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ORIGINAL ARTICLE

Prevalence and incidence of rheumatoid arthritis in South Korea

Yoon-Kyoung Sung · Soo-Kyung Cho · Chan-Bum Choi · Sang-Cheol Bae

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Abstract Several studies of rheumatoid arthritis (RA) incidence and prevalence indicate that occurrence of the disease varies significantly among different populations. We aimed to estimate the prevalence and incidence of RA in South Korea. We used Korean National Health Insurance (NHI) claims data to estimate the prevalence of RA in 2007–2009 and the incidence of RA in 2008. On the basis of our previous validation study, the presence of RA was defined by the diagnostic code for RA with biologic or non-biologic disease-modifying anti-rheumatic drugs in the same claim in each year. To estimate the incidence of RA, we identified cases of RA in 2008 and set the 12-month period prior to 2008 as a disease-free period. Among the incident case of 2008, only patients who continued treatment in 2009 were defined as true incident case of RA in 2008. The corresponding prevalence estimates were 0.26 % (95 % CI 0.25–0.27) in 2006, 0.27 % (95 % CI 0.26–0.28) in 2007, and 0.27 % (95 % CI 0.26–0.28) in 2008. The incidence of RA in 2008 was estimated at 42/100,000 (95 % CI 29.3–54.7) in the general population of South Korea. Data gathered nationwide through the NHI yielded estimates of RA prevalence and incidence in South Korea. This study is the first report of nationwide prevalence and incidence of South Korea and those are comparable to values for other countries in Asia.

Keywords Prevalence · Incidence · Rheumatoid arthritis · Korea

Yoon-Kyoung Sung and Soo-Kyung Cho contributed equally to this work and are joint first authors.

Y.-K. Sung · S.-K. Cho · C.-B. Choi · S.-C. Bae (✉)
Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul 133-792, South Korea
e-mail: scbae@hanyang.ac.kr

Introduction

Rheumatoid arthritis (RA) is one of the principal chronic autoimmune diseases. An extensive review of epidemiological studies found that among adult white populations of Europe and America, the prevalence of definite or classical RA by the 1958 ARA or 1987 ACR criteria is approximately 1 %. The corresponding incidence of RA among white populations is about 0.03 % per annum [1].

Other studies of RA incidence and prevalence indicate that occurrence of the disease varies significantly among different populations [2–5]. The prevalence of RA in rural African was low with 0.0026 % [3], while the RA prevalence was extremely high with 6.8–7.1 % in American Indian [4, 5]. Through this geographical difference, genetic and environmental factors have been implicated as risk factors for development of RA [6]. However, descriptive studies may be difficult to compare due to methodological differences in terms of case identification and ascertainment [2]. Prevalence estimates based on regional or small nationwide samples indicate variations in RA prevalence according to the socioeconomic position, geographically defined population segments, urban or rural residence and educational level [7]. In a study performed in 2008, the prevalence of RA in South Korea was estimated to be 1.9 % based on the Korean National Health and Nutrition Examination Survey (KNHANES) data from 2005 [8]. However, this estimate was based on patient reporting and represented only a subsample of the population. Moreover, the incidence of RA in South Korea has not been reported. Thus, we recognized the need for a new, reproducible method to estimate both RA prevalence and incidence.

In South Korea, the Korean National Health Insurance (NHI) database holds the medical and prescription claims data for almost 100 % of the population. As a function of

the mandatory universal health insurance system, the NHI database serves as a centralized health care information resource for use nationwide. We used the Korean NHI claims database to estimate the prevalence of RA from 2007 to 2009 and the incidence of RA in 2008. We also described the trend of disease-modifying anti-rheumatic drugs (DMARDs) use for RA nationally.

