

# Incidence and Mortality of Osteoporotic Fracture in Rheumatoid Arthritis in South Korea Using Nationwide Claims Data

Hye-Young Kwon<sup>1,\*</sup>, Hyun-Ho Kim<sup>2,\*</sup>, Yoon-Kyoung Sung<sup>3</sup>, Yong-Chan Ha<sup>2</sup>

<sup>1</sup>Division of Biology & Public Health, Mokwon University, Daejeon;

<sup>2</sup>Department of Orthopaedic Surgery, Chung-Ang University College of Medicine, Seoul;

<sup>3</sup>Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea

## Corresponding author

Yong-Chan Ha

Department of Orthopaedic Surgery, Chung-Ang University College of Medicine, 102 Heukseok-ro, Dongjak-gu, Seoul 06973, Korea  
Tel: +82-2-6299-1577  
Fax: +82-2-822-1710  
E-mail: hayongch@naver.com

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\*Hye-Young Kwon and Hyun-Ho Kim contributed equally to this work and should be considered co-first authors.

**Background:** To investigate incidence and mortality of osteoporotic fractures (including hip, spine, distal radius, and proximal humerus) in rheumatoid arthritis (RA) patients and compare them with those in the general population. **Methods:** Data provided by National Health Insurance Service were used to identify osteoporotic fractures in patients aged >50 years between 2010 and 2012. Patients with RA were identified by the diagnostic code for seropositive RA. Standardized mortality ratios (SMRs; observed/expected deaths) of osteoporotic fractures were calculated based on age and gender-specific rates in the entire Korean population. Incidence, mortality, and SMR of osteoporotic fractures in RA patients and the general population were calculated and compared. **Results:** Osteoporotic fractures in the general population and RA patients were increased by 11.6% and 17.4% over 3 years (195,271 and 1,356 in 2010; 217,985 and 1,592 in 2012), respectively. Mean age-specific incidence of osteoporotic fracture in women and men with RA increased from 932.1/100,000 and 306.1/100,000 for aged 50 to 59 year to 9,377.0/100,000 and 3,700.9/100,000 for aged ≥ 80 years, respectively. Cumulative mortality rate in the first year after osteoporotic fracture in patients with RA was higher than that in the general population (7.8% in RA and 6.6% in the general population). SMR of osteoporotic fracture in RA patients was 1.4 times higher in men and 1.3 times higher in women than that for the general population. **Conclusions:** This study demonstrated that incidence, 1-year mortality, and SMR of osteoporotic fracture in RA patients aged 50 years and older were higher than those in the general population.

**Key Words:** Arthritis, rheumatoid · Incidence · Mortality · Osteoporotic fractures

## INTRODUCTION

Rheumatoid arthritis (RA) is the most common form of inflammatory arthritis. It changes biomechanical properties of bones and leads to alterations in bone components.[1] Bone loss due to pharmacologic treatment and physical impairment in RA patients can result in osteoporosis and related fractures.[2,3]

Although the prevalence of osteoporosis in patients with RA depends on patient characteristics, the prevalence of osteoporosis usually ranges from 15% to 59%.[4-6] It has been reported that the prevalence of osteoporosis in RA is generally higher than that in the general populations.[7] Although several studies have

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persistently reported that incidences and risk factors of osteoporotic fractures in patients with RA are higher than those in the general population, only a few studies have investigated the proportion and prognosis of RA patients among osteoporotic fractures in the general population.

Since February 2009, RA has been classified as a rare disease with insurance coverage by National Health Insurance (NHI) of Korea. Patients with RA are reimbursement for 90% of the total cost. However, patients with RA should be confirmed by hematology (seropositive RA factor or anti-cyclic citrullinated peptide antibody). They should receive specific code of rare disease to have insurance coverage.

This retrospective observational study was designed as a nationwide population study using database from NHI Service (NHIS) of Korea. The purpose of this study was to investigate incidence and mortality of osteoporotic fractures (including hip, spine, distal radius, and proximal humerus) in RA patients and compare them with those in the general population.

## MEHTODS

This retrospective study was approved by ethics committee and weaved informed consents (NHIS-2018-4-007).

