Osteoporosis International (2019) 30:1617–1625
https://doi.org/10.1007/s00198-019-04966-z

ORIGINAL ARTICLE

Increased risk of osteoporotic vertebral fracture in rheumatoid arthritis patients with new-onset cardiovascular diseases: a retrospective nationwide cohort study in Taiwan

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Received: 31 August 2018 / Accepted: 7 April 2019 / Published online: 24 May 2019

Abstract

Introduction Both cardiovascular diseases (CVD) and osteoporosis are common comorbidities in rheumatoid arthritis (RA) patients. Although accumulating evidence indicates a link between CVD and osteoporotic fracture, whether CVD contributes to osteoporotic fracture risk in RA has yet to be explored. We examined the incidence rate and risk factors of osteoporotic vertebral fracture in RA patients with new-onset CVD (RA-CVD) and evaluated the effects of medications on such fracture risk.

Methods A retrospective study was conducted using a nationwide database from 2000 to 2010: 1267 RA-CVD and 1267 non-CVD patients were enrolled from 30,507 patients with newly diagnosed RA. The main outcome was the development of osteoporotic vertebral fracture. After being adjusted for age, gender, and comorbidities, the Cox proportional hazard model was used to identify independent factors contributing to osteoporotic vertebral fracture.

Results The adjusted hazard ratio (aHR) of developing osteoporotic vertebral fracture was 1.47-fold greater in RA-CVD group than in non-CVD group (95% confidence interval 1.19–1.81, $p < 0.001$). Both the age above 40 years and female gender were significant risk factors for developing osteoporotic vertebral fracture in RA-CVD patients. Using patients not taking medication as a reference group, the aHR of osteoporotic vertebral fracture was significantly lower in those receiving statins (0.50), low-dose corticosteroids (0.57), or hydroxychloroquine (0.12).

Conclusions The risk of osteoporotic vertebral fracture was significantly increased in RA-CVD patients, particularly women above 40 years of age, and could be reduced by statin therapy. However, the protective effect of low-dose corticosteroids or hydroxychloroquine on osteoporotic vertebral fracture risk needs further validation.

Keywords Cardiovascular diseases · Nationwide · Osteoporosis · Osteoporotic vertebral fracture · Rheumatoid arthritis

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00198-019-04966-z) contains supplementary material, which is available to authorized users.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory articular disease [1] that is complicated by accelerated atherosclerosis and subsequently leads to increased risks of cardiovascular disease (CVD) [2]. Schett et al. revealed decreased bone mineral densities (BMD) in patients with various status of chronic inflammation including rheumatic diseases [3]. Increased risks of osteoporosis (OP) or osteoporotic fractures have been reported in RA patients compared with healthy controls [4, 5]. Hence, CVD and osteoporotic fracture are important causes of morbidity in RA patients [6, 7]. Although CVD and osteoporotic fractures are traditionally viewed as unrelated disorders, there is increasing biological and epidemiological evidence of a link between both conditions [8–10]. In addition, the beneficial effects of statins on both vascular walls and bones suggest a possible common pathophysiological basis [11, 12]. However, whether CVD contributes to the risk of osteoporotic vertebral fracture in RA patients remained unclear.

Therefore, we utilized a nationwide database, NHI Research Database (NHIRD), for this research. The National Health Insurance (NHI) program in Taiwan is a mandatory universal health insurance program that provides comprehensive medical care to more than 99% of the population [8, 13], and its database, NHIRD, is confidentiality maintained according to the guidelines of the Bureau of NHI [14]. Herein, we examined the incidence rate and risk factors of osteoporotic vertebral fracture and the hazard ratio among RA patients with new-onset CVD (RA-CVD). In addition, we evaluated the influence of medications, including statins, corticosteroids, various conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and tumor necrosis factor (TNF)-α inhibitors, on the risks of osteoporotic vertebral fracture in RA-CVD patients.

Methods

Data source and study design

This retrospective population-based cohort study was conducted using 2000–2011 claim data retrieved from NHIRD, which consists of detailed health care information from more than 23 million enrollees, representing more than 99% of Taiwan's entire population. The NHIRD contains detailed information about pharmacy claims such as drug therapies and doses, registration files, and original claim records for reimbursement for each study subject, with the diagnoses based on the ICD-9-CM codes. However, personal information including weight, height, family history, laboratory examination results, lifestyle, and habits such as smoking and alcohol use is not provided by the NHIRD. The Institutional Review Board, China Medical University Hospital Research Ethics Committee (CMUH-104-REC2-115) approved this study.

