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Review Article

Epidemiology of Rheumatoid Arthritis in Korea

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Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterised by symmetrical involvement of the joints, associated extra-articular manifestations and functional disability. In Korea, several epidemiologic studies reporting prevalence and incidence rates of RA have been conducted using large databases such as claims databases, national surveys, prospective cohort databases or electronic health records; according to these data sources, the estimated prevalence ranged from 0.27% to 1.85%. The prevalence of extra-articular manifestations such as interstitial lung disease (ILD) and Sjögren's syndrome (SS) were also reported, but an issue of external validity of the study results persisted. In this review, we detail the epidemiology of Korean RA patients, focusing on the prevalence of RA and the frequency of systemic extra-articular manifestations including ILD and SS reported in previous studies. In addition, we discuss the current methodological issues which are inherent in Korean epidemiologic studies for patients with RA with understanding of the characteristics of each database. **(J Rheum Dis 2021;28:60-67)**

Key Words. Rheumatoid arthritis, Epidemiology, Comorbidity, Data sources

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterised by symmetrical involvement of the peripheral joints, associated extra-articular manifestations, functional disability and increased mortality if treated inadequately. RA is present worldwide, with an estimated prevalence of 0.5% to 2%, and both the incidence and prevalence of RA are two to three times greater in females than males [1].

In the past two decades, paradigm shifts for the diagnosis and management of RA have been revolutionised by a greater understanding of the pathogenic mechanisms and the development of new targeted therapies. Serum anti-citrullinated protein antibodies (ACPAs) and rheumatoid factor (RF) play a role as prognostic biomarkers as they are routinely checked in patients with suspected RA. According to the profiles of the presence or absence of autoantibodies (immunoglobulin M RF and/or ACPAs), the disease can be classified into the categories of seropositive RA and seronegative RA, respectively [2]. Studies on RA have highlighted new disease-associated genes and environmental factors and explained the pathogenesis of RA clearly. This progress contributes to develop targeted biologic agents and small-molecule inhibitors. Much of this work has enabled the expansion of treatment options and earlier treatment intervention.

Although the hallmark clinical manifestation of RA is painful inflammatory arthritis, extra-articular manifestations contribute to excess morbidity and mortality [3]. Rheumatoid nodules and osteoporosis are relatively common manifestations, and systemic manifestations such as vasculitis, Sjögren's syndrome (SS) or pulmonary fibrosis also occasionally appear. However, the frequency of extra-articular manifestations in RA differs between countries, and their incidence and prevalence rates vary according to study design [4]. In this review, we detail the epidemiology of Korean patients with RA, focusing on its prevalence and the frequency of systemic extra-articular manifestations, such as interstitial lung disease (ILD)

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and SS, reported in previous studies. In addition, we discuss the methodological issues that exist in Korean epidemiologic studies for patients with RA.

MAIN SUBJECTS

Prevalence and incidence rate of RA in Korea

1) Prevalence of RA

Seven studies have reported the prevalence of RA in Korea [5-11]. The prevalence of RA in Korea ranges from 0.27% to 1.85% and the female-to-male ratio is between 2.7:1 and 13.5:1 (Table 1). The prevalence of RA in each Korean study is different according to the methodology as well as the case definition of RA employed; however, all of the included studies employed a cross-sectional design in a population-based cohort investigation. Interestingly, the prevalence was less than 0.5% as the studies were performed based on national health insurance (NHI) claims data, though the prevalence exceeds 1.4% if the case definition of RA was defined by patient-reported questionnaire.

