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ORIGINAL ARTICLE
Acute Coronary Syndrome

Risk of New-Onset Acute Coronary Syndrome and Atrial Fibrillation in Patients With Rheumatoid Arthritis Compared With a Risk-Set and Propensity Score-Matched Cohort

— A Nationwide Cohort Study —

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Background: Rheumatoid arthritis (RA) has extra-articular manifestations of cardiovascular diseases and is associated with a high mortality rate in Western populations. This study aimed to investigate the risk of acute coronary syndrome (ACS) and atrial fibrillation (AF) associated with RA in a Korean population.

Methods and Results: Patients were selected from a senior cohort from the Korean National Health Insurance Service in 2002, and followed until 31 December 2015. Patients with newly developed ACS and AF were identified and compared with controls for a 10-year period using time-dependent propensity and risk-set matching. A total of 4,217 incident RA patients and their 8,432 controls comprised the incident RA and matched cohorts, respectively. ACS was identified during 24,642 person-years [incidence rate (IR) 402 per 10,000 person-years, 95% confidence interval (CI) 330–489] among the RA cohort. In the matched cohort, 141 ACS patients were identified during 50,011 person-years (IR 282 per 100,000 person-years, 95% CI 239–333). RA patients were 1.43-fold more likely to develop ACS than the matched controls [hazard ratio (HR) 1.43, 95% CI 1.10–1.84], but showed similar occurrence risk of AF (HR 1.06, 95% CI 0.83–1.35).

Conclusions: A higher risk for ACS and a similar risk for AF were found by risk-set matched analysis in a senior RA cohort compared with the control, using Korean nationwide long-term data.

Key Words: Acute coronary syndrome; Atrial fibrillation; Rheumatoid arthritis

Rheumatoid arthritis (RA) is a progressive inflammatory disease characterized by articular and extra-articular manifestations, especially cardiovascular disease (CVD), which accounts for nearly half of all-cause deaths.[1,2] CVD is a common pathophysiology in patients with RA because of the inflammatory cascade. Furthermore, patients with RA have a significantly higher risk of acute myocardial infarction (AMI) than patients without RA.[3] However, there are conflicting results regarding the incidence rate (IR) and risk of developing AMI in patients with RA. Most of the previous study results were classically analyzed without adjusting for many confounding factors, especially in the Western populations.[4–7] therefore, they may not have had adequate power to provide statistical significance. In addition, the outcome of AMI with RA seems to be higher in senior than in non-senior patients with RA, according to analyses of in-hospital data.[8] Furthermore, significant racial and ethnic variation in disease activity existed in a large Western-based cohort of RA patients,[9] and long-term data in large Asian-based cohorts are limited.[10,11] Therefore, the purpose of the present study was to demonstrate the comparative occurrence and risk of acute coronary syndrome (ACS), including unstable angina and atrial fibrillation (AF), using contemporary risk-set matching analysis of a nationwide large cohort of senior RA patients in Korea.

Methods

Data Source

To ensure generalizability, the Korean National Health Insurance Service-Senior cohort (NHIS-Senior cohort; NHIS-2018-2-261), which is a representative population-based cohort for the entire elderly population of South

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Korean, was used in this study.[12] The NHIS-Senior cohort was compiled by the Korean NHIS, and the data can be accessed through the National Health Insurance Data Sharing Service website (https://nhiss.nhis.or.kr/bd/ay/bdaya001iv.do). Using 10% simple random sampling from a population of approximately 5.5 million South Korean enrollees older than 60 years of age in 2002, a total of 588,147 participants were selected as the NHIS-Senior cohort. Unless there was a death or disqualification for National Health Insurance, such as emigration, all included individuals in the NHIS-Senior cohort were followed until 31 December 2015. As a single payer under the single-insurer system of universal health coverage, the NHIS maintains all data for Korean citizens, including personal information, demographics, and medical treatment. Citizens are categorized as insured employees, insured self-employed individuals, or medical aid beneficiaries.[13,14] The information in the data set includes all inpatient and outpatient medical claims data, including treatment procedure codes and primary and secondary diagnostic codes. The protocol of this study was approved by the Institutional Review Board (IRB no: EMC EUIRB2018-27) of Eulji University, Daejeon, Republic of Korea.