Patients

Patients with RA were identified primarily by using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. In addition, those identified cases should be registered with the Catastrophic Illness Patient Database (CIPD), which requires the diagnosis of RA to be verified by two board-certified rheumatologists. We ensured that the diagnosis of RA (ICD-9-CM code 714.0) was made according to the 1987 American College of Rheumatology criteria [15] and the Registry of Catastrophic Illness Database (RCIPD) of the NHIRD.

We considered some comorbidities and statin therapy as confounding factors in the present study. The definitions of comorbidities were made according to the published literatures and ICD-9-CM codes [13, 16], including heart failure (ICD-9-CM 428), hypertension (ICD-9-CM 401-405), diabetes mellitus (DM, ICD-9-CM 250), vascular disease (ICD-9-CM 440-445), hyperlipidemia (ICD-9-CM 272), valvular heart disease (VHD, ICD-9-CM 093.2, 394-397, 424, 746.3-746.6), chronic obstructive pulmonary disease (COPD, ICD-9-CM 490-493 and 496), and chronic kidney disease (CKD, ICD-9-CM 580-587). The Anatomical Therapeutic Chemical (ATC) code of statin was C10AA01-10AA08. All comorbidities were defined by the presence of disease in two outpatient visits or one inpatient visit prior to the index date.

Identification and definition of RA cohorts

As shown in Fig. 1, we selected RA patients above 40 years of age as of January 1, 2000 and then excluded subjects with a history of CVD (ischemic heart disease ICD-9-CM 411, 413, 414; myocardial infarction ICD-9-CM 410, 412; and cerebrovascular disease ICD-9-CM 430-438) before being diagnosed with RA. The RA-CVD group was composed of RA patients with newly diagnosed, while non-CVD group was selected from the based population with each subject randomly assigned a date between the day when the diagnosis of RA was made and December 31, 2010. RA patients who coincidentally had osteoporotic vertebral fracture before the index date were also excluded from both groups. The censor of the follow-up was considered when RA patients dismissed the health insurance, developed osteoporotic vertebral fracture, or until December 31, 2011. Then, the non-CVD group was 1-fold size frequency matched with the CVD group by index year, age (every 5 years), gender, and the year of RA diagnosis, and the unmatched cases were then excluded. In 2003, biologics were first introduced to Taiwan for RA treatment, i.e., TNF-α inhibitors (etanercept the first, followed by adalimumab). Because rituximab, golimumab, infliximab,

