BMJ Open

Association of age-related macular degeneration on fracture risks among osteoporosis population: a nationwide population-based cohort study

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ABSTRACT

Objectives Visual impairment is an important risk factor for fracture in the elderly population. Age-related macular degeneration (AMD) is the leading cause of irreversible visual impairment in elderly people. This study was conducted to explore the relationship between AMD and incident fractures in patients with osteoporosis (OS).

Design Retrospective analysis of Taiwan's National Health Insurance Research Database (NHIRD).

Setting A multicenter study conducted in Taiwan.

Participants and controls The current study used the NHIRD in Taiwan between 1996 and 2011. A total of 13 584 and 54 336 patients with OS were enrolled in the AMD group and the non-AMD group, respectively.

Intervention Patients with OS were included from the Taiwan's NHIRD after exclusion, and each patient with AMD was matched for age, sex and comorbidities to four patients with non-AMD OS, who served as the control group. A Cox proportional hazard model was used for the multivariable analysis.

Primary outcome measures Transitions for OS to spine fracture, OS to hip fracture, OS to humero-radio-ulnar fracture and OS to death.

Results The risks of spine and hip fractures were significantly higher in the AMD group (HR=1.09, 95% CI=1.04 to 1.15, p<0.001; HR=1.18; 95% CI=1.08 to 1.30, p=0.001, respectively) than in the non-AMD group. The incidence of humero-radio-ulnar fracture between AMD and non-AMD individuals was similar (HR=0.98; 95% CI=0.90 to 1.06; p=0.599). However, the risk of death was higher in patients with OS with older age, male sex and all types of comorbidity (p<0.05), except for hyperthyroidism (p=0.200).

Conclusion Patients with OS with AMD had a greater risk of spine and hip fractures than did patients without AMD.

Strengths and limitations of this study

► The current study enrolled a large number of participants 13 548 (age-related macular degeneration (AMD) group) patients and 54 336 (a non-AMD group) patients.
► Each participant can be followed up to 16 years even when visited to different hospitals.
► The causal relationship between AMD and subsequent bone fracture in patients with osteoporosis (OS) has not yet been established in the current study.
► The disease severity of OS is inaccessible in the Taiwan's National Health Insurance Research Database because of simply using the *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic codes.
► The severity of ocular disease leading to fractures or higher mortality rate has not yet been determined.

leading causes of irreversible visual impairment in elderly people in developed countries.[6–8] The estimated incidence of AMD in Taiwan is approximately 10.8%.[9] Although, it does not result in complete blindness; however, the loss of central vision can make it difficult to perform daily activities such as recognising faces, driving and reading.[10] According to a previous report, patients with AMD are in greater fear of falling down, which can restrict their social activities.[11] Moreover, individuals with AMD have a higher probability to fall with more unsteady gait patterns.[12 13]

Osteoporosis (OS) is a chronic metabolic bone disease in which bones become relatively weak and have a probability to break.[14] The prevalence of OS is estimated to be 11.35% among women over 50 years old.[15] It has been observed that patients with OS tend to develop fractures of the hip, vertebrae, distal forearm and humerus,[16] and fractures among elderly patients represent

INTRODUCTION

Poor vision is common in the elderly population. Ocular diseases such as cataract, glaucoma and age-related macular degeneration (AMD) are strongly age-related,[1–4] and there is accumulating evidence demonstrating that many elderly people would benefit from changing eyeglasses.[2 5] AMD is one of the

an important public health issue.[17] Taiwan's population is ageing at an alarming rate[15]; OS and related fractures pose an unprecedented threat to the elderly population in Taiwan since the prevalence of OS increases rapidly with age.[14] As fractures in the elderly would contribute to a higher probability of mortality despite promptly surgical intervention,[18 19] potential risk factors for individuals vulnerable to fractures, such as those with OS, should be further investigated and identified.

Visual impairment is an important risk factor for hip fracture in the elderly population.[20–22] Studies have revealed that macular degeneration and glaucoma suspect would lead to a higher risk of hip fractures.[22] Therefore, it is important to understand the ocular risk factors and take measures to prevent future fractures in patients with OS. However, only a limited number of studies have examined the association between fractures in patients with OS and specific ocular disorders.[22–24] Taking AMD as an example, studies focused only on patients with AMD and hip fractures, ignoring spine and humero-radio-ulnar fractures.[22–24] Moreover, the number of participants in previous studies was relatively small,[22–24] while a population-based study should be conducted to investigate the relationship between AMD and fractures in patients with OS since both disorders affect most population.[1 14]

Therefore, we used the Taiwan's National Health Insurance Research Database (NHIRD) in this nationwide study with a retrospective cohort and a case–control design to investigate the association between AMD and subsequent fractures in patients with OS.