Methods

Data sources and study population

The Korean National Health Insurance (NHI) claims database

This study was conducted using data from the Korean NHI claims database. Large computerized administrative and claims datasets compiled by the Health Insurance Review and Assessment (HIRA) agency, Seoul, South Korea, are made available to investigators for research purposes after personally identifying information is removed. In this study, we used the inpatient and outpatient claims dataset from the NHI database. The source population for this study comprised all beneficiaries aged 16 years or older during 2007–2009. Demographic data, including age and sex, information about physicians and hospitals, comorbidities described by diagnostic codes, prescribed medications, and other parameters for years 2007 to 2009 were retrieved. All data were deidentified to ensure patient confidentiality. The HIRA Research Ethics Committee of South Korea approved the protocol of this study.

Definition of RA

All claims for outpatient visits or hospital admissions of patients aged 16 years or older containing a diagnostic code for RA (ICD-10 code: M05 or M06) were identified and retrieved from the Korean NHI claims database. A separate validation study was performed to confirm RA in the patients identified in our NHI claims database [9]. In this previous study, we found that a claim that includes both an RA diagnostic code (ICD-10 code: M05 or M06) and a prescription for a biologic agent or any DMARD can identify a patient as having definite RA with high sensitivity (96.5 %), high positive predictive value (PPV, 92.4 %), moderate specificity (58.7 %), and relatively good comparability ratio (1.04) for true RA patients [9].

We identified as incident cases all persons entered into the database from January 2007 to December 2009, according to our case definition as incident cases. The 12-month period prior to 2008 (i.e., January–December, 2007) was set as a "disease-free period" such that a patient was defined as an incident case only if their first record of a visit or admission for RA was observed after this 12-month period (i.e., during 2008). Since most of the follow-up treatments for RA last longer than 1 year after the initial diagnosis, we defined any patient who had a claim for an RA diagnostic code that included a biologic drug or any DMARD in the following year (January–December, 2009) as a true incident case of RA. Under this definition, we could estimate only the incidence of RA in 2008 in this study.

Statistical analysis

Data were analyzed using SAS software (version 9.1, SAS Institute, Cary, NC, USA). Prevalence of RA during 2007–2009 and 95 % confidence interval (CI) were calculated overall, by sex, and by age. Age- and sex-specific annual incidence rates of RA per 100,000 inhabitants for the year 2008 and 95 % CI were calculated for ten-year age intervals. The number of inhabitants in South Korea, as of 2007–2009, was obtained from the Korean National Statistical Office. The age-standardized incidence rate was computed using the 2008 mid-year population estimate.

In order to identify the changes in the use of DMARDs during 2007–2009, we divided the study period into six-month intervals and analyzed the first prescription records for all defined RA patients in each period.

Results

Prevalence of RA in South Korea

Using our predefined operational definition of RA (any DMARD or biologic drug with a diagnostic code for RA in the same claim), these estimates for RA prevalence were 0.26 % (95 % CI 0.25–0.27) in 2007, 0.27 % (95 % CI 0.26–0.28) in 2008, and 0.27 % (95 % CI 0.26–0.28) in 2009. The demographic features of RA patients in each year are shown in Table 1. The mean (SD) ages of these patients were 52.6 (13.7), 53.4 (13.6), and 53.9 (13.5) years, and the numbers (proportions) of female patients were 98,136 (78.3 %), 103,732 (78.6 %), and 105,975 (79.0 %) in 2007, 2008, and 2009, respectively. In the age-stratified analysis, the crude overall prevalence of RA increased during 3 years of follow-up, especially in the age group less than 50 years old, and prevalence decreased during the three years in the age group older than 60 years (Fig. 1).