2) Incidence of RA

There were three studies found that assessed the incidence of RA in Korea [7,8,12], all of which used the NHI claims database; two included all beneficiaries of national healthcare insurance and the third study considered a cohort of one million Koreans based on the NHI claims database. All three studies used an operational definition for RA, including diagnostic codes of RA (M05 with or without M06) and any disease-modifying antirheumatic drug (DMARD) prescription. Among them, two studies were performed by our group and the latter one was an updated version of the first study. According to this study,

Table 1. Epidemiologic studies of the prevalence of patients with RA in Korea

Study	Prevalence (%)	Female/ Male ratio	Study period (yr)	Diagnostic criteria	Number of study population	Age of study population
Hur et al. 2008 [5]	1.85% (95% CI 1.66～2.04)	2.7	2005	Questionnaire	33,805	≥19
Park et al. 2003 [6]	1.40% (95% CI 0.68～2.17)	13.5	2000	ACR 1987 revised criteria	983	Mean age 49.9±14.0
Won et al. 2018 [7]	0.32%	3.6	2009～2012	Operational definition	All beneficiaries	19～99
Sung et al. 2013 [8]	0.27% (95% CI 0.26～0.28)	3.7	2007～2009	Operational definition	All beneficiaries	≥16
Kwon et al. 2012 [9]	1.45% (95% CI 1.27～1.64)	3.7	2007～2009	Questionnaires	17,311	≥19
Kim et al. 2020 [10]	0.19% (95% CI 0.188～0.189)	4.3	2012～2016	Operational definition (seropositive only)	All beneficiaries	19～99
Jeong et al. 2017 [11]	1.50%	3.3	2010～2012	Questionnaires	17,887	≥19

RA: rheumatoid arthritis, CI: confidence interval, ACR: American college for rheumatology.

Table 2. Epidemiologic studies of the incidence of patients with RA in Korea

Study	Incidence (PY or persons)	Female/ Male ratio	Study period (yr)	Diagnostic criteria	Number of study population	Age of study population
Won et al. 2018 [7]	28.5/100,000 PY	3.5	2010	Operational definition	All beneficiary	19～99
Sung et al. 2013 [8]	42.0/100,000 persons (95% CI 29.3～54.7)	3.4	2008	Operational definition	All beneficiary	≥16
Choi et al. [12]	16.5/100,000 PY Seropositive RA	3.4	2002～2013	Operational definition (seropositive only)	1 million cohort	All ages

RA: rheumatoid arthritis, CI: confidence interval, PY: person-year.

the incidence of Korean patients with RA was 28.5/100,000 person-years and the female-to-male ratio was about 3.5 [7,8] (Table 2). When compared with the incidence of RA in East Asian countries, which ranges from 15.8 to 42.0 per 100,000 people [13-18], the incidence rate of RA patients in Korea was comparable. The other study performed by Choi et al. [12] was not a definite epidemiologic study, but the authors selected the incidence cases of RA between 2002 and 2013 to calculate the mortality, disability and healthcare expenditures of patients with RA. However, they include only seropositive RA patients, and their incidence rate was only 16.5/100,000 person-years [12].

3) Data sources of epidemiologic study for RA in Korea

Using the claims data, we could estimate healthcare utilization and healthcare costs macroscopically, and assess distribution of certain diseases, treatment patterns, as well as clinical outcome of specific drug and disease in real world. Korea utilized universal mandatory health insurance system which offers claims data characterised as an enormous, detailed amount of information. Even though it represents the status of a nationwide large population, errors such as inaccurate diagnosis codes may occur when it is utilized in epidemiologic studies. Park et al. [23] reported inconsistency in major and minor diagnoses of RA in medical records compared to the claims databases as 58.6% and 38.4%. A patient selection according to the diagnostic code is not sufficient enough to identify overall RA patients in claims databases [19-23].

Several years ago, we compared the diagnostic validity between several algorithms for identifying RA patients in the NHI claims database [24]. We found that patients having at least one claim in a year with a prescription of biologics or any DMARD under an RA code had high sensitivity and accuracy rates and a positive predictive value (PPV) of 96.46%, 90.33% and 92.35%, respectively, when the fulfilment of more than four of the 1987 American College of Rheumatology (ACR) classification criteria for RA was adopted as the gold standard. There is a limitation in the possibility of a false-negative result when using our algorithm; RA patients without any history of DMARDs might be excluded if they had a successful treatment response or were pregnant. However, our approach was rational because a conservative approach is generally acceptable for estimating the prevalence, incidence or outcomes in epidemiologic studies.