### 1. Subjects

Patients aged 50 years or older with osteoporotic fractures including spine, hip, distal radius, and humerus were identified from the nationwide database provided by NHIS of South Korea between 2010 and 2012.

The Korean NHI program covers 100% of the population with exception of cosmetic surgery and services for traffic accident. All clinics and hospitals submit patient's data including the diagnosis (as defined by the International Classification of Diseases, 10th revision [ICD-10]) and medical costs for claims to the NHIS. NHIS database has advantage for studying non-traumatic osteoporotic fractures because it does not include high energy injuries such as traffic and industrial accident. All information about the patient and disease is available from NHIS data. These data have been used in several epidemiologic studies in Korea.[8]

In this study, diagnostic codes including ICD-10 code and operational definition for hip, spine, distal radius, and humerus fracture were based on previous epidemiologic studies.[9-13]

Patients with RA were identified by the specific code for seropositive RA (V.223) with confirmed hematology (seropositive RA factor or anti-cyclic citrullinated peptide antibody).

### 1) Incidence of osteoporotic fractures in patients with RA

From 2010 to 2012, annual incidence rates of osteoporotic fractures were calculated using the annual number of osteoporotic fractures divided by mid-year population estimate. Incidence of osteoporotic fracture during period of 2010 to 2012 was also calculated.

### 2) Mortality and standardized mortality ratio (SMR) after osteoporotic fractures in patients with RA

NHIS data were merged with national mortality data from the National Statistical Office to determine the survival of each patient in the first year after osteoporotic fracture. One-year mortality rate of patients with osteoporotic fractures during the study period was calculated and presented in 10-year age intervals. In order to find excess mortality after osteoporotic fracture, SMR was calculated and presented in 10-year age interval.[10,14] Age and gender distribution as well as mortality data of the Korean population in 2010 to 2012 were used as standard. They were obtained from the Korean Statistical Information Service. Excess mortality was considered when SMR was greater than one.

## 2. Statistical analyses

Average incidence rates, mortality rates, and SMRs of osteoporotic fractures and patients with RA considering age and gender in 10 year interval were calculated. All database management and analyses were performed using SAS statistical package version 9.4 (SAS Institute, Cary, NC, USA).

## RESULTS

### 1. Incidence of osteoporotic fractures in patents with RA

Osteoporotic fractures in the general population and RA patients were increased by 11.6% and 17.4%, respectively, from 2010 to 2012 (195,271 and 1,356 in 2010; 217,985 and 1,592 in 2012, respectively) (Table 1 and Fig. 1). In terms of

**Table 1.** Gender-specific incidence (per 100,000) of osteoporotic fracture in Korean over 50 years old and patients with rheumatoid arthritis during 3 years

	2010			2011			2012		
	Men	Women	Total	Men	Women	Total	Men	Women	Total
<b>Any type</b>									
No. of fractures	40,019	155,252	195,271	42,013	155,357	197,370	46,923	172,062	217,985
Incidence of fractures	604	2,017	1,363	604	1,932	1,316	631	2,053	1,392
No. of fracture in RA	147	1,209	1,356	171	1,262	1,433	179	1,413	1,592
Incidence of fractures in RA	1,353	2,871	2,559	1,456	2,741	2,480	1,366	2,760	2,479
<b>Hip</b>									
No. of fractures	7,000	18,362	25,362	7,504	19,078	26,582	8,043	20,383	28,426
Incidence of fractures	106	239	177	108	237	177	111	243	182
No. of fracture among RA	30	189	219	31	207	238	31	235	266
Incidence of fractures among RA	276	449	413	264	450	412	237	459	414
<b>Spine</b>									
No. of fractures	18,553	67,054	85,607	19,993	69,804	89,797	21,843	76,156	97,999
Incidence of fractures	291	910	624	299	909	626	312	953	656
No. of fracture among RA	89	666	755	116	747	863	115	823	938
Incidence of fractures among RA	819	1,581	1,425	988	1,622	1,493	877	1,608	1,460
<b>Distal radius</b>									
No. of fractures	10,718	57,692	68,410	10,594	53,700	64,294	11,565	61,005	72,570
Incidence of fractures	165	764	487	155	682	438	163	744	474
No. of fracture among RA	16	280	296	16	253	269	24	260	284
Incidence of fractures among RA	147	665	559	136	549	465	183	508	442
<b>Proximal humerus</b>									
No. of fractures	2,744	7,877	10,621	2,818	8,186	11,004	3,223	9,239	12,462
Incidence of fractures	42	104	75	41	104	75	45	112	81
No. of fracture among RA	14	85	99	9	78	87	10	115	125
Incidence of fractures among RA	129	202	187	77	169	151	76	225	195