METHODS

Ethics declaration and patient involvement statement
Participants in this study were adhered to the 1964 Declaration of Helsinki and its later amendments.

Patient and public involvement statement
As this is a claimed data-based study, data were collected and produced by the National Health Insurance (NHI) Administration of Taiwan without patient recruitment; the requirement for informed consent was waived by both the NHI Administration and the Institutional Review Board of Chang Gung Memorial Hospital.

Data source
This population-based cohort study used the NHIRD of Taiwan (approximately 26 million insured individuals) for the period January 1996 to December 2011. By the end of 2007, NHIRD had enrolled more than 99% of Taiwan's population into this insurance programme, which had contracts with 97% of the country's clinics and hospitals. The data available through the NHIRD included all medical services provided to each enrollee from 1 January 1996 to 31 December 2011, as well as the patients' characteristics and the features of the hospitals and physicians.

Study population enrolment and exclusion criteria
We identified patients with diagnosis of OS using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9) codes 733.00, 733.01, 733.02, 733.03 and 733.09. The osteoporotic population of the NHIRD was identified by the presence of either the abovementioned diagnostic codes in their outpatient records or the discharge codes from hospitalisation records. Eligible patients were those 50 years of age or older with diagnosis of OS. Exclusion criteria were as follows: (1) received osteoporotic medical treatments for more than 30 days before the index date; (2) any fractures documented before the index date (ICD-9 codes 800.x–829.x); (3) having a diagnosis of HIV (ICD-9 codes 042) and (4) being diagnosed with metastatic solid tumours (ICD-9 codes 196.x–198.x). Furthermore, we divided patients into those with AMD (AMD group with primary diagnosis codes of ICD-9 362.50–362.52) and those without AMD (non-AMD group). After propensity score matching, 13 548 patients and 54 336 patients were analysed in the AMD and non-AMD group, respectively.

Outcome definition
We identified hospitalised patients who were admitted with a primary diagnosis of hip fracture (ICD-9 codes 820.x), spine fracture (ICD-9 codes 806 .x) and humero-radio-ulnar fractures (ICD-9 codes 812.x and 813.x) for the first time after 2002 (ensuring no previous hip, spine and humero-radio-ulnar fractures between 1996 and 2001) and who received surgery for fractures to make sure the diagnostic accuracy (surgery code of NHIRD: 64245C, 64042C, 64160B, 64271B, 64271C, 64032B). The date of death was defined as the expired date recorded in the catastrophic illness registry data files, the discharge date from a patient's insurance coverage within 1 month after being critical against medical advice discharge or the discharge date from a patient's insurance coverage within 1 month after emergency department discharge with intravenous epinephrine use. We defined it as such because the NHI is mandatory in Taiwan; therefore, patients, especially sick ones, can rarely stop their own insurance coverage. If the insurance coverage ended, death was the reason. Furthermore, NHI premiums are paid monthly, so coverage can be stopped immediately following a death. The time-to-event outcome was determined as the time from the OS diagnosis date to the date of hip fracture, spine fracture and humero-radio-ulnar fractures, or all-cause death, respectively.