Electronic health records (EHRs) are generated by clinician and it contains a comprehensive information for patient's health state and treatment. EHRs present mixtures of structured information including diagnoses, physical examinations, radiologic/laboratory test results or management as well as unstructured notes. Although these data contain more detailed clinical information than a claims database in general, data are often inaccurately coded with substantial missing and even informatively missing information [25]. The claims and EHR records of each person are started when they participate in a health system or are first treated under a health system and stop when they leave the health system or dies. Claims data could define a particular population at a certain time point, while EHR data are more complicated to use to identify the population under specific care of interest at any point in time. These censoring issues may affect the estimation of the prevalence and incidence of chronic diseases.

Another data source is the Korea National Health and Nutrition Examination Survey (KNHANES), which is a nationwide cross-sectional study of selected sample of the Korean population. This survey employed a stratified multistage design based on age, sex and residence geographic area [19,21-23] and provides a presentative and cost-efficient method to collect clinical data in the form of self-report questionnaires.

Although EHRs are restricted for the latest records and under-reporting of conditions before admission [25,26], they provide a mixture of primary data including comprehensive information of both patient self-reporting and physicians' documentation [25-27]. Self-reports and EHR reviews are still the most common methods of assessment due to their availability, efficiency and relatively low cost [28]. Several studies have indicated that the corporate use of comorbidity data-collection methods using both sources is required to analyse or predict certain health outcomes [25,26,29,30]. However, self-reports and EHRs is still inconsistent. Previous studies have compared the two data sources in terms of assessing medical history, medication use and other risk factors [9,11,19,28]. The agreement level varied from high to low depending upon the variables in the comparison and the study populations [26-31].

Seropositivity of Korean patients with RA

1) Proportions of seronegative RA

The identification of RF and ACPAs has contributed to

the classification of the subgroups of seropositive and seronegative RA, respectively [32]. Previously, seropositivity was defined in terms of RF, especially as we used the 1987 ACR classification criteria. A seronegative status means that tests do not show the presence of RF. Following the introduction of the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA, the meaning of a seronegative test result for RA changed to be when a person tests negative for both RF and ACPA. While most patients positive for ACPAs are also positive for RF, the RF antibody can occur in patients with many other conditions, including viral hepatitis and other rheumatic diseases. Conversely, ACPA is more specific for RA and is becoming the preferred test for making this distinction. Seropositive RA patients present certain genetic and environmental risk factors in common and have been observed to have more severe clinical presentations [33,34]. Seronegative RA has not been fully assessed, but evidence of genetic associations for ACPA-negative RA has been offered [35].

The largest Korean multicentre cohort, the Korean Observational Study Network for Arthritis (KORONA) database, had enrolled 4,721 RA patients who fulfilled the 1987 ACR classification criteria as of December 2010 [36]. This group had a mean age of 54.25±12.19 years and included 4,023 women (85.21%). Their RF positivity and ACPA positivity rates were 86.8% (4,098/4,719) and 83.9% (3,018/3,599), respectively. Meanwhile, recent data from the Korean College of Rheumatology Biologics (KOBIO) registry, a nationwide biologics registry, shows that RF positivity and ACPA positivity rates in RA patients on targeted therapy were 87.0% and 86.3%, respectively [37]. Among conventional synthetic DMARD users, RF positivity and ACPA positivity rates were slightly lower at 83.9% and 85.3%. This suggested that confounding by indication is another important issue in the observational-type study.

