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The incidence and risk of osteoporosis in patients with anxiety disorder

A Population-based retrospective cohort study

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Abstract

The purpose of this study was to investigate the relationship between anxiety disorder (AD) and the subsequent development of osteoporosis.

We conducted a population-based retrospective cohort analysis according to the data in the Longitudinal Health Insurance Database 2000 of Taiwan. We included 7098 patients in both the AD and no-anxiety cohort who were matched according to age and sex between January 1, 2000, and December 31, 2013. The incidence rate and the risk ratios (RRs) of subsequent new-onset osteoporosis were calculated for both cohorts. We used Cox proportional hazards models to assess the effect of AD. The Kaplan–Meier method was applied to estimate the cumulative osteoporosis incidence curves.

The AD cohort consisted of 7098 patients, and the comparison cohort comprised the same matched control patients without anxiety. The risk of osteoporosis was higher in the AD cohort than in the comparison cohort. In addition, the incidence of newly diagnosed osteoporosis remained significantly increased in all of the stratified follow-up durations (0–1, 1–5, 5–10, ≥10years). Patients with AD were 1.79 times more likely to get osteoporosis than those without AD. We also observed a significant increase in osteoporotic risk in AD patients who are comorbid with hypertension, diabetes mellitus, and chronic liver disease.

The incidence of osteoporosis in Taiwan is associated with an a priori AD history. The risk ratios are the highest for osteoporosis within 1 year of AD diagnosis, but the risk remains statistically significant for >1 year. Clinicians should pay particular attention to osteoporotic comorbidities in AD patients.

Abbreviations: AD = anxiety disorder, RRs = risk ratios, BMD = bone mineral density, CRP = C-reactive protein, IL-6 = interleukin-6, TNF-α = tumor necrosis factor-alpha, NHI = National Health Insurance, NHIRD = National Health Insurance Database, ICD-9-CM = International Classification of Disease Ninth Revision Clinical Modification, LHID2000 = Longitudinal Health Insurance Database 2000, COPD = chronic obstructive pulmonary disease, HRs = hazard ratios, CI = confidence interval.

Keywords: anxiety disorders, epidemiology, osteoporosis, risk factors

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KC-Y and CH-J contributed equally to this manuscript.

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1. Introduction

Anxiety disorder (AD) is one of the highly prevalent psychiatric diseases and is a major public health problem in many countries.[1–3] AD causes unexpected or unhelpful anxiety that seriously affects people's lives, including work, friendship, and thought, among others. AD is related to several disorders, such as panic, phobias, and generalized anxiety disorder. In the general population, the 12-month prevalence rates are approximately 18% for AD.[4] AD has now been implicated in several chronic physical illnesses, including heart disease, hypertension, chronic respiratory disorders, and gastrointestinal conditions.[5–8]

Osteoporosis is a silent disease caused by the systemic impairment of bone mass and microarchitecture, leading to increased probability of fractures of the vertebrate, wrist, hip, and other skeletal bones.[9] Osteoporosis is a chronic and worldwide medical condition, which is on the rise for ageing population and bad habits such as smoking and inactivity. The prevalence of osteoporosis in Taiwan was 1.63% in men and 11.35% in women.[10] Osteoporotic fracture is the major complication of osteoporosis and its lifetime risk is within the range of 40% to 50% in women and 13% to 22% in men without medical interventions.[11] The tremendously increased economic burden caused by osteoporotic fracture is also noted all over the world.[12,13]

Increasing research has been conducted on the interplay between psychiatric disorders and osteoporosis. Studies suggest psychiatric disorders including depression, substance use disorder, anorexia nervosa, and schizophrenia may be risk factors for decreased bone mineral density (BMD).[14–17]

However, few studies have been reported concerning the association between AD and osteoporosis.[17] No epidemiologic study has investigated this relationship in Taiwan.