Covariates
The comorbidities were defined as an outpatient diagnosis listed on two or more visits or a one-time inpatient diagnosis before the index date. Study comorbidities included diabetes mellitus (DM), moderate to severe liver disease, chronic renal disease, hyperthyroidism, rheumatic disease, malignancy, hyperparathyroidism and ocular diseases including cataract, corneal diseases and glaucoma. The Charlson Comorbidity Index score
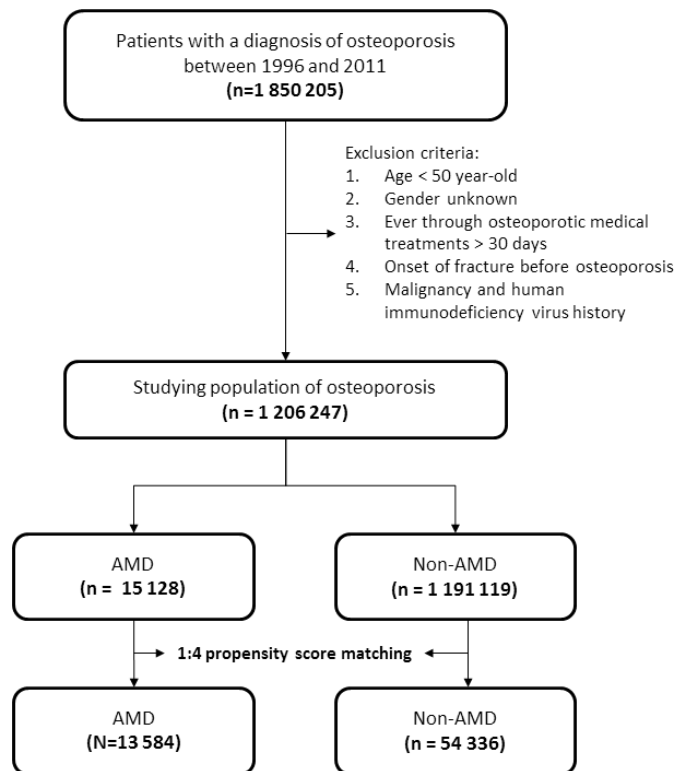
Figure 1 Flowchart of the patient selection in AMD and non-AMD cohort with a one-to-four match. AMD, age-related macular degeneration.

(CCIs) that merges the abovementioned diseases into one numerical score was also recorded.

Statistical analysis

To compare the AMD and each transition, we performed propensity score matching. The propensity score was the predicted probability of being the AMD group given the values of covariates including age, sex, rheumatologic diseases, DM with and without complications, malignancy, moderate to severe liver diseases, hyperthyroidism, chronic renal diseases, cataract, corneal disease, glaucoma, hyperparathyroidism and CCIs. Each patient in the AMD group was matched with four counterparts in the non-AMD group to achieve minimal bias. The cumulative incidence of follow-up outcomes was generated and the comparisons between the two groups for the risk of spine, hip and humero-radio-ulnar fractures were made using the Cox proportional hazards model in which death was considered a competing risk. We checked the proportional hazards assumption using modified Schoenfeld residuals test and residual plots in each Cox model. For the violation of proportional hazards assumption, we demonstrated the interaction between the variable and time using step functions or functions guided from residual plots. To investigate the cumulative incidence of each fracture and cause of death, we engaged in the competing risk model with the HR adjusted all the above mentioned covariates to analyse the transitions, including 'OS to spine fracture', 'OS to hip fracture', 'OS to humero-radio-ulnar fracture' between AMD and non-AMD subjects, and the transition of 'OS to death' for the abovementioned covariates. Finally, to

facilitate the interpretation of time-varying coefficients, we conducted postestimation simulation techniques and graphs with visual weight to demonstrate the results. All reported CIs and tests were two-sided with a 5% significance level. All analyses were performed with R V.3.3.0 (R Foundation for Statistical Computing, Vienna, Austria) with contributed packages 'tableone', 'ReporteRs', 'mstate', 'survival', 'ggplot2' and 'simPH'.

RESULTS

Patient characteristics

A total of 1 850 205 patients with OS were enrolled in this nationwide study. After applying the exclusion criteria, a total of 1 206 247 patients participated, of which 15 128 were in the AMD group and 18 191 119 were in the non-AMD group. After propensity score matching, 13 548 patients and 54 336 patients were analysed in the AMD and non-AMD group, respectively (figure 1). The selected characteristics—including age, sex, related covariates and CCIs—were well balanced between the AMD and non-AMD groups after propensity score matching (table 1).

Estimates of cumulative hazards and probabilities of transition

During the follow-up period in the study population, 8930 (13.1%) patients with OS had spine fractures, 2461 (3.6%) hip fractures, humero-radio-ulnar fractures occurred in 3470 (5.1%) patients with OS and 8123 (13.0%) patients with OS unfortunately died. During the follow-up period, the entire study population had higher risks for spine fracture and death compared with humero-radio-ulnar fracture and hip fracture (figure 2).