Another important point to consider when conducting analysis based on claims data is the inclusion of inaccurate diagnostic codes (unpublished data, Table 3). We selected all RA patients in Korea according to three definitions. If we selected RA patients with diagnostic codes only, the numbers of seropositive RA (M05) and seronegative RA (M06) cases in 2016 were 150,058 and 688,053, respectively. However, after applying the operational definition of a diagnostic code with any DMARD, the numbers of seropositive and seronegative RA cases decreased to 103,083 and 74,038, respectively. This shows that many of the patients with RA diagnostic codes are not taking any DMARDs and this phenomenon is more pronounced in seronegative RA patients. Patients who are negative for RF and ACPA may also have another form of inflammatory arthritis—such as psoriatic arthritis or a spondyloarthropathy. A definition of RA with diagnostic codes and inclusion in the rare and intractable disease registration (RIDR) program is most specific for RA patients since registration in the RIDR program by a physician is required. Therefore, the latter definition is useful for outcomes and pharmacoeconomic studies assessing definite RA patients. The limitation of this definition is that it would not be applicable to seronegative RA patients because only seropositive RA patients are able to be registered in the RIDR program in Korea.

2) Disease severity of seronegative RA

Until now, patients with seropositive RA are considered to be at greater risk for severe RA, but these tests could not accurately predict the prognosis of RA in each patient.

Table 3. Proportions of seropositive and seronegative RA patients using claims database based on their definitions

Year	Seropositive RA			Seronegative RA		
	Diagnostic code*	Diagnostic code with RIDR program†	Operational definition‡	Diagnostic code*	Diagnostic code with RIDR program†	Operational definition‡
2012	112,983 (224.4)	70,276 (139.6)	79,337 (157.6)	646,459 (1,284.1)	NA	69,709 (138.5)
2016	150,058 (293.6)	96,330 (188.5)	103,083 (201.7)	688,053 (1,346.3)	NA	74,038 (144.9)

Values are presented as number (prevalence). Prevalence presented as n/100,000 persons. RA: rheumatoid arthritis, NA: not applicable, RIDR: Rare Intractable Disease registration, ICD: International Classification of Diseases, DMARD: disease-modifying antirheumatic drug. *Estimated prevalence by ICD-10 diagnostic codes. †Estimated prevalence by diagnostic codes which was applicable to RIDR program. ‡Operational definition of RA was confined to prescription of any DMARDs under specific diagnostic codes (M05.X) at least once for each calendar year.

Furthermore, along with seropositive patients having a higher risk of severe disease, they tend to have more extra-articular manifestations than those who are seronegative. Generally, the clinical presentation and prognosis of seronegative RA have been reported as less severe than those for seropositive RA, although the literature is still in conflict [2]. Recent studies have suggested that seronegative patients to have greater disease activity than seropositive patients when evaluated by ultrasonography scores for joints (median 55 vs. 25, $p<0.001$) and tendons (median 3 vs. 0, $p<0.001$), by the number of swollen joints (median 17 vs. 8, $p<0.001$), by the Disease Activity Score (mean 3.9 vs. 3.4, $p=0.03$) and by the Physician's Global Assessment (mean 49.1 vs. 38.9, $p=0.006$) [38]. It implicated that the high number of involved joints required for seronegative patients to fulfil the 2010 ACR/EULAR classification criteria for RA, which led to redefining the patient population by enacting greater weights of serology [39]. In comparison with the 1987 criteria [40], more number of seropositive RA with a milder disease activity could be classified as having RA.

In a Korean study, among the 241 RA patients who were naive to any DMARDs according to the 1987 ACR criteria or the 2010 ACR/EULAR criteria [41], seronegative patients totalled 16.6% and had more severe disease activity and similar radiographic damage relative to seropositive RA patients.

When we consider the differences between our experiences and the evidence, further studies are necessary involving seronegative RA patients to identify their genetic risk, drug responses to biologic DMARDs and the long-term prognosis relative to seropositive patients.