Vogelzangs et al[18] found elevated inflammation is present in men with current AD. Persons with AD were considered as having chronic inflammation disease. Studies have correlated anxiety symptoms with increased C-reactive protein (CRP), amyloid-A, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), white blood cell in relation to the anxious state.[19] Compared with nonanxious cohort, 1 study showed anxious cohort had significantly lower levels of morning cortisol and significantly higher levels of IL-6.[20]

There are lots of risk factors such as systematic inflammation been identified for osteoporosis and abnormal bone turnover.[21] Chronic inflammation results in systemic bone loss, which is one of the mechanisms of osteoporosis.[22] During inflammation, several growth factors and cytokines are increased inducing osteoclast differentiation and activation, and chronic inflammation is a condition that initiates systemic bone loss. One study showed that hip bone loss was found to be associated with raised baseline CRP and sacroiliitis diagnosed by magnetic resonance imaging.[23] Another study found expression of activated nuclear factor-kappaB-inducing kinase in the osteoclasts lineage enhances the osteolytic response to inflammation.[24] These inflammatory cytokines and chemokines activate immune cell recruitment and migration and may play a crucial role in the development of osteoporosis.

Therefore, we hypothesized that AD may play an essential role in the pathogenesis of osteoporosis. In response to the lack of national data and few longitudinal studies concerning the association between AD and the subsequent risk of osteoporosis, we designed a nationwide population-based study to investigate the incidence of osteoporosis among patients with AD.

2. Patients and methods

2.1. Data source

The National Health Insurance (NHI) program in Taiwan was instituted in 1995. In this compulsory program, comprehensive medical care coverage, including outpatient, inpatient, emergency, and traditional Chinese medicine, is offered to all residents, with a coverage rate up to 98%. The NHI Research Database (NHIRD) contains complete information regarding clinical visits, including prescription elements and diagnostic codes based on the A code and the International Classification of Diseases, Ninth Revision, Clinical Modification (*ICD-9-CM*). The NHIRD is managed and openly released for research purposes by the National Health Research Institutes, with confidentiality being maintained according to the directives of the Bureau of the NHI. The data source for this study was the Longitudinal Health Insurance Database 2000 (LHID 2000), which was constructed by systematic and random sampling from the NHIRD and includes the data of one million individuals. According to the Taiwanese National Health Research Institutes reports, no significant differences were observed for the distributions of age and sex or the average insured payroll-related amount between the data in the LHID 2000 and the original NHIRD.

2.2. Ethics statement

This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (2013-03-035AC). Written consent was not obtained from the study participants because the data were obtained from the LHID 2000, which contains deidentified secondary data. In addition, the Institutional Review Board issued a formal written waiver for the need for consent.

2.3. Study population

In the present study, the data were extracted from the LHID 2000. First, we selected the patients with newly diagnosed osteoporosis from January 1, 2000 to December 31, 2013. Second, we excluded the patients with AD and those with osteoporosis between January 1, 1996, and December 31, 1999. The definitions of AD and osteoporosis in the study were based on the *ICD-9-CM* codes (AD: 300.0X, 300.2X, 308.3X and osteoporosis: 733.0, 733.1). In addition, only patients who were diagnosed with AD by a psychiatrist were selected.

For each patient with AD included in the study cohort, a control patient without AD was matched for age and sex from the LHID 2000. We defined the first diagnosis date of AD as the index date for the both cohorts and all participants were observed until they were diagnosed with osteoporosis; or until death, withdrawal from the insurance system, or December 31, 2013.

2.4. Statistical analysis

The incidence of newly diagnosed osteoporosis in the AD and control cases was the primary outcome in this study. We compared the distributions of the demographic characteristics including common comorbidities between the 2 cohorts by using independent t tests for continuous variables and a χ^2 test for categorical variables. To investigate potential surveillance bias, subgroups were stratified according to the follow-up periods. Furthermore, a Cox proportional hazard regression model was used to calculate the hazard ratios (HR) of newly diagnosed osteoporosis in the AD and control cohorts.

We used the SAS statistical software for Windows, Version 9.3 (SAS Institute, Cary, NC) for all data processing and analyses. Some statistical analyses were performed using the SPSS software, Version 20 (IBM, Armonk, NY). $P<0.05$ was considered to be statistically significant.