The effect of AMD on transition of fractures

In the multivariate analysis, a patient with OS with AMD was significantly associated with a high risk of spine fracture after adjusting for covariates (HR=1.09; 95% CI=1.04 to 1.15; p<0.001) compared with a non-AMD individual. Similarly, AMD was significantly associated with a high risk of hip fracture (HR=1.18; 95% CI=1.08 to 1.30; p<0.001) than a patient without AMD. However, AMD was not associated with risks for the humero-radio-ulnar fracture (HR=0.98; 95% CI=0.90 to 1.06; p=0.599). Additionally, multivariate analysis also revealed that older age, male sex and all non-ocular medical comorbidities, except for hyperthyroidism (p=0.200), were significantly associated with higher risks for death (p<0.05) (table 2). The fact that with increasing age and being female are vulnerable to any type of incident fractures is also shown in our results (table 2). It is also noteworthy that other ocular comorbidities, including cataract and corneal diseases, are associated with a high risk of spine fractures (HR=1.23; 95% CI=1.17 to 1.31; p<0.001 and HR=1.18; 95% CI=1.12 to 1.23; p<0.001) and humero-radio-ulnar fractures (HR=1.16; 95% CI=1.06 to 1.26; p<0.001 and HR=1.08; 95% CI=1.00 to 1.17; p=0.041). However, a patient with OS with glaucoma is not associated with a high risk of any incident fractures, which

Table 1 Baseline characteristics between the AMD and non-AMD groups

	AMD (n=13 584)	Non-AMD (n=54 336)	P value
Age, median (IQR)	73.8 (67.2–79.3)	73.8 (67.2–79.3)	1
Age group, No (%)			
≥50 to <60	1277 (9.4)	5075 (9.3)	0.98
≥60 to <70	3372 (24.8)	13 424 (24.7)	
≥70 to <80	5881 (43.3)	23 603 (43.4)	
80	3054 (22.5)	12 234 (22.5)	
Sex, No (%)			
Female	8081 (59.5)	32 324 (59.5)	1
Rheumatologic diseases, No (%)	846 (6.2)	3384 (6.2)	1
DM without complications, No (%)	4101 (30.2)	16 404 (30.2)	1
DM with complications, No (%)	1629 (12.0)	6516 (12.0)	1
Malignancy, No (%)	1470 (10.8)	5880 (10.8)	1
Moderate to severe liver diseases, No (%)	19 (0.1)	76 (0.1)	1
Hyperthyroidism, No (%)	204 (1.5)	816 (1.5)	1
Chronic renal diseases, No (%)	598 (4.4)	2392 (4.4)	1
Cataract, No (%)	10 276 (75.6)	41 104 (75.6)	1
Corneal disease, No (%)	2665 (19.6)	10 660 (19.6)	1
Glaucoma, No (%)	2037 (15.0)	8148 (15.0)	1
CCIs, median (IQR)	5.00 (3.00–7.00)	5.00 (3.00–7.00)	0.22

AMD, age-related macular degeneration; CCIs, Charlson Comorbidity Index score; DM, diabetes mellitus; No, number of patients.

is due to the relatively fewer cases and the heterogeneous disease stages in this study cohort.

DISCUSSION

In this study, our results showed that AMD incurred a 1.09-fold and 1.18-fold risk of subsequent spine hip fractures, respectively, in patients with OS older than 50 years after adjusting for demography, ocular and systemic

Figure 2 Estimates of cumulative hazards of transition among patients with OS. OS, osteoporosis.

comorbidities. However, AMD did not increase the risk of humero-radio-ulnar fracture in this multivariate model.

About a third of the elderly population living in the community suffered from one or more falls each year,[25] which can damage one that has OS easily and lead to severe injury, physical deterioration, institutionalisation and incident deaths.[26] Most falls resulted from the interactions of multiple risk factors, including age, muscle weakness, poor vision, difficulties with gait and balance, previous falls, fear of falling and chronic illnesses such as arthritis, DM, stroke, Parkinson's disease, incontinence and dementia.[25 27 28] It is well recognised that fall-related ocular risk factors are also major contributors to fractures in the elderly,[22] which was supported by the findings of the current study.