In 2008, the nationwide cumulative prevalence of RA was 0.27 %, and it peaked at 0.73 % between the ages of 60 and 69 years. Women showed a higher prevalence than men in all age groups; overall prevalence ratio is 3.7, but

Table 1 Baseline characteristics of RA patients

Characteristics	2007 (n = 125,320)	2008 (n = 131,999)	2009 (n = 134,161)
Age, mean ± SD (range), years	52.6 ± 13.7 (16–97)	53.4 ± 13.6 (16–97)	53.9 ± 13.5 (16–99)
Female, number (%)	98,136 (78.31)	103,732 (78.59)	105,975 (78.99)
Number of claims for RA per 6 months, mean ± SD (range)	6.93 ± 7.46 (1–187)	7.46 ± 9.98 (1–328)	7.50 ± 9.66 (1–307)
Payer type			
National Health Insurance, number (%)	116,151 (92.68)	122,192 (92.57)	124,711 (92.96)
Medicaid, number (%)	9,169 (7.32)	9,807 (7.43)	9,450 (7.04)
Type of institutions, number (%)			
Tertiary hospitals	22,189 (17.71)	22,692 (17.19)	23,996 (17.89)
General hospitals	16,111 (12.86)	17,380 (13.17)	16,880 (12.58)
Community hospitals/clinics	87,020 (69.44)	91,927 (69.64)	93,285 (69.53)
Physician's specialties (first RA claims), number (%)			
Internal medicine	58,348 (46.56)	60,529 (45.86)	62,675 (46.72)
Other	66,972 (53.44)	71,470 (54.14)	71,486 (53.28)

RA rheumatoid arthritis, *SD* standard deviation

the prevalence ratio decreased from 4.6 in the age interval 50–59 years to 1.2 in the youngest age group.

Incidence of RA in South Korea

During the one-year observation period from January through December 2008, there were 20,592 incident cases of RA in persons aged 16 years and older in South Korea, including 16,006 females (77.7 %) and 4,586 males (22.3 %). The mean (SD) age was 52.10 (13.83) years. The mean (SD) age was lower in men (50.95 (15.37) years) than in women (52.43 (13.34) years). The age-standardized annual incidence of RA was 42 per 100,000 (95 % CI 29.3–54.7), with 65 per 100,000 women (95 % CI 49.2–80.8) and 19 per 100,000 men (95 % CI 10.5–27.5), yielding a female/male ratio of 3.4. RA incidence increased with age, from 7 per 100,000 for the youngest group, 16–19 years old, to 109 per 100,000 for the group aged 60–69 years. The incidence of RA peaked in the age interval 60–69 years for both women and men. Women had a higher incidence than men in all age groups, but the incidence ratio decreased from 4.6 in the group 50–59 years old to 1.3 in the oldest group, aged 80–89 years (Table 2).

Trends in use of biologic drugs and DMARDs, 2007–2009

Trends in DMARD and biologic drug use for the years 2007 through 2009 are presented in Fig. 2. The prevalence of biologics use by RA patients increased from 0.84 % in the first half of 2007 to 1.91 % in the second half of 2009. Among the non-biologic DMARDs, the most commonly prescribed drug was hydroxychloroquine (HCQ), which was used by 47.4–50.4 % of patients, followed by

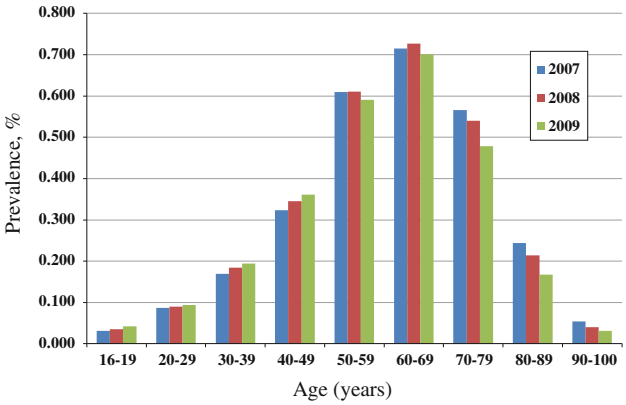

Fig. 1 Age-stratified RA prevalence in South Korea

methotrexate (MTX), which was used by 36.0–40.9 % of RA patients. During the same period, the prevalence of leflunomide (LFN) use increased from 5.9 to 11.5 %. More than 33 % of all patients received DMARDs as combination therapy. Since 2007, the MTX-plus-HCQ regimen was used most commonly (10.7–11.1 %), followed by MTX plus SSZ (3.5 %) in 2007 and MTX plus LFN (3.6–6.41 %) in 2008–2009. The most commonly prescribed triple DMARD during 2007–2009 was the combination of MTX, HCQ, and SSZ (4.5–4.8 %).