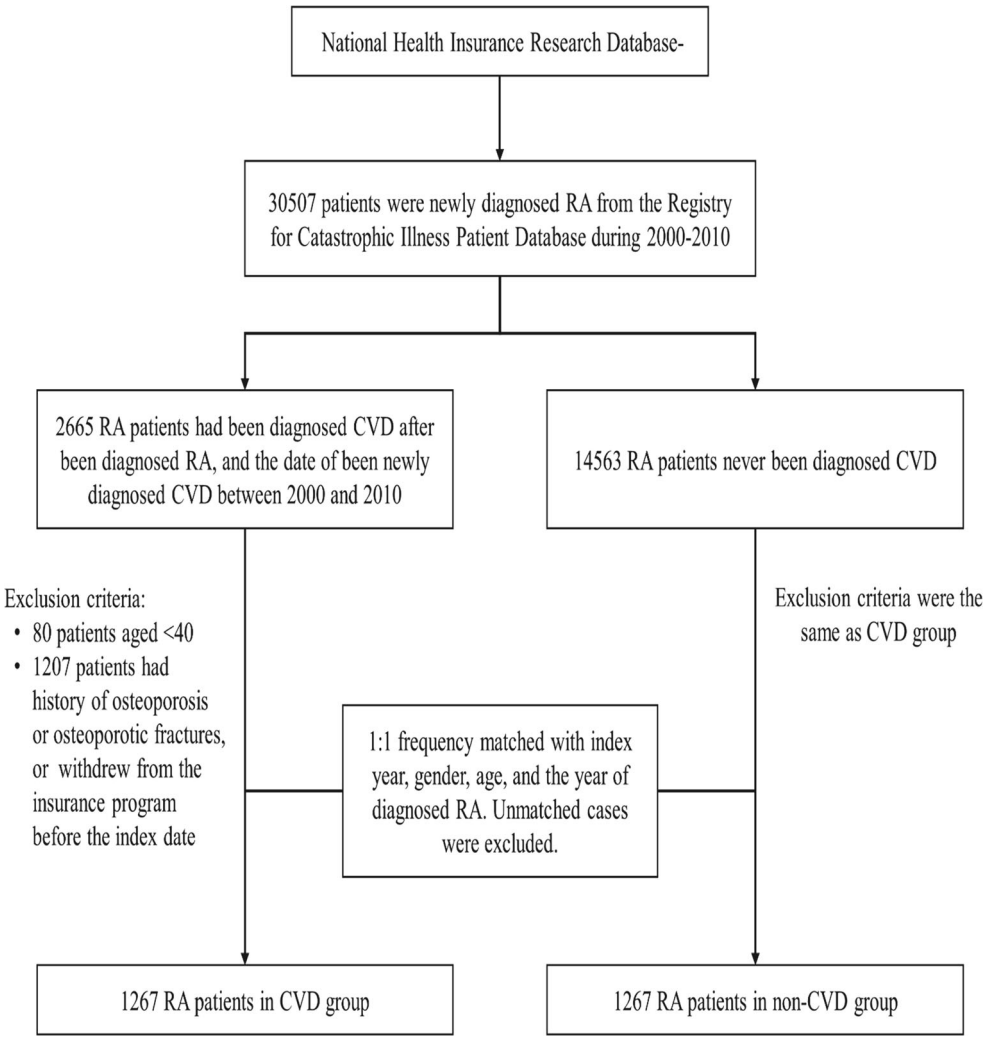

Fig. 1 Flow chart of case selection in this study. The rheumatoid arthritis (RA) patients with new-onset cardiovascular disease (CVD), and age- and sex-matched non-CVD control subjects were selected from the Taiwan National Health Insurance research database (NHIRD)

certolizumab, tocilizumab, abatacept, or tofacitinib had not been available until 2010, they were not included in this study.

Main outcome measurements

The main outcome was the development of osteoporotic vertebral fracture. Moreover, at least one of the following enrollment criteria had to be met for the inclusion into our study: the diagnosis of osteoporotic vertebral fracture was established after (1) two or more outpatient visits or (2) one or more inpatient admissions. Bone mineral density (BMD) of the lumbar spine, total hip, and femoral neck was measured by a dual-energy X-ray absorptiometry (DEXA), with a T-score of − 2.5 or lower indicative of the diagnosis of OP [17]. The presence of vertebral fracture was detected by radiography of spine. Patients with osteoporotic vertebral fracture were defined as those having both a new diagnosis of OP (ICD-9-CM 733) [13, 18] and vertebral fracture (ICD-9-CM 733.13 or 805).

Statistical analysis

The data were presented as the mean ± standard deviations (SD) for continuous variables and proportions for categorical variables. The differences between continuous values were analyzed using the independent *t* test for continuous variables and the Chi-square test for categorical variables. The incidences of newly diagnosed osteoporotic vertebral fracture in RA-CVD group and the non-CVD group were calculated. The multivariate Cox proportional hazard model was adjusted for age, gender, and comorbidities and was used to identify independent factors contributing to the development of osteoporotic vertebral fracture; the 95% confidence interval (CI) for each variable was determined. We calculated the incidence rate of osteoporotic vertebral fracture related to the use of each DMARD agent and estimated DMARDs-specific hazard ratio (HR) using non-user as reference. All analyses were conducted using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA). A p value of < 0.05 was considered statistically significant.

Results

From 2000 to 2010, a total of 30,507 newly diagnosed RA patients were identified. After the exclusion of those with CVD prior to RA diagnosis or having history of osteoporotic vertebral fracture before the index date, a total of 1267 RA with new-onset CVD were enrolled, and with other 1267 non-CVD subjects selected and matched for age and gender with the ratio of 1:1 (Fig. 1). Compared with the non-CVD subjects, RA patients with CVD had a significantly higher prevalence of comorbidities, including heart failure, vascular disease, vascular heart disease, hypertension, hyperlipidemia, DM, COPD, and CKD (Table 1).

We demonstrated that 241 RA-CAD patients developed osteoporotic vertebral fracture during 4888 person-years (py) of follow-up (incidence rate [IR] 4.93 per 100 py), while 205 non-CVD subjects contracted osteoporotic vertebral fracture during 5451 py (IR 3.76 per 100 py). The adjusted HR (aHR) was 1.47-fold greater in the RA-CVD group than in the non-CVD group (95% CI = 1.19–1.81, $p < 0.001$, Table 2). The age groups 40–64 and ≥ 65 years were significant risk factors for developing osteoporotic vertebral fracture in RA-CVD patients. RA-CVD patients had significantly higher risk of developing osteoporotic vertebral fracture than the non-CVD subjects, which was independent of the comorbidities (Table 2).