3. Results

A total of 7098 patients with AD and 7098 age- and sex-matched patients without AD were selected in the present study (Table 1). The median follow-up duration was 10.79 and 10.87 years, separately. The 3 most common comorbidities among both cohorts were the same, including chronic liver disease, hypertension, and dyslipidemia. There were 573 patients diagnosed with osteoporosis in AD group during the follow-up duration. Patients with AD were more likely to be diagnosed with osteoporosis than those in the comparison cohort (IRR = 2.00, 95% confidence interval [CI] = 1.73–2.31) (Table 2). In addition, we performed a subanalysis based on the stratification of the follow-up duration, which revealed that the highest risk ratio for developing osteoporosis was within the first year after a AD diagnosis. However, it remains statistically significant for >1 year after AD diagnosis. Furthermore, most of the patients among both cohorts developed the subsequent osteoporosis during the follow-up duration of 1 to 5 and 5 to 10 years.

Table 1

Baseline characteristics of patients with and without anxiety.

Demographic data	Patients with anxiety, n = 7098		Patients without anxiety, n = 7098		*P*
	N	%	n	%	
Age, y*	37.23 (28.46–47.22)		37.23 (28.46–47.22)		
≥50	1370	19.3	1370	19.3	0.999
<50	5728	80.7	5728	80.7	
Sex					
Male	3218	45.3	3218	45.3	0.999
Female	3880	54.7	3880	54.7	
Comorbidities					
Depressive disorder	703	9.9	56	0.8	<0.001
Hypertension	1242	17.5	816	11.5	<0.001
Diabetes mellitus	740	10.4	515	7.3	<0.001
Dyslipidemia	995	14.0	618	8.7	<0.001
Cerebrovascular disease	570	8.0	258	3.6	<0.001
COPD	741	10.4	459	6.5	<0.001
Nephropathy	690	9.7	442	6.2	<0.001
Autoimmune disease	203	2.9	113	1.6	<0.001
Obesity	60	0.8	22	0.3	<0.001
Congestive heart failure	110	1.5	65	0.9	<0.001
Chronic liver disease	2241	31.6	1320	18.6	<0.001
Degree of urbanization					<0.001
Urban	4518	63.7	4461	62.8	
Suburban	2060	29.0	2235	31.5	
Rural	520	7.3	402	5.7	
Income group					0.005
High income	970	13.7	916	12.9	
Medium income	1340	18.9	1509	21.3	
Low income	3398	47.9	3304	46.5	
No income	1390	19.6	1369	19.3	
Follow-up years*	10.79 (9.57–12.31)		10.87 (9.67–12.34)		<0.001

COPD = chronic obstructive pulmonary disease.
* Median (interquartile range).

The Cox proportional hazard regression analysis was conducted to calculate the crude HR of the newly diagnosed osteoporosis for patients in the AD and control cohorts. In addition, multivariate analysis for adjusting the confounding factors between AD and osteoporosis was performed and the adjusted HR shown that the patients with AD still have higher risk of developing subsequent osteoporosis (adjusted HR = 1.79, 95% CI = 1.54–2.07) (Table 3 and Fig. 1).

We performed the Cox regression model again to detect potential risk factors for osteoporosis among the patients with AD. The results of the analysis indicated that the comorbidities of hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), and chronic liver disease may have higher risk for subsequent development of osteoporosis among the patients with AD (Table 4).

Table 2

Incidence Rates of osteoporosis in patients with and without anxiety.

	Patients with anxiety		Patients without anxiety			
	No. of osteoporosis	Per 1000 person-years	No. of osteoporosis	Per 1000 person-years	Risk ratio (95% CI)	*P*
Total	573	7.75	291	3.88	2.00 (1.73–2.31)	<0.001
Age, y						
≥50	295	24.08	166	12.85	1.87 (1.54–2.28)	<0.001
<50	278	4.51	125	2.01	2.24 (1.81–2.79)	<0.001
Sex						
Male	137	4.08	73	2.16	1.89 (1.41–2.55)	<0.001
Female	436	10.81	218	5.28	2.05 (1.74–2.42)	<0.001
Follow-up						
0–1	79	1645.83	41	706.90	2.33 (1.58–3.48)	<0.001
1–5	219	204.86	113	135.98	1.51 (1.20–1.91)	<0.001
5–10	212	11.84	107	6.10	1.94 (1.53–2.47)	<0.001
≥10	63	1.15	30	0.53	2.17 (1.38–3.47)	<0.001

CI = confidence interval.

Table 3

Analyses of risk factors for osteoporosis in patients with and without anxiety.