RA, rheumatoid arthritis.

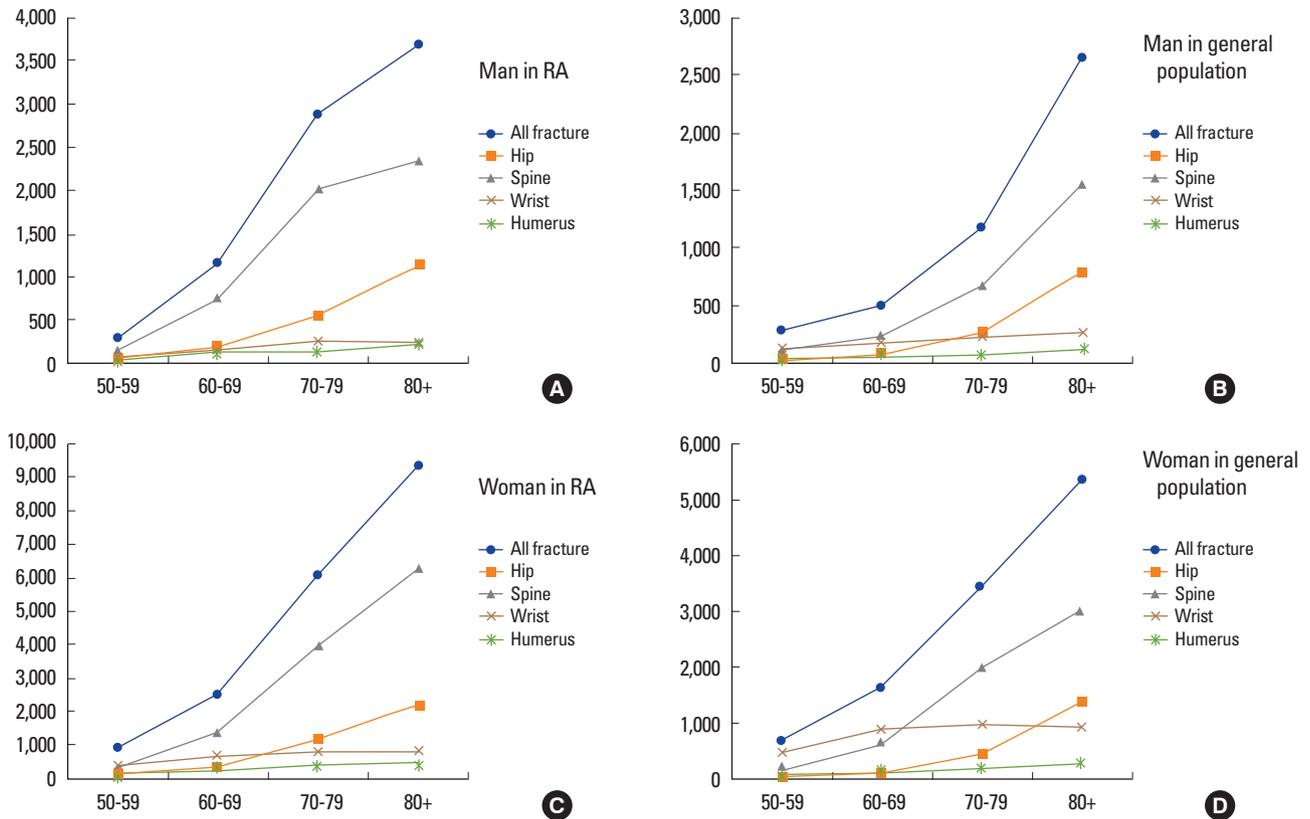
gender-specific distribution of osteoporotic fractures, similarly to osteoporotic fractures in the general population, incidence of osteoporotic fractures in men with RA was lower than that in women with RA. However, mean incidence of osteoporotic fractures in RA patients was 2.3 times higher in men and 1.4 times in women than that in the general population during 2010 to 2012 period (Table 1). Considering anatomical distribution of osteoporotic fractures in RA patients, incidence rates of hip, spine, and proximal humerus fracture in RA patients were higher than those in the general population. However, incidence of distal radius fractures in RA patients was similar to or lower than that in the general population.