After stratification by the gender, the aHR of developing osteoporotic vertebral fracture was 1.62-fold greater in the female RA-CVD group than in the non-CVD group (95% CI = 1.28–2.04, $p < 0.001$, Table 3). Both the age groups 40–64 and ≥ 65 years were also significant risk factors for developing osteoporotic fracture in female RA-CVD patients (Table 3). In addition, female RA-CVD patients had significantly higher risk of developing osteoporotic vertebral fracture than the non-CVD subjects, which was independent of the comorbidities. However, there was no significant difference in the risks of osteoporotic vertebral fracture between the male RA-CVD group and the non-CVD group (Table 3).

As shown in Fig. 2a, Kaplan-Meier analysis showed that the cumulative incidence of osteoporotic vertebral fracture was significantly higher in RA-CVD group than in the non-CVD group during the first 8 years of follow-up. After stratification based on gender, the cumulative incidence of osteoporotic fracture was significantly higher in the female RA-CVD group, but not in the male RA-CVD group, compared with the non-CVD group during the first 8 years of follow-up (as shown in Fig. 2b, c).

The RA-CVD patients undergoing statin therapy had a significantly lower aHR of osteoporotic vertebral fracture compared to those without (0.50, 95% CI 0.36–0.69, $p < 0.0001$, Table 4). In comparison to RA-CVD patients not receiving corticosteroids, the aHR of osteoporotic vertebral fracture was lower for those receiving low-dose corticosteroid (0.57, 95% CI 0.42–0.78, $p < 0.001$, Table 4), but not significantly different in those taking high-dose corticosteroid (> 7.5 mg/day). Using patients not receiving individual DMARD as a reference group, only hydroxychloroquine-treated patients had lower aHR of osteoporotic vertebral fracture (0.12, 95% CI 0.03–0.47, $p < 0.005$), and the aHR did not show significant change in those receiving other csDMARDs or TNF-α inhibitors.

To validate the results of our nationwide database, we analyzed the risks of osteoporotic vertebral fracture in 558 RA patients who had been examined for BMD with DXA at one medical center between January 2014 and December 2017. Our results showed significantly higher risks of osteoporotic vertebral fracture in the RA-CVD patients (53.3%) compared with the non-CVD patients (10.7%, $p < 0.001$) (Supplementary Table 1). The RA-CVD patients also had significantly lower BMD of the lumbar spine and femoral neck compared to the non-CVD group. Besides, having a smoking habit was associated with a significantly higher rate of osteoporotic vertebral fracture among the RA-CVD patients (37.5% versus 14.3%, $p < 0.05$). RA patients receiving high-dose corticosteroids (> 7.5 mg/day) also had a significantly higher rate of osteoporotic vertebral fracture than those not receiving corticosteroids (30.2% versus 12.6%, $p < 0.05$).

Table 1 Demographic status and comorbidities for rheumatoid arthritis patients with cardiovascular diseases or not

Cardiovascular diseases in rheumatoid arthritis patients					
	Yes		No		*P* value*
	(*n* = 1267)		(*n* = 1267)		
	n	%	*n*	%	
Gender					> 0.99
Female	799	63.1	799	63.1	
Male	468	36.9	468	36.9	
Age, years					> 0.99
40–64	832	65.7	832	65.7	
≧ 65	435	34.3	435	34.3	
Mean (SD)	60.3 (9.96)		60.2 (9.98)		0.83[a]
Comorbidities					
Heart failure	98	7.73	0	0	< 0.0001
Vascular disease	93	7.34	0	0	< 0.0001
VHD	104	8.21	20	1.58	< 0.0001
Hypertension	761	60.1	397	31.3	< 0.0001
Hyperlipidemia	468	36.9	248	19.6	< 0.0001
Diabetes mellitus	329	26.0	160	12.6	< 0.0001
COPD	502	39.6	354	27.9	< 0.0001
CKD	228	18.0	117	9.23	< 0.0001

VHD valvular heart disease, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease

* Chi-square test

[a] *t* test

Table 2 Incidence rate and hazard ratio of osteoporotic vertebral fractures between two groups in overall patients with rheumatoid arthritis (RA) stratified by gender, age, and comorbidities