Predictive variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Anxiety	2.00 (1.74–2.30)	<0.001	1.79 (1.54–2.07)	<0.001
Age (<50 = 0, ≥50 = 1)	5.56 (4.86–6.36)	<0.001	4.90 (4.19–5.72)	<0.001
Sex (male = 0, female = 1)	2.57 (2.20–3.00)	<0.001	3.49 (2.97–4.10)	<0.001
Comorbidities				
Depressive disorder	1.52 (1.18–1.96)	<0.001	1.16 (0.90–1.51)	0.256
Hypertension	3.39 (2.95–3.91)	<0.001	1.40 (1.18–1.66)	<0.001
Diabetes mellitus	2.83 (2.39–3.35)	<0.001	1.26 (1.04–1.52)	0.019
Dyslipidemia	2.48 (2.11–2.91)	<0.001	0.96 (0.80–1.16)	0.663
Cerebrovascular disease	2.76 (2.26–3.36)	<0.001	1.12 (0.91–1.39)	0.298
COPD	2.40 (2.01–2.87)	<0.001	1.35 (1.12–1.63)	0.002
Nephropathy	2.02 (1.66–2.44)	<0.001	1.00 (0.82–1.23)	0.970
Autoimmune disease	1.51 (1.03–2.21)	0.036	1.08 (0.73–1.59)	0.704
Obesity	0.79 (0.30–2.12)	0.643		
Congestive heart failure	3.84 (2.68–5.49)	<0.001	1.10 (0.76–1.60)	0.622
Chronic liver disease	2.14 (1.87–2.45)	<0.001	1.63 (1.41–1.89)	<0.001
Degree of urbanization				
Urban	Reference			
Suburban	1.12 (0.97–1.30)	0.129	1.10 (0.95–1.27)	0.220
Rural	1.55 (1.22–1.96)	<0.001	1.20 (0.94–1.52)	0.144
Income group				
High income	Reference		Reference	
Medium income	1.93 (1.49–2.50)	<0.001	1.05 (0.81–1.37)	0.709
Low income	1.68 (1.32–2.14)	<0.001	1.22 (0.96–1.56)	0.112
No income	1.13 (0.86–1.50)	0.386	1.02 (0.77–1.36)	0.867

CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio.

4. Discussion

The results of our study showed that significantly higher risk of osteoporosis development among the patients with AD after adjustment for the potential confounding factors among both cohorts. In addition, older age, female sex, and several physical comorbidities including hypertension, diabetes mellitus, COPD, and chronic liver disease could be considered as risk factors for developing osteoporosis among the patients with AD.

According to the results of our study, AD might be a risk factor for subsequent osteoporosis. We hypothesize that this may be attributable to several mechanisms. First, the development of osteoporosis may be the result of an inflammatory process caused by AD. Inflammation may play a role in AD and link to the association between AD and cardiovascular burden.[25] Studies have correlated anxiety symptoms with increased cytokine levels, in particular CRP.[19,26] Increases in inflammatory cytokines and chemokines can affect osteoporosis. Inflammatory processes such as high-sensitivity CRP levels are evident association with high bone turnover rate and bone mass loss, which contributes to osteoporosis.[27] Bone remodeling is affected by several factors, including inflammation and hormonal changes. Besides, studies suggest that proinflammatory cytokines (receptor activator of nuclear factor-B and its functional ligand, also known as TNF-related activation induced cytokine) is a common mediator of osteoclast function. Besides, osteoclastogenesis can be modulated by macrophage colony-stimulating factor.[28] Above studies supported that inflammation definitely has a major impact on bone metabolism leading to osteoporosis. Second, high plasma cortisol in AD patients may result in osteoporosis. Adrenal gland of anxiety disorder patients might produce more substantial elevation in cortisol level.[29] Studies revealed that generalized AD has been associated with elevated cortisol.[30,31] Cortisol plays a role in reducing bone apposition and increasing bone resorption leading to osteoporosis.[32] The association between cortisol level in AD and osteoporosis patients needs more investigation for further interpretation. Third, several researches found the significance of oxidative stress to mediate the pathogenesis of AD. Atmaca et al[33] found antioxidant enzymes' (superoxide dismutase, glutathione peroxidase, and catalase) activity levels and malondialdehyde elevation in patients with anxiety such as social phobia. Clinical researches presented a raised lipid peroxidation, which was oxidative biomarker in patients with