Many older people living in the community were affected by poor vision or eye disease such as cataract, glaucoma and macular degeneration.[1 29] Studies have also demonstrated that AMD is associated with an increased risk of hip fractures by analysing the medicare database.[23 24 30] Anastasopoulos et al[30] found that the risk of hip fractures was significantly higher in cases that were coded with atrophic (dry) AMD.[30] However, the risk was similar in cases that were coded with exudative AMD and cases with no AMD. This study revealed that patients with a code for both types of AMD had significantly greater risk of hip fractures than patients without a code for AMD in osteoporotic population. The higher risk in this study reflected the fact that patients with OS are a potentially
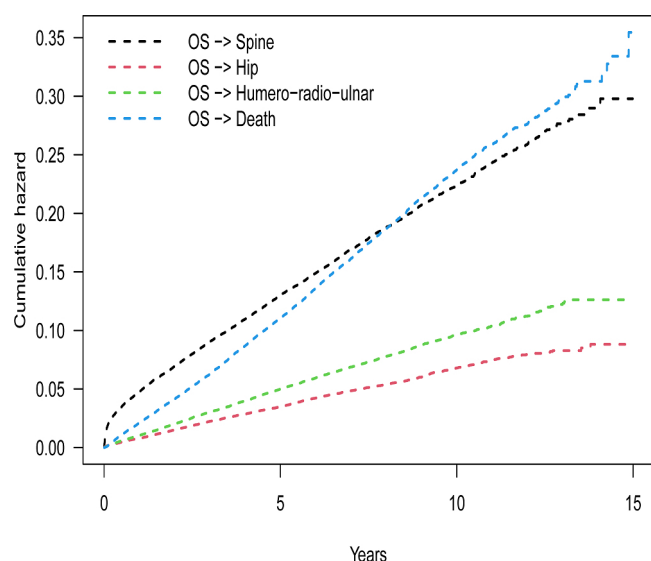
Table 2 The effect of AMD on transition of fractures and death

	Osteoporosis to death		Osteoporosis to spine fracture		Osteoporosis to hip fracture		Osteoporosis to humero-radio-ulnar fracture	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
AMD								
No	N/A	N/A	Reference		Reference		Reference	
Yes	N/A		1.09 (1.04 to 1.15)	<0.001	1.18 (1.08 to 1.30)	0.001	0.98 (0.90 to 1.06)	0.599
Age								
50–59	Reference		Reference		Reference		Reference	
60–69	1.46 (1.28 to 1.66)	<0.001	2.37 (2.11 to 2.66)	<0.001	3.03 (2.21 to 4.16)	<0.001	1.08 (0.96 to 1.22)	0.203
70–79	2.67 (2.36 to 3.02)	<0.001	3.71 (3.31 to 4.15)	<0.001	7.92 (5.85 to 10.73)	<0.001	1.25 (1.12 to 1.41)	<0.001
>80	4.72 (4.16 to 5.36)	<0.001	4.70 (4.19 to 5.29)	<0.001	16.33 (12.04 to 22.16)	<0.001	1.20 (1.05 to 1.37)	0.007
Sex								
Female	Reference		Reference		Reference		Reference	
Male	1.30 (1.24 to 1.36)	<0.001	0.58 (0.55 to 0.61)	<0.001	0.66 (0.61 to 0.72)	<0.001	0.42 (0.39 to 0.46)	<0.001
Rheumatologic diseases								
No	Reference		Reference		Reference		Reference	
Yes	1.11 (1.03 to 1.20)	0.005	1.20 (1.12 to 1.29)	<0.001	1.10 (0.96 to 1.26)	0.156	1.11 (1.00 to 1.24)	0.059
DM without complications								
No	Reference		Reference		Reference		Reference	
Yes	1.27 (1.21 to 1.34)	<0.001	1.00 (0.95 to 1.05)	0.957	1.04 (0.94 to 1.15)	0.399	1.12 (1.04 to 1.22)	0.005
DM with complications								
No	Reference		Reference		Reference		Reference	
Yes	1.41 (1.33 to 1.50)	<0.001	0.99 (0.92 to 1.06)	0.717	1.50 (1.33 to 1.69)	0.817	1.05 (0.94 to 1.17)	0.37
Malignancy								
No	Reference		Reference		Reference		Reference	
Yes	4.41 (4.19 to 4.63)	<0.001	1.09 (1.03 to 1.16)	0.004	1.02 (0.92 to 1.15)	0.666	1.03 (0.93 to 1.14)	0.581
Moderate to severe liver diseases								
No	Reference		Reference		Reference		Reference	
Yes	4.69 (4.24 to 5.18)	<0.001	1.29 (0.99 to 1.69)	0.06	1.06 (0.63 to 1.80)	0.203	0.69 (0.40 to 1.19)	0.178
Hyperthyroidism								
No	Reference		Reference		Reference		Reference	
Yes	0.90 (0.76 to 1.06)	0.2	1.07 (0.93 to 1.23)	0.338	1.19 (0.91 to 1.56)		1.15 (0.95 to 1.39)	0.151
Chronic renal diseases								
No	Reference		Reference		Reference		Reference	