Discussion

This is the first nationwide, population-based, epidemiologic study of RA in South Korea to be performed using NHI claims data. The estimates of RA prevalence during 2007–2009 were 0.26–0.27 %, which are lower than the estimate from an earlier study of individuals residing in

Table 2 Sex- and age-specific annual incidence rates of RA in South Korea in 2008

Age (years)	Total			Female			Male			Female/male ratio of incidence
	Number of population 2008	Number of RA patients	Incidence per 100,000 (95 % CI)	Number of population 2008	Number of RA patients	Incidence per 100,000 (95 % CI)	Number of population 2008	Number of RA patients	Incidence per 100,000 (95 % CI)	
0–14	8,641,833	0	0 (NC)	4,120,184	0	0 (NC)	4,521,649	0	0 (NC)	NC
15–19	3,359,505	232	7 (1.8–12.2)	1,579,662	128	8 (2.5–13.5)	1,779,843	104	6 (3.5–8.5)	1.3
20–29	7,273,832	1,053	14 (6.7–21.7)	3,522,600	691	20 (11.2–28.8)	3,751,232	362	10 (3.8–16.2)	2.0
30–39	8,570,850	2,639	31 (20.1–41.9)	4,204,411	1,944	46 (32.7–59.3)	4,366,439	695	16 (8.2–23.8)	2.9
40–49	8,602,965	4,585	53 (38.7–67.3)	4,225,095	3,710	88 (69.6–106.4)	4,377,870	875	20 (11.2–28.8)	4.4
50–59	5,991,652	5,646	94 (75.0–113.0)	2,989,520	4,634	155 (130.6–179.4)	3,002,132	1,012	34 (22.6–45.4)	4.6
60–69	3,909,751	4,266	109 (78.5–129.5)	2,072,525	3,247	157 (132.5–181.5)	1,837,226	1,019	55 (40.5–69.5)	2.9
70–79	2,269,327	1,918	85 (66.9–103.1)	1,375,533	1,460	106 (85.8–126.2)	893,794	458	51 (37.0–65.0)	2.1
80–89	701,201	251	36 (24.2–47.8)	491,541	190	39 (26.8–51.2)	209,660	61	29 (18.4–39.6)	1.3
90–100	83,744	2	2 (−0.8–4.8)	66,510	2	3 (−0.4–6.4)	17,234	0	0 (NC)	NC
Overall	49,404,660	20,592	42 (29.3–54.7)	24,647,581	16,006	65 (49.2–80.8)	24,757,079	4,586	19 (10.5–27.5)	3.4