	Cardiovascular diseases (CVD) in RA patients						Compared to the non-CVD RA cohort			
	Yes			No			Crude		Adjusted	
	Event	PY	IR	Event	PY	IR	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Overall	241	4888	4.93	205	5451	3.76	1.30 (1.08,1.57)	0.006	1.47 (1.19,1.81)	0.0003
Gender										
Female	199	3023	6.58	163	3478	4.69	1.39 (1.13,1.71)	0.002	1.62 (1.28,2.04)	< 0.0001
Male	42	1865	2.25	42	1973	2.13	1.05 (0.68,1.61)	0.83	0.96 (0.60,1.55)	0.87
Age										
40–64	144	3459	4.16	117	3774	3.10	1.33 (1.04,1.70)	0.02	1.42 (1.08,1.88)	0.01
≧ 65	97	1430	6.78	88	1677	5.25	1.29 (0.97,1.72)	0.08	1.53 (1.10,2.11)	0.01
Comorbidity[a]										
Yes	206	4118	5.00	131	3014	4.35	1.15 (0.93,1.43)	0.20	1.37 (1.08,1.74)	0.01
No	35	770	4.55	74	2437	3.04	1.48 (0.99,2.21)	0.06	1.78 (1.18,2.67)	0.005

PY person-years, *IR* incidence rate, per 100 person-years, *HR* hazard ratio, *CI* confidence interval

Models adjusted by gender, age, and comorbidities including heart failure, vascular diseases, valvular heart disease, hypertension, hyperlipidemia, diabetes mellitus, chronic obstructive pulmonary disease, and chronic kidney disease

[a] Patients with any one of comorbidity were classified as the comorbidity group

Discussion

Although the link between osteoporotic fracture risk and RA is well established [5, 19, 20], data regarding the association between CVD and osteoporotic fracture risk in RA patients remain limited. This is the first nationwide population-based longitudinal cohort study to examine the impact of CVD on the development of osteoporotic fracture in RA patients. We

Table 3 Incidence rate and hazard ratio of osteoporotic vertebral fractures between two groups in patients with rheumatoid arthritis (RA) stratified by gender and age and adjusted by comorbidities

	Cardiovascular diseases (CVD) in RA patients						Compared to the non-CVD RA cohort			
	Yes			No			Crude		Adjusted	
	event	PY	IR	event	PY	IR	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Female	199	3023	6.58	163	3478	4.69	1.39 (1.13,1.71)	0.002	1.62 (1.28,2.04)	<0.0001
Age										
40-64	124	2222	5.58	100	2501	4.00	1.37 (1.05,1.79)	0.02	1.50 (1.11,2.03)	0.008
≧65	75	801	9.36	63	977	6.45	1.46 (1.04,2.05)	0.03	1.79 (1.23,2.61)	0.002
Comorbidity[†]										
Yes	167	2601	6.42	105	1876	5.60	1.15 (0.90,1.46)	0.27	1.43 (1.09,1.87)	0.009
No	32	422	7.58	58	1603	3.62	2.11 (1.37,3.26)	0.00	2.26 (1.46,3.49)	0.0003
Male	42	1865	2.25	42	1973	2.13	1.05 (0.68,1.61)	0.83	0.96 (0.60,1.55)	0.87
Age										
40-64	20	1237	1.62	17	1273	1.34	1.20 (0.63,2.29)	0.58	1.11 (0.55,2.23)	0.78
≧65	22	628	3.50	25	700	3.57	0.95 (0.54,1.69)	0.87	0.88 (0.45,1.71)	0.71
Comorbidity[†]										
Yes	39	1517	2.57	26	1139	2.28	1.13 (0.69,1.85)	0.64	1.12 (0.65,1.93)	0.67
No	3	348	0.86	16	834	1.92	0.41 (0.12,1.42)	0.16	0.45 (0.13,1.58)	0.21

PY, person-years; IR, incidence rate, per 100 person-years; HR, hazard ratio; CI, confidence interval;

Models adjusted by gender, age, and comorbidities including heart failure, vascular diseases, valvular heart disease, hypertension, hyperlipidemia, diabetes mellitus, chronic obstructive pulmonary disease, and chronic kidney disease

[†] Patients with any one of comorbidity were classified as the comorbidity group