Continued

Table 2 Continued

	Osteoporosis to death		Osteoporosis to spine fracture		Osteoporosis to hip fracture		Osteoporosis to humero-radio-ulnar fracture	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Yes	2.22 (2.10 to 2.35)	<0.001	1.01 (0.93 to 1.10)	0.786	1.57 (1.38 to 1.77)	<0.001	0.99 (0.86 to 1.14)	0.876
Cataract								
No	N/A	N/A	Reference		Reference		Reference	
Yes	N/A	N/A	1.23 (1.17 to 1.31)	<0.001	1.05 (0.94 to 1.16)	0.39	1.16 (1.06 to 1.26)	<0.001
Corneal diseases								
No	N/A	N/A	Reference		Reference		Reference	
Yes	N/A	N/A	1.18 (1.12 to 1.23)	<0.001	1.05 (0.96 to 1.15)	0.322	1.08 (1.00 to 1.17)	0.041
Glaucoma								
No	N/A	N/A	Reference		Reference		Reference	
Yes	N/A	N/A	1.00 (0.95 to 1.06)	0.871	1.02 (0.92 to 1.12)	0.773	1.04 (0.96 to 1.13)	0.355
Hyperparathyroidism								
No	Reference		N/A		N/A		N/A	
Yes	1.89 (1.42 to 2.52)	<0.001	N/A	N/A	N/A	N/A	N/A	N/A
CCIs								
Every point increase	1.08 (1.07 to 1.08)	<0.001	N/A	N/A	N/A	N/A	N/A	N/A

AMD, age-related macular degeneration; CCIs, Charlson Comorbidity Index score; DM, diabetes mellitus; N/A, the analysis did not perform since it is not necessary for the purpose of the current study.

vulnerable population to developing fractures secondary to an accidental fall.

Fractures caused by OS most frequently occur in the spine.[14] These spinal fractures occur in nearly 700 000 patients each year in the USA and is twice as common as other OS-related fractures such as hip and wrist fractures.[31] Generally, spinal compression fractures result from falls,[32] but patients with OS can suffer fractures even when doing routine works, such as twisting, coughing and sneezing.[33] However, there are very few reports on the association between AMD and spine fractures in patients with OS. In this study, patients with AMD have a significantly greater risk of spine fractures. Therefore, it is important to screen ocular comorbidity such as AMD in elderly patients with OS to prevent both hip and spine fractures.

This study demonstrated that AMD was not associated with a greater risk of humero-radio-ulnar fractures. Primarily because humerus fractures occur in a relatively young population after physical trauma, falls, excess physical stress such as baseball games[34] and even with the presence of AMD, it did not cause significant visual impairment at a relatively younger age. However, proximal humerus fractures occur among elderly patients with OS who fall on an outstretched arm,[35] which corresponded to our finding in which 70 years or older were associated with an increased risk of humero-radio-ulnar fractures (table 2).

The risk of death was significantly higher in patients with OS with older age, male sex and the majority of systemic diseases in the current study. It is reasonable since the factors are related to a relatively unhealthy status; however, the non-significant relationship between hyperparathyroidism and death in OS individuals needs further validation. Although the chance of death is increased in patients with OS with systemic comorbidities, attention should be paid to the fact that these patients with additional AMD diagnosis have a higher risk of spine and hip fractures and subsequent death caused by fractures.[18 19] Therefore, we should aggressively treat AMD to prevent fractures in patients with OS if they are not affected by severe systemic diseases.

A major limitation of this study is that the disease severity is inaccessible in the NHIRD and the effects of different severities of ocular comorbidities on different fractures cannot be obtained. However, it seemed unlikely that selection bias was a factor given that the basis of subject selection was not associated with the magnitude of fractures and the severity of ocular comorbidities. A minor limitation lies in the absence of outcome measures after treatment for both AMD and OS, which cannot provide therapeutic guidelines.

In conclusion, patients with OS with AMD are at a significantly higher risk of subsequent development of spine and hip fractures, but not humero-radio-ulnar fractures than matched controls. Moreover, older age, male sex and major systemic comorbidities in patients with OS are related to death. Further investigations are needed to clarify if the treatment of AMD, such as vitrectomy and intravitreal anti-vascular endothelial growth factor injection, would prevent primary fractures in patients with OS.

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