The mean age-specific incidence of osteoporotic fracture in RA patients increased from 932.1/100,000 for those aged 50 to 59 years to 9,377.0/100,000 for those aged  $\geq 80$  years

in women and from 306.1/100,000 for those aged 50 to 59 years to 3,700.9/100,000 for those aged  $\geq 80$  years in men (Table 2). Osteoporotic fracture rates of both genders showed similar patterns. They were increased substantially for those older than 70 years. The incidence of osteoporotic fractures in women was increased more rapidly than that in men (Table 2). Regarding anatomical distribution of osteoporotic fracture in RA patients, although age-specific incidence rates of hip, spine, and proximal humerus fracture showed increasing trends in both genders, wrist fractures in women was decreased for those aged  $\geq 80$  years (Fig. 1).

## 2. Mortality and SMRs after osteoporotic fractures in patients with RA

Cumulative mortality rate at first year after osteoporotic fracture in patients with RA was higher than that in the



**Fig. 1.** Age-specific incidences of osteoporosis fractures (including hip, spine, wrist, and humerus) over 50 years of age in (A) rheumatoid arthritis (RA) patients in man, (B) general population in man, (C) RA patients in woman, and (D) general population in woman.

general population (7.8% in RA and 6.6% in the general population). Regarding gender specific distribution, average 1-year mortality rates in the general population and RA patients were 14.2% and 19.7% in men and 4.6% and 6.2% in women, respectively. Mortality rates of RA patients were 1.2 times higher in men and 1.3 times higher in women than those in the general population. Although cumulative 1-year mortality rates of all types of osteoporotic and spine fractures in both genders of RA patients were higher than those in the general population, those of hip, humerus, and distal radius fractures in RA patients were similar to or slightly lower than mortality rates in the general population (Table 3).

Average SMRs of osteoporotic fractures in those who aged 50 years or more in both groups were higher than general population. SMRs of osteoporotic fractures in RA patients for those in their 60s were the highest in both genders. SMR of osteoporotic fracture in RA patients was 1.4 times higher in men and 1.3 times higher in women. In assessment of gender-specific differences, SMR in men

with RA was higher than that in women with RA (Table 4).

## DISCUSSION

The objective of the current study was to investigate the incidence and mortality of RA patients with osteoporotic fractures, including hip, spine, distal radius, and proximal humerus, and compare them with those in the general population (matched for gender and age) from 2010 to 2012. Using data from KNHIS, our results demonstrated that the number of osteoporotic fracture in RA patients was increased by 17.4% over 2010 to 2012 period. Incidence of osteoporotic fracture in RA patients was 2.3 times higher in men and 1.4 times higher in women than that in the general population for the period of 2010 to 2012. Although crude mortality and SMR of osteoporotic fracture in RA patients were higher than crude mortality and SMR of osteoporotic fracture in the general population, those of individualized type of fractures (including hip, distal radius, and proximal humerus) were diverse compared to those in

**Table 2.** Age-specific mean-incidence (per 100,000) of osteoporotic fracture in Korean over 50 years old and patients with rheumatoid arthritis