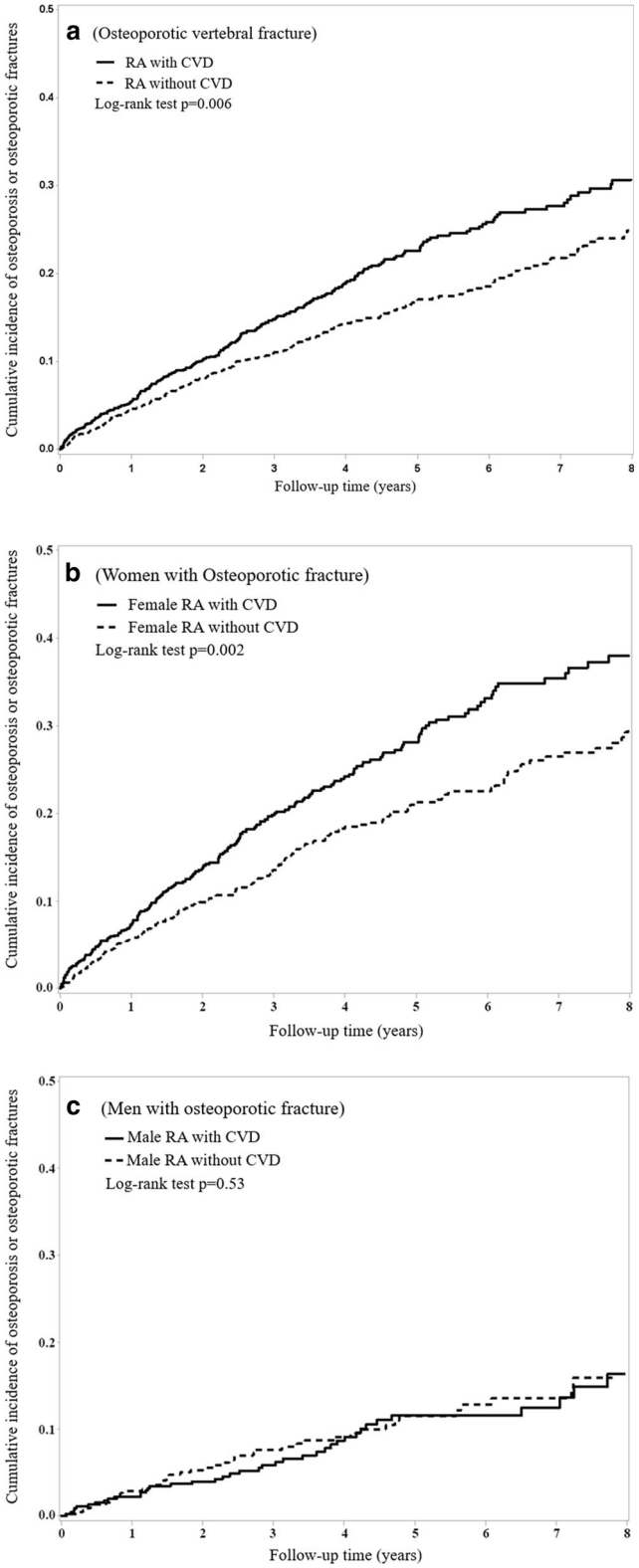

Fig. 2 Cumulative incidence of **a** osteoporotic vertebral fracture, **b** women with osteoporotic vertebral fracture, and **c** men with osteoporotic vertebral fracture in RA patients with new-onset CVD (RA-CVD) compared to the non-CVD subjects. CVD: cardiovascular diseases

revealed that the risks of developing osteoporotic vertebral fracture were significantly higher in RA-CVD patients than in the non-CVD group by 47%. Our hospital-based study also demonstrated significantly higher risks of osteoporotic vertebral fracture in the RA-CVD group compared with the non-CVD group. In this nationwide database research, the age above 40 years, female gender, and the presence of comorbidities were identified as significant risk factors for developing osteoporotic vertebral fracture in the RA-CVD group. Therefore, it is clinically important to check for osteoporotic vertebral fracture in the RA-CVD patients, particularly women with high-risk factors.

Similar to previous reports [8–10, 21], we revealed an increased risk of osteoporotic vertebral fracture in RA-CVD patients compared to non-CVD group in a nationwide cohort study and a hospital-based study. In Kaplan-Meier analysis, the cumulative incidence of osteoporotic vertebral fracture was also significantly higher in the RA-CVD group than in the non-CVD group during a longitudinal follow-up. Several large epidemiological studies similarly showed that osteoporotic fracture was associated with increased CVD risks [21, 22]. Various theories have been proposed to explain the link between them, including the shared lifestyle factors such as physical inactivity, dyslipidemia, falls, and RA-related inflammation. Parhami et al. also observed that oxidized LDL, a pathogenic factor, could inhibit osteoblast differentiation [23]. In addition, it has been shown that vascular atherosclerosis, by reducing blood flow to extremities, could alter bone metabolism and result in increased bone loss as well as fracture risks [24]. Given that data such as lifestyle factors and laboratory results are not available in the present nationwide database, we cannot provide full explanation for the causal relationship between osteoporotic vertebral fracture and CVD in RA patients.