RA rheumatoid arthritis, *CI* confidence interval, *NC* not countable

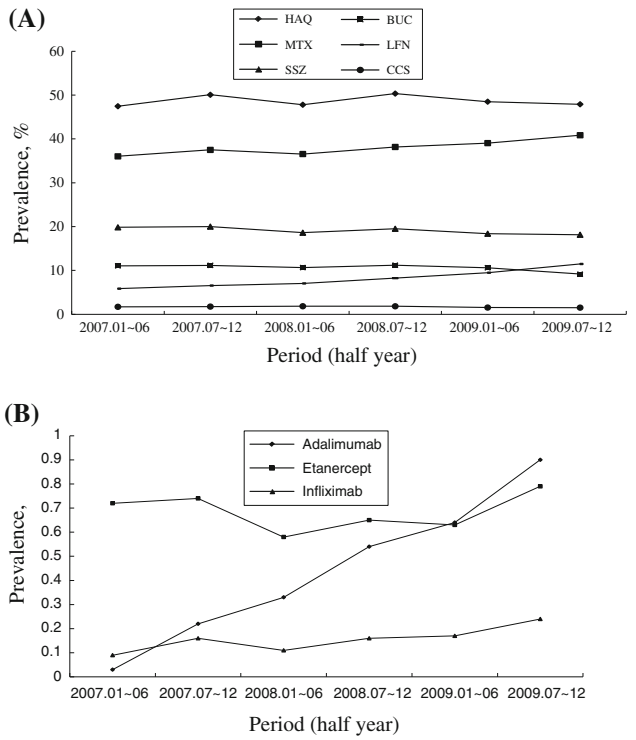

Fig. 2 Trends in biologic drug and DMARD use. **a** Prevalence of non-biologic DMARDs use. **b** Prevalence of biologic drugs use

selected regions of South Korea in 2005 (1.9 %) [8]. This difference in the estimated RA prevalence may be explained by differences in the data sources and analytical methods used to identify prevalent cases. In the earlier study, RA patients were identified using data from the KNHANES III conducted in 2005. The KNHANES is a nationwide cross-sectional study using a stratified, multistage probability sampling design to select household units. Annual self-reported RA prevalence in adults 19 years of age and older was determined using the Health Interview Survey in KNHANES. Among the prevalent RA patients identified in that study, only 43.1 % were receiving treatment. Applying this treatment rate to the prevalence of 1.9 % lowered the prevalence of actively treated RA patients to 0.8 %. This indicates that use of data from the self-reported questionnaire may overestimate the RA prevalence. The prevalence estimates based on the ICD-10 diagnostic code for RA in 2007, 2008, and 2009 were 1.4, 1.3, and 1.2 %, respectively. This decrease in prevalence with time is not reasonable and indicates the possibility of misdiagnosis or miscoding. To minimize this possibility, we defined the RA patient as one with an RA diagnostic code (ICD-10 code: M05 or M06) and the prescription for a biologic drug or any DMARD included in same claim. This operational definition, obtained from an earlier validation study [9], showed high sensitivity (96.5 %), PPV (92.4 %), accuracy (90.3 %), specificity (58.69 %), and comparability ratio (1.04) in identifying actively treated RA patients in South Korea. Using this definition, the estimates of RA prevalence in South Korea for years 2007, 2008, and 2009 were 0.26, 0.27, and 0.27 %, respectively. This approach yields a quite conservative estimate of RA prevalence.

We also estimated the annual incidence rate for RA in South Korea for the first time. To define an incident case of RA, we set the 12-month period prior to 2008 (i.e., January–December, 2007) as a "disease-free period," and any patient who had a claim that included an RA diagnostic code with a prescription for a biologic drug or any DMARD in 2008 was defined as an incident case. Although it might be estimated incidence rate conservatively under this definition, it is reasonable because about 98 % patients have taken biologic drug or any DMARDs in

Table 3 RA prevalence and incidence worldwide (cases per 100 inhabitants)