Prevalence of comorbidities of Korean patients with RA

1) Prevalence of interstitial lung disease in patients with RA

In Korea, several studies were performed to identify the prognosis and outcomes of ILD in patients with RA. ILD itself increased mortality of RA patients [42], and age over 65 at the time of ILD diagnosis, Usual interstitial pneumonia pattern [43], and higher Kerbs von den Lungen-6 (KL-6) level [44] were revealed as poor prognostic factors for survival of RA-ILD patients. However, it is scarce that the prevalence of ILD is identified among representative patients with RA in Korea. A single-centre study retrospectively reviewed EHRs and computed tomography (CT) scans and reported the prevalence of ILD in 507 patients with RA to be 12.6% [45]. It is worth noting that, although the presence of ILD was confirmed by CT scan, there was a possibility of indication bias for CT scan among RA patients.

In a multicentre study using the KORONA database, we reported the prevalence of ILD. Among 3,555 patients with RA whose chest X-rays (CXRs) or CT scans were taken within one year of enrolment, 64 (1.8%) patients had ILD. A comparison of the prevalence of ILD detected by CXR and chest CT revealed an obvious difference; of those RA patients for whom only CXR results were accessible (n=3,311; 93.1% of the total 3,555 patients), 1.2% had ILD. However, 9.8% were found to have ILD among the patients whose chest CT scans were available (n=244; 6.9% of the total 3,555 patients). This result suggests both the possibility of underestimation of the prevalence of ILD by CXR and the potential confounding by indication for chest CT in calculating the prevalence of ILD in RA patients [42].

Recently, a study group in the United States developed and validated claims-based algorithms to identify ILD in patients with RA using the Medicare database [46] and found that ILD was present or later developed in nearly 5% of patients in this nationwide study of older patients with RA [47]. This nationwide study's use of claims data to identify the impact of ILD on the outcomes of RA patients was meaningful and valuable. However, the remaining unmeasured confounders and the low PPV were problematic, which is similarly true for the use of Korean claims data. Further validation research is also required in Korea.

2) Prevalence of Sjögren's syndrome in patients with RA

A recent Korean cross-sectional study in a single centre showed that 72 (8.7%) of 827 RA patients were diagnosed as having SS by a rheumatologist, although 60 patients (7.3%) fulfilled the 2002 American–European Consensus Group (AECG) classification criteria for SS. Fifty-two patients (6.3%) and 56 patients (6.8%) satisfied the 2012 ACR and 2016 ACR/EULAR classification criteria [48]. The prevalence rate of SS among RA patients in this study was higher than was reported in former studies conducted in Denmark (3.6%) and Turkey (5.3%) and lower than that reported in the United States (10.3%), China (14.5%) and Italy (17.5%) [49-54].

Designs of the study and case definitions of SS have affected estimates of the SS prevalence in RA patients. In terms of disease definition, the 2002 AECG criteria were utilized in the American and Chinese studies, while the studies in Denmark, Italy and Turkey applied clinical diagnoses.

Epidemiologic study of SS in patients with RA is more complex than studies for each disease. Frequent change in classification criteria and the low performance rate of labial salivary gland biopsy and ophthalmologic examination interferes in the estimation of the exact prevalence of SS. We can also use claims database in epidemiologic research for SS as a primary or secondary form of information. However, a more novel operational definition with high PPV is needed for selecting the exact cases of SS in Korea.

CONCLUSION

Various epidemiologic studies involving Korean patients with RA have been conducted using multiple databases such as a claims database, KNHANES, prospective cohort database and EHRs. We should be aware of the strengths and limitations of each database and select the appropriate data source to accurately calculate the prevalence and incidence rates of RA and related comorbidities. Further methodological revision for effective epidemiologic study not just of RA but other rheumatic diseases is needed.

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CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

Y.K.S. was involved in conception and design of study. Y.K.S. and H.Y.K. were contributed to acquisition, analysis, and interpretation of data. All authors were involved in drafting and revising the manuscript critically for important intellectual content and final approval of the version to be published.

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