	No. of fracture in RA		RA patients		No. of fracture in general population		General population		Incidence of fracture among RA		Incidence of fracture	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Any type												
50-59	38	567	12,415	60,832	30,306	74,048	10,738,209	10,701,528	306.1	932.1	282.2	691.9
60-69	160	1,192	13,687	47,390	29,904	107,084	5,956,183	6,504,814	1,169.0	2,515.3	502.1	1,646.2
70-79	240	1,621	8,291	26,560	39,253	163,378	3,307,684	4,745,885	2,894.7	6,103.2	1,186.7	3,442.5
≥80	49	429	1,324	4,575	22,286	111,366	840,592	2,072,631	3,700.9	9,377.0	2,651.2	5,373.2
Total	487	3,809	35,717	139,357	121,749	455,876	20,842,667	24,024,857	1,363.5	2,733.3	584.1	1,897.5
Hip												
50-59	6	52	12,415	60,832	2,918	2,189	10,738,209	10,701,528	48.3	85.5	27.2	20.5
60-69	26	164	13,687	47,390	4,196	5,569	5,956,183	6,504,814	190.0	346.1	70.4	85.6
70-79	45	316	8,291	26,560	8,744	21,165	3,307,684	4,745,885	542.8	1,189.8	264.4	446.0
≥80	15	99	1,324	4,575	6,630	28,693	840,592	2,072,631	1,132.9	2,163.9	788.7	1,384.4
Total	92	631	35,717	139,357	22,488	57,616	20,842,667	24,024,857	257.6	452.8	107.9	239.8
Spine												
50-59	20	233	12,415	60,832	11,422	16,221	10,738,209	10,701,528	161.1	383.0	106.4	151.6
60-69	101	663	13,687	47,390	13,986	41,201	5,956,183	6,504,814	737.9	1,399.0	234.8	633.4
70-79	168	1,053	8,291	26,560	21,855	93,034	3,307,684	4,745,885	2,026.3	3,964.6	660.7	1,960.3
≥80	31	287	1,324	4,575	13,126	62,558	840,592	2,072,631	2,341.4	6,273.2	1,561.5	3,018.3
Total	320	2,236	35,717	139,357	60,389	213,014	20,842,667	24,024,857	895.9	1,604.5	289.7	886.6
Distal radius												
50-59	9	233	12,415	60,832	13,441	51,085	10,738,209	10,701,528	72.5	383.0	125.2	477.4
60-69	22	315	13,687	47,390	9,931	56,432	5,956,183	6,504,814	160.7	664.7	166.7	867.5
70-79	22	209	8,291	26,560	7,305	45,928	3,307,684	4,745,885	265.3	786.9	220.8	967.7
≥80	3	36	1,324	4,575	2,200	18,952	840,592	2,072,631	226.6	786.9	261.7	914.4
Total	56	793	35,717	139,357	32,877	172,397	20,842,667	24,024,857	156.8	569.0	157.7	717.6
Proximal humerus												
50-59	3	60	12,415	60,832	3,147	5,364	10,738,209	10,701,528	24.2	98.6	29.3	50.1
60-69	16	89	13,687	47,390	2,386	5,835	5,956,183	6,504,814	116.9	187.8	40.1	89.7
70-79	11	105	8,291	26,560	2,287	8,279	3,307,684	4,745,885	132.7	395.3	69.1	174.4
≥80	3	24	1,324	4,575	965	5,824	840,592	2,072,631	226.6	524.6	114.8	281.0
Total	33	278	35,717	139,357	8,785	25,302	20,842,667	24,024,857	92.4	199.5	42.1	105.3

RA, rheumatoid arthritis.

the general population.

Although many studies have reported the high risk of osteoporosis and related fracture in patients with RA, comprehensive studies on the incidence and mortality of osteoporotic fracture in patients with RA are limited due to relatively small number of RA patients.[7,15-17] In this retrospective observational study, mean incidence of osteoporotic fractures in those aged 50 years and older was 2,453.8/100,000 (1,363.5 in men and 2,733.3/100,000 in women) in RA patients and 1,287.4/100,000 (584.1/100,000 in men and 1,897.5/100,000 in women) in the general population. Most fracture studies regarding the incidence of

fractures in RA patients have reported results with short-term or long-term follow-up.[1,18-20] Kim et al.[21] have reported that, of 3,557 RA patients with a mean follow-up of 18 months, there are 152 osteoporotic fractures, including vertebrae, clavicle, humerus, wrist, femur, and ankle fractures. The estimated incidence of osteoporotic fracture was 2,926.3/100,000 person-year. Female RA patients had higher incidence of fractures than male RA patients (3,061.9 in females vs. 2,125.7 in males per 100,000 person-years). [21] Kim et al.[1] have performed a retrospective cohort study using a health care utilization database and reported that the incidence of osteoporotic fractures (including hip,