Population	Nation	Reference	Incidence	Subjects/methods	Prevalence	Subjects/methods
North America	USA	[11]	0.075	425 residents/inception cohort of Rochester, Minnesota residents	1	425 residents/inception cohort of Rochester, Minnesota residents
		[12]	0.044 (0.032–0.061)	609 patients/inception cohort of Rochester, Minnesota residents	N/A	N/A
Northern Europe	Norway	[13]	0.028	Records were reviewed at the university hospital in the county of Troms, northern Norway	0.39–0.47	Records were reviewed at the university hospital in the county of Troms, northern Norway
		[20]	N/A	N/A	0.51	3,928 subjects/as a random sample of the population in two communities in the county of Halland
		[14]	0.024	Prospective referral study in Kronoberg County in southern Sweden	N/A	N/A
	Sweden	[15]	0.05	Inpatient and outpatient health care is registered in the Skane Health Care Register (SHCR)/in the southernmost county of Sweden	0.66	Inpatient and outpatient health care is registered in the Skane Health Care Register (SHCR)/in the southernmost county of Sweden
		[21]	N/A	N/A	0.77	National patient register and the Swedish rheumatology quality register
	England	[22]	N/A	N/A	0.44 in men 1.16 in women,	Stratified random sample, 7,050 individuals/matched against NOAR(Norfolk Arthritis Register)-incident cases of inflammatory polyarthritis
		[16]	0.015 in men 0.036 in women	Prospective population-based register in Norwich Health Authority	N/A	N/A
	Ireland	[23]	N/A	N/A	0.5	2,500 people chosen at random/ electoral register.
	Finland	[17]	0.04	Nationwide registers	0.8	Nationwide registers
Southern Europe	Spain	[24]	N/A	N/A	0.5	2,998 selected randomly/20 municipalities
	France	[18]	0.008	In the Lorraine district, eastern France	N/A	N/A
	Italy	[25]	N/A	N/A	0.33	4,456 subjects/in Chiavari, a small town located on the Ligurian coast
	Greece	[19]	0.015–0.036	Records of patients at rheumatology clinics/Ioannina in northwest Greece	0.23	Records of patients at rheumatology clinics/Ioannina in northwest Greece
		[26]	N/A	N/A	0.27	2,100 subjects randomly selected/in 1 suburban, 1 rural communities
	Yugoslavia	[27]	N/A	N/A	0.18	2,184 subjects, randomly selected/ the urban population of Belgrade
South America	Argentina	[28]	N/A	N/A	0.19	Outpatients and hospitalization medical records were reviewed/in Tucuman province in northwest Argentina
	Brazil	[29]	N/A	N/A	0.5	3,038 people/sampling

Table 3 continued

Population	Nation	Reference	Incidence	Subjects/methods	Prevalence	Subjects/methods
Asia	Japan	[32]	0.008–0.039	3,000 subjects/in the Kamitonda district, Wakayama	0.24–0.54	3,000 subjects/in the Kamitonda district, Wakayama
	China	[33]	N/A	N/A	0.28	7,603 subjects randomly selected from 13 communities/in Shanghai
	Hong Kong	[34]	N/A	N/A	0.35	2,000 subjects in 2 housing blocks/ urbanized Chinese of Hong Kong,
	Indonesia	[35]	N/A	N/A	0.2 in rural 0.3 in urban	4,683 rural subjects and 1,071 urban subjects
Middle East	Oman	[30]	N/A	N/A	0.36	1,925 subjects, a house-to-house survey/in Sultanate, representative areas of Oman
	Turkey	[31]	N/A	N/A	0.49	2,887 subjects/urban area in Izmir
Africa	South Africa	[3]	N/A	N/A	0.0026	543 subjects/in Venda, a very remote part of South Africa

N/A not available

RA patients within first year after their diagnosis in our nationwide RA cohort named for the KORean Observational study Network for Arthritis (KORONA, $n = 4{,}721$) [10]. The age-standardized annual incidence rate for the entire population of South Korea older than 16 years in 2008 was estimated to be 42 per 100,000 inhabitants (95 % CI 29.3–54.7), which represents 65 per 100,000 women (95 % CI 49.2–80.8) and 19 per 100,000 men (95 % CI 10.5–27.5), and yields a female/male ratio of 3.4. This sex ratio was comparable to that for RA prevalence in 2008 (3.67) but lower than that for KORONA (5.67). The incidence rate peaked in the age interval 60–69 years, which differs from the peak age at onset in the KORONA database (50–59 years). This difference may represent the time gap between symptom onset and diagnosis of RA by a physician because onset age is estimated as the time at which a patient reports symptoms in a questionnaire, while claims data show only the dates of a patient's clinic visits and dates on which their RA medications began.