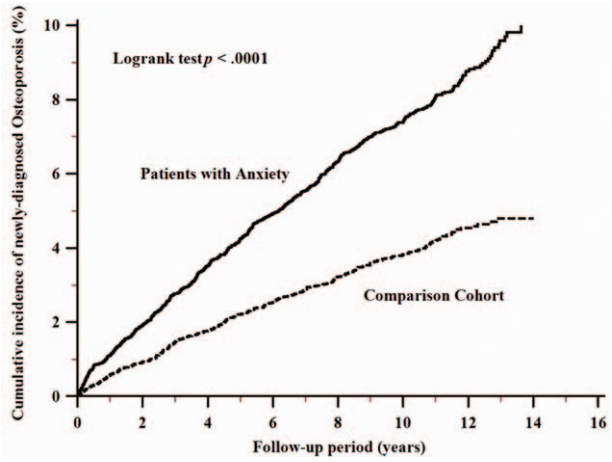

Figure 1. Cummulative incidence comparison of newly diagnosed osteoporosis for patients with (solid line) and without (dashed line) anxiety.

Table 4

Analyses of risk factors for osteoporosis in patients with anxiety.

Predictive variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (<50 = 0, ≥50 = 1)	5.27 (4.47–6.21)	<0.001	4.65 (3.84–5.64)	<0.001
Sex (male = 0, female = 1)	2.65 (2.19–3.21)	<0.001	3.63 (2.97–4.43)	<0.001
Comorbidities				
Depressive disorder	1.18 (0.91–1.54)	0.207		
Hypertension	2.98 (2.52–3.54)	<0.001	1.53 (1.24–1.88)	<0.001
Diabetes mellitus	2.52 (2.06–3.08)	<0.001	1.31 (1.05–1.65)	0.019
Dyslipidemia	2.12 (1.75–2.56)	<0.001	0.95 (0.76–1.18)	0.636
Cerebrovascular disease	2.10 (1.66–2.65)	<0.001	1.05 (0.82–1.35)	0.694
COPD	1.77 (1.41–2.21)	<0.001	1.14 (0.90–1.44)	0.275
Nephropathy	1.50 (1.18–1.91)	<0.001	0.86 (0.67–1.10)	0.229
Autoimmune disease	1.40 (0.90–2.16)		.133	
Obesity	0.81 (0.30–2.17)	0.679		
Congestive heart failure	3.07 (1.99–4.75)	<0.001	1.01 (0.64–1.60)	0.953
Chronic liver disease	1.85 (1.57–2.18)	<0.001	1.64 (1.38–1.95)	<0.001
Degree of urbanization				
Urban	Reference		Reference	
Suburban	1.18 (0.98–1.41)	0.080	1.18 (0.98–1.42)	0.074
Rural	1.40 (1.05–1.87)	0.022	1.20 (0.89–1.61)	0.236
Income group				
High income	Reference		Reference	
Medium income	1.88 (1.38–2.57)	<0.001	1.04 (0.75–1.43)	0.822
Low income	1.56 (1.17–2.08)	0.003	1.17 (0.87–1.57)	0.292
No income	1.17 (0.84–1.64)	0.354	1.04 (0.74–1.46)	0.831

CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio.

social phobia and panic disorder.[33,34] Total oxidant status and oxidative stress index were significantly higher in generalized AD than control group.[35] The involvement of oxidative stress in the development of postmenopausal osteoporosis has recently been well documented.[36,37] AD maybe implicated with osteoporosis by oxidative stress. Fourth, behavioral patterns typically associated with common psychiatric disorders, including increased cigarette smoking and alcohol, which have been shown to have negative effects on bone metabolism leading to osteoporosis.[38–40] Fifth, lysophosphatidic acid (LPA), a water-soluble phospholipid derivative, plays an essential role in anxiety and bone formation.[41–43] In 2011, a study found that absence of LPA1 receptor may result in abnormal bone development and decreased bone mass.[44] In addition, another study focused on LPA1 receptor also revealed that anxiety-like responses could be observed in LPA1 receptor knockout mice.[45] Although it is difficult to explore the temporal relationship between the anxiety and osteoporosis based on these results, these studies on LPA may implicate a possible linkage between them, which is consistent with the results of our present study.