**Table 3.** Cumulative mean of one-year mortality of osteoporotic fracture in Korean over 50 years old and patients with rheumatoid arthritis

	No. of fracture in RA		No. of death in RA patients		No. of fracture		No. of death		Mortality of fracture in RA		Mortality of fracture	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Any type												
50-59	38	567	1	8	30,306	74,048	768	656	2.6	1.4	2.5	0.9
60-69	160	1,192	27	52	29,904	107,084	1,785	1,810	16.9	4.4	6.0	1.7
70-79	240	1,621	57	121	39,253	163,378	5,954	6,628	23.8	7.5	15.2	4.1
≥80	49	429	11	56	22,286	111,366	8,822	11,751	22.4	13.1	39.6	10.6
Total	487	3,809	96	237	121,749	455,876	17,329	20,845	19.7	6.2	14.2	4.6
Hip												
50-59	6	52	0	2	2,918	2,189	173	93	0.0	3.8	5.9	4.2
60-69	26	164	4	9	4,196	5,569	436	351	15.4	5.5	10.4	6.3
70-79	45	316	8	21	8,744	21,165	1,716	2,003	17.8	6.6	19.6	9.5
≥80	15	99	5	18	6,630	28,693	2,371	5,954	33.3	18.2	35.8	20.8
Total	92	631	17	50	22,488	57,616	4,696	8,401	18.5	7.9	20.9	14.6
Spine												
50-59	20	233	1	7	11,422	16,221	546	259	5.0	3.0	4.8	1.6
60-69	101	663	24	43	13,986	41,201	1,208	1,077	23.8	6.5	8.6	2.6
70-79	168	1,053	48	97	21,855	93,034	3,228	4,514	28.6	9.2	14.8	4.9
80+	31	287	7	41	13,126	62,558	3,245	7,090	22.6	14.3	24.7	11.3
Total	320	2,236	80	188	60,389	213,014	8,227	12,940	25.0	8.4	13.6	6.1
Distal radius												
50-59	9	233	0	1	13,441	51,085	118	105	0.0	0.4	0.9	0.2
60-69	22	315	0	2	9,931	56,432	140	224	0.0	0.6	1.4	0.4
70-79	22	209	2	7	7,305	45,928	297	705	9.1	3.3	4.1	1.5
≥80	3	36	1	1	2,200	18,952	259	1,434	33.3	2.8	11.8	7.6
Total	56	793	3	11	32,877	172,397	814	2,468	5.4	1.4	2.5	1.4
Proximal humerus												
50-59	3	60	0	0	3,147	5,364	106	65	0.0	0.0	3.4	1.2
60-69	16	89	0	0	2,386	5,835	121	132	0.0	0.0	5.1	2.3
70-79	11	105	1	7	2,287	8,279	233	368	9.1	6.7	10.2	4.4
≥80	3	24	1	4	965	5,824	220	871	33.3	16.7	22.8	15.0
Total	33	278	2	11	8,785	25,302	680	1,436	6.1	4.0	7.7	5.7

RA, rheumatoid arthritis.

pelvis, wrist, and humerus) is 9.6/1,000 (5.2/1,000 in men and 11.1/1,000 in women), which is 1.5 times higher than the rate in non-RA patients. Direct comparison for incidence of osteoporotic fracture between studies is difficult due to divergence in cohort characteristics, including age, gender, type of study, difference in follow-up periods, and various definitions of osteoporotic fracture.[1,18-21] In this study, incidence of wrist fracture in RA patients was lower than general population and it might be related with lower activity in RA patients. Despite these limitations, the incidence of osteoporotic fracture in RA patients is generally higher than that in the general population. In addition, women

have higher incidence of osteoporotic fracture than men. These gender specific characteristics in RA patients are similar to those in the general populations.