An important strategy to improve bone health interventions for RA patients is to identify patients who are at high risk of developing osteoporotic vertebral fracture. In the present study, the age above 40 years was a significant risk factor of osteoporotic fracture in RA patients, which resonated with a previous study showing that the age 40–64 years was an independent risk factor for OP or osteoporotic fracture [25]. In addition, our female RA-CVD patients above the age of 40 years had higher risks of osteoporotic vertebral fracture compared with the non-CVD patients. Our findings were consistent with previous reports showing that female gender and postmenopausal status were risk factors of OP with or without osteoporotic fracture in RA [25, 26]. The lack of estrogen during menopause is probably responsible for osteoporotic fracture and CVD through some biological mechanisms involving both bone loss and CVD [4, 9]. However, there was no significant increase in the risk of osteoporotic vertebral fracture in our male RA-CVD patients compared with male

Table 4 Incidence rate and hazard ratio of osteoporotic vertebral fractures for RA patients with cardiovascular diseases had received medication or not

	N	Event	PY	IR	Crude		Adjusted	
					HR (95%CI)	*P* value	HR (95%CI)	*P* value
Statin								
No	855	188	3115	6.04	1 (reference)		1 (reference)	
Yes	405	53	1773	2.99	0.50 (0.37,0.68)	< 0.0001	0.50 (0.36,0.69)	< 0.0001
Corticosteroids								
No	837	183	2874	6.37	1 (reference)		1 (reference)	
≦ 7.5 mg/day	388	54	1897	2.85	0.46 (0.34,0.63)	< 0.0001	0.57 (0.42,0.78)	0.0004
> 7.5 mg/day	35	4	117	3.42	0.53 (0.2,1.43)	0.21	0.62 (0.23,1.67)	0.34
csDMARDs								
Methotrexate								
No	879	162	3220	5.03	1 (reference)		1 (reference)	
Yes	381	79	1668	4.74	0.96 (0.73,1.25)	0.76	0.98 (0.74,1.29)	0.88
Salazopyrin								
No	745	129	2549	5.06	1 (reference)		1 (reference)	
Yes	515	112	2339	4.79	0.98 (0.76,1.26)	0.86	0.94 (0.73,1.22)	0.65
HCQ								
No	1174	239	4529	5.28	1 (reference)		1 (reference)	
Yes	86	2	360	0.56	0.11 (0.03,0.43)	0.002	0.12 (0.03,0.47)	0.003
Ciclosporin								
No	1178	223	4497	4.96	1 (reference)		1 (reference)	
Yes	82	18	392	4.59	0.96 (0.6,1.56)	0.88	0.98 (0.61,1.59)	0.95
Azathioprine								
No	1222	237	4693	5.05	1 (reference)		1 (reference)	
Yes	38	4	196	2.04	0.43 (0.16,1.16)	0.10	0.43 (0.16,1.17)	0.10
TNF-α inhibitors								
No	1213	234	4679	5.00	1 (reference)		1 (reference)	
Yes	47	7	209	3.35	0.67 (0.32,1.42)	0.30	0.73 (0.34,1.55)	0.41

PY person-years, *IR* incidence rate per 100 person-years, *HR* hazard ratio, *CI* confidence interval

Models adjusted by gender, age, heart failure, hypertension, diabetes mellitus, vascular disease, hyperlipidemia, VHD, COPD, and CKD

non-CVD patients. The absence of statistical power could be due to the small case number of the male RA-CVD patients in this study and remained to be confirmed by further larger studies.

Notwithstanding the significantly higher prevalence of comorbidities in the RA-CVD patients, they still had a higher aHR of developing osteoporotic vertebral fracture than the non-CVD group after adjustment for comorbidities. The risk of osteoporotic vertebral fracture was therefore independent of the presence of comorbidities in the RA-CVD patients.

Statins could inhibit the HMG-CoA reductase, a critical enzyme in the pathways of cholesterol synthesis and the process of osteoclasts activation [11, 27]. They effectively reduce the cholesterol levels and thereby decrease the risk of CVD. In addition, statins have dual effects of increasing bone formation and reducing bone resorption [28], and their beneficial effects on the risk of OP or osteoporotic fracture in general population have been reported [13, 18, 29]. Resonating with previous findings [11, 28, 29], we revealed a preventive effect of statins on the risk of osteoporotic fracture in the RA-CVD patients compared with non-users.