Incident RA Cohort

RA was defined operationally at outpatient visits using both the diagnostic M05 code of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) and prescription of biologic agents or any disease-modifying antirheumatic drug (DMARD). This definition was validated by a previous study using the Korean National Health Insurance claims database of 2009.[15] In order to include recent trends in prescriptions, DMARDs described in a recent Korean

Table 1. Baseline Characteristics of Incident Rheumatoid Arthritis Patients and Their Propensity Score-Matched Cohort

Characteristics	No. (%) of persons		
	RA cohort (n=4,217)	Matched cohort (n=8,434)	STD*
Age (years)	66.4 (4.79)	66.4 (4.79)	0.000
Female sex	3,074 (72.9)	6,148 (72.9)	0.000
Household income level (decile)			0.056
1 st	437 (10.4)	874 (10.4)	
2nd	270 (6.4)	486 (5.8)	
3rd	262 (6.2)	590 (7.0)	
4th	297 (7.0)	605 (7.2)	
5th	301 (7.1)	583 (6.9)	
6th	328 (7.8)	718 (8.5)	
7th	424 (10.1)	893 (10.6)	
8th	518 (12.3)	1,033 (12.2)	
9th	660 (15.7)	1,278 (15.2)	
10th	720 (17.1)	1,374 (16.3)	
Type of NHI			0.015
Employee insured	961 (22.8)	1,929 (22.9)	
Dependants of employee	862 (20.4)	1,714 (20.3)	
Self-employed insured	229 (5.4)	432 (5.1)	
Dependants of self-employed	2,165 (51.3)	4,359 (51.7)	
Registered disability	12 (0.28)	23 (0.27)	0.002
Residential district			0.049
Seoul	795 (18.9)	1,545 (18.3)	
Pusan	259 (6.1)	480 (5.7)	
Daegu	195 (4.6)	371 (4.4)	
Incheon	141 (3.3)	260 (3.1)	
Gwanju	102 (2.4)	195 (2.3)	
Daejeon	79 (1.9)	150 (1.8)	
Gyeonggi-do	781 (18.5)	1,536 (18.2)	
Gangwon-do	172 (4.1)	348 (4.1)	
Chungcheongbuk-do	168 (4.0)	347 (4.1)	
Chungcheongnam-do	191 (4.5)	386 (4.6)	
Jeollabuk-do	322 (7.6)	711 (8.4)	
Jeollanam-do	263 (6.2)	531 (6.3)	
Gyeongsangbuk-do	461 (10.9)	973 (11.5)	
Gyeongsangnam-do	250 (5.9)	526 (6.3)	
Jeju-do	38 (0.90)	72 (0.85)	

(**Table 1** continued the next page.)

Characteristics	No. (%) of persons		
	RA cohort (n=4,217)	Matched cohort (n=8,434)	STD*
CCI score			0.068
0	2,416 (57.3)	5,012 (59.4)	
1	1,151 (27.3)	2,312 (27.4)	
2	425 (10.1)	719 (8.5)	
3	148 (3.5)	257 (3.0)	
4	46 (1.1)	71 (0.84)	
≥5	31 (0.74)	63 (0.75)	
Past medication history			
Antiplatelet agents	713 (16.9)	1,282 (15.2)	0.047
NSAIDs	2,159 (51.2)	4,334 (51.4)	0.004
COX-2 agents	146 (3.5)	303 (3.6)	0.007
Glucocorticoids	1,089 (25.8)	2,167 (25.7)	0.003
No. of hospital admissions			0.039
0	3,442 (81.6)	7,007 (83.1)	
1	529 (12.5)	986 (11.7)	
≥2	246 (5.8)	441 (5.2)	
Past medical history			
Hypertension	1,340 (31.8)	2,646 (31.4)	0.009
Diabetes mellitus	321 (7.6)	533 (6.3)	0.051
Dyslipidemia	296 (7.0)	479 (5.7)	0.055
Congestive heart failure	46 (1.1)	87 (1.0)	0.006
Chronic kidney disease	10 (0.24)	11 (0.13)	0.025
Stroke	93 (2.2)	175 (2.1)	0.009
Cancer	99 (2.3)	172 (2.0)	0.021