Studies regarding mortality rate after osteoporotic fracture in RA patients are rare. Lin et al.[16] have reported that cumulative mortality rates at 6-month and 1-year follow-up are significantly higher among patients with RA (9.47% and 18.47%, respectively) compared to those in the control (8.47% and 13.62%, respectively). It is difficult to assess cumulative mortality after osteoporotic fracture in RA patients due to the small number of death. In this study, we calculated mean mortality rate of 3 years (2010-2012)

**Table 4.** Standardized mortality rate of one-year mortality of osteoporotic fracture in Korean over 50 years old and patients with rheumatoid arthritis

	No. of fracture		No. of death		Mortality rate		SMR (95% CI)	
	Men	Women	Men	Women	Men	Women	Men	Women
RA patients								
50-59	38	567	1	8	2.6	1.4	4.53 (0.12-25.33)	7.15 (3.08-14.07)
60-69	160	1,192	27	52	16.9	4.4	13.01 (8.60-18.98)	9.04 (6.75-11.86)
70-79	240	1,621	57	121	23.8	7.5	6.34 (4.80-8.21)	4.14 (3.43-4.95)
≥80	49	429	11	56	22.4	13.1	1.91 (0.95-3.41)	1.53 (1.16-1.99)
Total	487	3,809	96	237	19.7	6.2	11.23 (9.04-13.63)	4.69 (4.11-5.33)
General population								
50-59	30,306	74,048	768	656	2.5	0.9	4.36 (4.06-4.68)	4.49 (4.15-4.84)
60-69	29,904	107,084	1,785	1,810	6.0	1.7	4.60 (4.39-4.82)	3.50 (3.34-3.67)
70-79	39,253	163,378	5,954	6,628	15.2	4.1	4.05 (3.95-4.15)	2.25 (2.20-2.30)
≥80	22,286	111,366	8,822	11,751	39.6	10.6	3.36 (3.29-3.43)	1.24 (1.22-1.26)
Total	121,749	455,876	17,329	20,845	14.2	4.6	8.11 (7.99-8.23)	3.45 (3.40-3.49)

RA, rheumatoid arthritis; SMR, standardized mortality ratio; CI, confidence interval.

due to a small number of mortality. Cumulative mortality rate after osteoporotic fracture in RA patients at 1 year follow-up was 19.7% in men and 6.2% in women. They were higher than those in the general population (14.2% in men and 4.6% in women). Although cumulative mortality after spine fracture in RA patients had similar pattern (higher than that in the general population), cumulative mortalities after hip, distal radius, and proximal humerus in RA patients were similar to or slightly lower than those in the general population. Among osteoporotic fractures in both groups (RA patients and general population), mortality rate after hip fracture was the highest, followed by that after spine, proximal humerus, and distal radius fractures in order.[13,14,22,23] Mortality after spine fracture in RA patients was higher than mortality after hip fracture. This finding is different from mortality after osteoporotic fractures in general populations. It is possible to explain relatively young ages of RA patients and characteristics of cohorts.

This study has some limitations. First, this was a retrospective and cross-sectional study using nationwide claim database with possible selection bias. Second, this study defined RA patients as those who received specific code of rare disease while seronegative RA patients were excluded. Therefore, the incidence of fracture might have been underestimated. Finally, mortality rates of osteoporotic fracture in RA patients were compared to mortality rates of an age matched general population which included some osteoporotic fracture patients. This might potentially cause

underestimation of excess mortality.

## CONCLUSIONS

This study demonstrated that the incidence, 1-year mortality, and SMR of osteoporotic fracture in RA patients aged 50 and older were higher than those in the general population.

## DECLARATIONS

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### Conflict of interest

No potential conflict of interest relevant to this article was reported.

### ORCID

Hye-Young Kwon <http://orcid.org/0000-0001-9772-1354>

Yoon-Kyoung Sung <http://orcid.org/0000-0001-6691-8939>

Yong-Chan Ha <http://orcid.org/0000-0002-6249-0581>

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