health education regarding osteoporosis prevention [28]. The prevention of osteoporosis in patients with COPD is important, and medical personnel should provide relevant health education to patients with COPD treated with steroids.

Study limitations

The present study has some limitations. First, the data were obtained from the NHIRD from 1997 to 2009. The database did not have relevant clinical and laboratory data, such as lung function tests, radiography, or bone mineral density (BMD) tests; therefore, the associations between osteoporosis and COPD severity were unclear. Furthermore, this study may have underestimated the incidence of osteoporosis owing to incorrect NHI claims resulting from incomplete data provided by the treating physicians, wrong diagnostic codes, wrong diagnosis order, the strict definition for the first diagnosis of osteoporosis, and missed diagnosis, such as BMD value in patients not yet diagnosed with osteoporosis. It is important to overcome these limitations in order to improve the diagnostic validity of osteoporosis. However, there are no published studies on the accuracy of osteoporosis-related coding in the NHIRD. Further studies are needed to determine methods to improve the diagnosis accuracy of osteoporosis on investigating the NHIRD.

Conclusion

In conclusion, the present study found that the incidence of osteoporosis was 1343.0 per 100,000 person-years in patients with COPD. Female sex, old age, and use of a high OCS dose with a cDDD >56 might be associated with osteoporosis in patients with COPD. Additionally, female patients aged >50 years and male patients aged >70 years have a higher risk of osteoporosis. Therefore, medical personnel should actively provide health education for the prevention of osteoporosis in these patients. In order to achieve effective prevention in patients with COPD and long-term use of high-dose OCSs, medical personnel should actively provide health education and patients should undergo bone mineral density tests and drug dose control. In such high-risk patients with COPD, the possibility of osteoporosis with steroid use should be considered, and these patients should be referred to pulmonary rehabilitation or exercise programs.

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Compliance with ethical standards

Conflicts of interest Financial support was received from the Chang Gung Medical Foundation (CMRPG6D0161, CORPF6D0021, and CMRPF6B0071) and National Science Council (NSC101-2410-H-255-002). This funding body played no role in study design, data analysis, or data interpretation. Pei-Chien Lu, Yao-Hsu Yang, Su-Er Guo, and Tsung-Ming Yang declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Ethical approval This study was approved by the ethics review boards of Chang-Gung Memorial Hospital and the National Health Research Institutes, Taiwan.

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