The two groups were matched 1:2 on follow-up time and propensity score calculated by Cox proportional hazard model with predictors listed in this table. *STD of <0.1 (10%) is generally considered as negligible. CCI, Charlson comorbidity index; NHI, National Health Insurance; NSAID, nonsteroidal anti-inflammatory drug; RA, rheumatoid arthritis; STD, standardized differences.

publication[16] were added to the list of DMARDs in this study. To reduce false positivity in identifying RA patients, at least 2 outpatient visits were needed for patients with any DMARD prescription. To avoid immortal time bias, the date when the subjects were identified as RA patients was defined as the date of the second outpatient visit.[17] Due to the lack of information about past medical history, if the defined date of diagnosis was between 1 January 2002 and 31 December 2003, the patients were classified as prevalent RA patients and excluded from the study. If patients were diagnosed after 1 January 2004 (with at least a 2-year RA-free period), they were classified as incident RA patients. Patients in the Medical Aid program were excluded because of the possibility of incomplete claims information. Finally, patients with a prior history of ACS, AF, and other ischemic heart diseases (IHDs: ICD-10 I20–I25) were excluded from the identification of incidence of ACS.

Identification of ACS and AF

New-onset of ACS was defined as: (1) hospital admission with diagnostic code of ICD-10 I21 (AMI) or I200 (unstable angina pectoris); (2) treatment by coronary bypass graft surgery, primary coronary intervention, thrombolytic agents (streptokinase, urokinase, and tenecteplase), or death certification codes of ACS within 30 days; and (3) first diagnosis after a 2-year (2002–2003) washout period to identify incident cases. A similar definition was recommended and validated by a previous study using Korean administrative claims data.[18] The time of event was defined as the date of admission fulfilling the above definition of ACS. New-onset AF was identified by: (1) first-time admission to an acute care hospital or ≥2 outpatient visits with primary or first secondary diagnostic codes of AF; and (2) first diagnosis after a 2-year (2002–2003) washout period to identify incident cases. The time of event was defined as the date of admission or outpatient visit fulfilling the above definition of AF.

Risk-Set Matching on Propensity Score

Although the NHIS-Senior cohort was constructed retrospectively, the design of this study mimicked that of a prospective study. From among the NHIS-Senior cohort, during the process of incident RA case selection patients were excluded to avoid misclassification of the explanatory variable. Patients in the Medical Aid program were also excluded during incident RA case selection. The time-dependent propensity score was calculated first, and then risk-set matching was performed.[19,20] To adjust for confounding factors, the effect of RA on ACS and AF risk was examined using time-dependent propensity score matching.[20] Hazard components (as propensity score) were estimated from a Cox proportional hazards model, with 1 January 2004 as the baseline and RA as an event. All variables are shown in **Table 1**, and square of age data were included as independent variables. All variables were identified 2 years (2002–2003) before the baseline. Age and square of age were included as continuous variables; sex, household income level (decile), type of National Health