Possibly due to the strong anti-inflammatory effects of corticosteroid that may contain the bone loss and low BMD associated with chronic inflammation in RA [30], we interestingly revealed that RA-CVD patients receiving low-dose corticosteroids had a lower risk of osteoporotic fracture compared with non-users. Other previous reports also indicated that corticosteroid use was associated with a low risk of vertebral fracture through effective control of disease activity and inflammation [31, 32]. However, another hospital-based study oppositely revealed that RA patients receiving low-dose corticosteroids (2.5–7.5 mg daily) therapy had a higher risk of osteoporotic fracture [33]. Meanwhile, the used high-dose corticosteroids (> 7.5 mg daily) did not show significant beneficial effect on osteoporotic fracture risk in the present nationwide study and were even associated with increased osteoporotic fracture risk in our hospital-

based study. The anti-inflammatory (protective) effect of high-dose corticosteroids may be counteracted by the detrimental effects on bone health or/and high disease activity. Previous studies similarly revealed that the osteoporotic fracture risk during corticosteroid therapy seemed to be dose-dependent [34, 35]. Given the conflicting results regarding the impact of corticosteroid dosage on osteoporotic fracture risk in RA, the protective effect of low-dose corticosteroids needs further validation.

Among the various csDMARDs used in RA-CVD patients, hydroxychloroquine (HCQ) most significantly reduced the risk of osteoporotic vertebral fracture in users compared with non-users (Table 4). One recent study similarly revealed that HCQ could suppress bone resorption both in vitro and in vivo [36]. However, because RA patients with mild disease activity are more likely to be prescribed HCQ rather than more potent DMARDS, and only two RA-CVD patients receiving HCQ therapy developed osteoporotic fracture, the protective effect of HCQ against the development of osteoporotic vertebral fracture still needs further verification.

Although the beneficial effect of anti-TNF therapy on bone loss has been shown in RA patients [37], such preventive effect against osteoporotic vertebral fracture could not be found in our RA-CVD patients. Other large cohort studies also showed no significant difference in the risk of osteoporotic fracture between biologics-treated patients and those treated with non-biologics [38, 39]. It is possible that the strong anti-inflammatory action of biologics was offset by the high baseline fracture risk in biologics-treated patients who tended to have a high disease activity.

Despite the potential clinical implications in our study results, there are still some limitations. Taiwan NHIRD neither contain detailed information about lifestyle factors or individual health status (e.g., smoking or body mass index) that may contribute to the risk of osteoporotic vertebral fracture, nor include the results of laboratory examinations data such as anti-citrullinated peptide antibodies, which have a significant impact on BMD [40]. The matching of groups 1:1 and simply on the basis of 2 factors age and gender is another limitation. In addition, the absence of data regarding individual RA disease activity, which was associated with the risk of osteoporotic fracture or the dosage of corticosteroids, is an important limitation. Further large and hospital-based studies are required to validate our findings.

The major strength of this study was the utilization of the nationwide database, which provides detailed medical care records and is widely accepted as an instrument for epidemiological studies [13, 18]. The NHIRD contains detailed pharmacy claims, registration files, and original claim records of reimbursement for each study subject, with the diagnoses based on ICD-9-CM. The large sample size of the NHIRD (23 million enrollees) and the long-term design enhanced the statistical power and accuracy of this study. We also evaluated the effect of commonly used medication on the risk of osteoporotic vertebral fracture in RA-CVD patients.

In conclusion, the risk of developing osteoporotic vertebral fracture was significantly increased in RA-CVD patients, particularly women above 40 years of age. Our results may facilitate early identification of RA patients with high risk of osteoporotic vertebral fracture and timely provide therapeutic interventions targeting both osteoporotic vertebral fracture and CVD. The use of statins may be beneficial to skeletal health of RA-CVD patients. The protective effect of low-dose corticosteroids or HCQ on osteoporotic vertebral fracture risk needs further validation.

Funding information This work was supported by grants from the Ministry of Health and Welfare, Taiwan (MOHW107-TDU-B-212-123004), China Medical University Hospital, Academia Sinica Stroke Biosignature Project (BM10701010021), MOST Clinical Trial Consortium for Stroke (MOST 106-2321-B-039-005), Tseng-Lien Lin Foundation, Taichung, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan.

Compliance with ethical standards

Conflicts of interest None.

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