In our study, the result of multivariate analysis among the patients with AD revealed that comorbidities including hypertension, diabetes mellitus, and chronic liver disease could be seen as potential risk factors for the subsequent development of osteoporosis. Numerous epidemiological investigations show that patients with AD may have a higher risk of hypertension than those without AD and concluded that AD is associated with hypertension.[6,46] Anxiety increases blood pressure, systemic vascular resistance, sympathetic activity, and plasma renin activity that contribute to the risk factors of hypertension. Hypertension has been demonstrated to be a risk factor for osteoporosis. In hypertension patients, excess urinary calcium secretion induces secondary parathyroidism to increase serum calcium level by calcium release from bone, which may accelerate osteoporosis.[47] Based on the above-mentioned reason, comorbid hypertension in patients with AD might be more vulnerable to the pathophysiologic processes that contribute to osteoporosis.

Kai et al[48] found AD is independently associated with the metabolic syndrome in a population at higher risk for type 2 diabetes mellitus. To cope with the influences from anxiety symptoms, patients place themselves at further risk for diabetes, such as more overeating. It is well known that type 1 diabetes mellitus increase vulnerability to bone microstructure.[49,50] Type 2 diabetes mellitus increases trabecular defects and cortical porosity, and compromised bone mechanical properties.[51,52] In addition, hyperglycemia and insulin resistance may further induce osteoblast apoptosis and diminished activities of osteoblasts, osteoclasts, and osteocytes.[53] According to listed results of researches, diabetes mellitus may be considered a potential risk factor for osteoporosis especially among the patients with AD.

Anxiety-related psychological distress is associated with liver disease mortality and evidence has shown that possible mechanisms may be associated with the release of proinflammatory factors (eg, IL-6, TNF-α) caused by unhealthy behaviors, including alcohol intake, tobacco use, and poor diet habit.[54] Osteoporosis is a complication of chronic liver disease. Chen et al[55] found hepatitis B virus increases the risk of osteoporosis. Patients with ultrasound-defined nonalcoholic fatty liver disease had an increased independent risk of lower bone mass density.[56] The mechanism included chronic inflammation and impaired osteoblast and overactive osteoclast in decompensated liver or cirrhosis. We could postulate that chronic liver disease may indirectly result in osteoporosis among the patients with AD.

In our study, surveillance bias should be considered because patients with AD may have more possibilities to have frequent

clinical visits than the control patients, which may result in an earlier diagnosis of osteoporosis.[57] Therefore, we conducted a subgroup analysis by stratifying the follow-up periods among both cohorts. The results revealed that incident osteoporosis was still increased after the first year of a diagnosis of AD. Hence, we assume that the increased risk of osteoporosis in AD patients would not be a results caused by surveillance bias totally.

Although psychotropic agents, especially selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines (BZDs), have been seen as risk factors of osteoporosis, patients with depressive disorders, which may have more possibilities to receive more SSRIs than those with AD, were included in the Cox regression model and the result of the multivariate analysis revealed that patients with AD, not depressive disorders, would have a higher risk of developing osteoporosis. In addition, there are still some studies which emphasized that SSRIs or BZDs should be seen as risk factors of osteoporotic fracture rather than of the development of osteoporosis.[58–61]

However, this study had several limitations. First, the NHIRD lacks essential data related to the primary outcome of the study, such as detailed demographic information of tobacco use, alcohol consumption, body mass index, socioeconomic status, and family history of osteoporosis. Therefore, we were unable to correlate osteoporosis with above-mentioned risk factors. Second, diagnostic delay of osteoporosis might occur in the study, which may indicate that the temporal relationship between the AD and the development of osteoporosis could not be confirmed in our study.

In conclusion, patients with AD may have elevated risk to develop osteoporosis. Moreover, in addition to the common risk factors of osteoporosis such as older age and female sex, hypertension, diabetes mellitus, COPD, and chronic liver disease may be considered as potential risk factors of osteoporosis, especially among the patients with AD. Further prospective epidemiological study on the relationship between AD and osteoporosis is warranted.

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