Several population-based studies in England, Northern Europe, and the United States have reported RA prevalence and incidence rates (Table 3). The annual RA incidence rates vary between 24 and 75 cases per 100,000 inhabitants in North American and Northern European countries [11–17]. The few studies from countries in Southern Europe report incidence rates of 8–36 new cases per 100,000 inhabitants per year [18, 19]. Estimates of RA prevalence in Northern Europe and North America range from 0.5–1.1 % [11, 13, 15, 17, 20–23]. RA prevalence from the studies of the South America (0.2–0.5 %), Southern Europe (0.2–0.5 %), and the Middle East (0.4–0.5 %) shows lower than in Northern Europe and North America [24–31]. In Asia, a few population-based studies in Japan, China, Hong Kong, and Indonesia estimate RA prevalence at 0.2–0.5 %, lower than in Western countries [32–35]. A single study of RA incidence in Japan shows 8–39 cases per 100,000 inhabitants [32]. Our prevalence estimate of 0.27 % and incidence rate of 42 cases per 100,000 are comparable to values for Japan and other Asian countries, though all of the studies except ours were of regional rather than nationwide extent. Using a nationwide approach, Neovius et al. [21] reported the cumulative RA prevalence for 2008 as 0.77 % and the corresponding prevalence of RA patients identified by use of DMARDs as 0.49 % in Sweden, which is higher than our prevalence estimate (0.27 %) in 2008.

We were unable to identify the distribution of specific anti-rheumatic drug use because all of our RA patients were predefined by their prescription for any biologic drug or DMARD. We therefore evaluated trends for DMARD use in the treatment of RA in South Korea during 2007–2009. Distinct features of these trends included marked increases in the use of biologic agents and leflunomide. Until 2009, only three anti-TNF agents (adalimumab, etanercept, and infliximab) had been approved by the Korean FDA for MTX-resistant RA patients, and rituximab is the only biologic agent for RA refractory to anti-TNF agents. In 2010, abatacept was approved in South Korea, and other biologics such as certolizumab pegol, golimumab, and tocilizumab were close to approval. Therefore, the use of biologic agent and their impact on health insurance and patient outcome are likely to increase.

The strengths of our study included the use of a nationwide database, which provided a large sample size, recently collected data, and documentation of drug use by RA patients. However, several methodological issues arise from studies that use administrative claims data. First, not all patients with RA have access to hospitals.

The incidence based on insurance claims records would be underestimated if many RA patients in South Korea were either not diagnosed or treated in health care institutions. In practice, we have an alternative health care system of traditional Korean medicine, and patients who have musculoskeletal symptoms tend to visit those clinics. However, due to the mandatory universal health insurance system of South Korea, doctors in clinics and hospitals are highly accessible. It is believed that virtually, all symptomatic RA patients eventually present to health services. Second, the reliance on ICD-10 diagnostic codes to identify incident cases may result in misclassification through the voluntary or involuntary miscoding that is inherent in data recorded in claims. For this reason, we performed a validation study of RA patient identification based on NHI database claims [9]. This study revealed that claims that included both an RA diagnostic code and a prescription for biologics or any DMARD identified actively treated RA patients in South Korea with high accuracy (90.3 %). This approach was quite conservative because it is likely that a number of RA patients who have no evidence of the disease on a prevalence date as a result of successful treatment were excluded. Additionally, there still remains a possibility that the incidence in old people has been underestimated, as previous research reported that older-onset RA patients have received less aggressive treatment [36]. However, underestimation is usually more acceptable than overestimation in the epidemiologic studies, and therefore, we believe that this kind of approach was reasonable.

In conclusion, this study is the first report of nationwide prevalence and incidence of South Korea and those are comparable to values for other countries in Asia. We believe that these estimates are robust and generalizable and provide the best currently available information on the epidemiology of RA in South Korean population.

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Conflict of interest None.

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