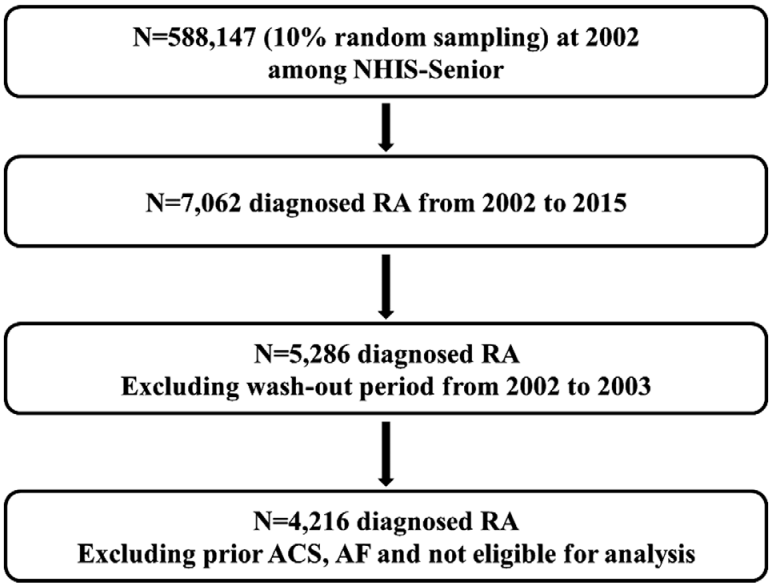

Figure 1. Flow chart of study enrollment. ACS, acute coronary syndrome; NHIS, National Health Insurance Service; RA, rheumatoid arthritis.

Insurance, registered disability, residential district, Charlson comorbidity index (CCI), number of hospital admissions, past medication history, and past medical history were categorical variables. Each subject's number of comorbidities was assessed by diagnostic codes using the Quan ICD-10 coding algorithm of the CCI score.[21] Prescription for >90 days of antihypertensive, antidiabetic, lipid-lowering, antidepressants, antiplatelet agents, cyclooxygenase-2 inhibitors, nonsteroidal anti-inflammatory drugs, and glucocorticoids was considered for patients who had taken the corresponding medications.

To emulate a prospective study, at the date when the first RA patient was identified, subjects of the same age and sex, but without RA or at risk of RA at that time, were matched to that patient. The RA patient and matched subjects constituted the first risk set or mini-trial. Next, this method of risk-set matching was repeated sequentially until the last RA patient was matched.[19,22,23] A 1 : 2 matching on the propensity score was then sequentially performed for each risk set using a nearest neighbor-matching algorithm with a maximum caliber of 0.1 of the hazard components. To make the matching independent of future events, the matched subjects could either be those who never developed or were yet to develop RA. An RA patient in the incident RA cohort could, therefore, enter the study as an RA patient or as a matched patient for the other RA patient, whose date of incidence was prior to that of the RA patient.[24] Next, to yield non-overlapping samples from the risk set, the matched subjects were removed from the next risk sets. The same process was continued and repeated with the next risk set. Finally, the incident cohort and a matched cohort were followed up.

Statistical Analysis

Using the final matched cohorts, statistical tests for the association between RA and the risk of ACS and AF incidence were performed, with the statistical nature of the matched pair analysis taken into consideration. To assess covariate balance between treatment groups, baseline characteristics were compared with standardized differences (STD), where a difference <0.1 (10%) was generally considered as negligible.[25,26] Cumulative incidence and its curve and the 95% confidence interval (CI) were calculated by the product limit (Kaplan-Meier) method of survival probability. The stratified log-rank test was used to compare the survival curves of both cohorts.[27] The IR and 95% CI were calculated by a generalized estimating equation with a Poisson distribution, and expressed as the number of events per 100,000 person-years. The effect size was presented as a hazard ratio (HR) using a Cox proportional hazard model with a robust variance estimator that accounts for clustering within matched pairs.[26,27] Time-zero was set as the date of RA incidence for both RA patients and their matched controls. Proportional hazard assumption was assessed graphically using the log of negative log of estimated survivor function, time-dependent explanatory variable, Schoenfeld residuals, cumulative sums of martingale residuals, and a supremum test for proportional hazard assumption.[28] Survival time used in survival analyses was defined separately for ACS and AF by days from time-zero to dates of event incidence, death, or 31 December 2015, whichever came first. In addition to these cause-specific models, a Fine and Gray subdistribution hazard model was performed as a sensitivity analysis. Statistical analyses were conducted using SAS Enterprise Guide version 7.1 and $P<0.05$ was considered statistically significant.

Results

From 1 January 2002 to 31 December 2015, a total of 7,062 patients met the inclusion criteria. Among them, RA diagnosis during the first 2-year (2002–2003) period (1,776 patients), enrollees of the Medical Aid program (420 patients), prior ACS or AF history patients (167 patients), and patients with prior history of other IHD (268 patients) were excluded according to the exclusion criteria. During the process of risk-set matching, 30 RA patients were not matched to control patients and 156 patients entered into

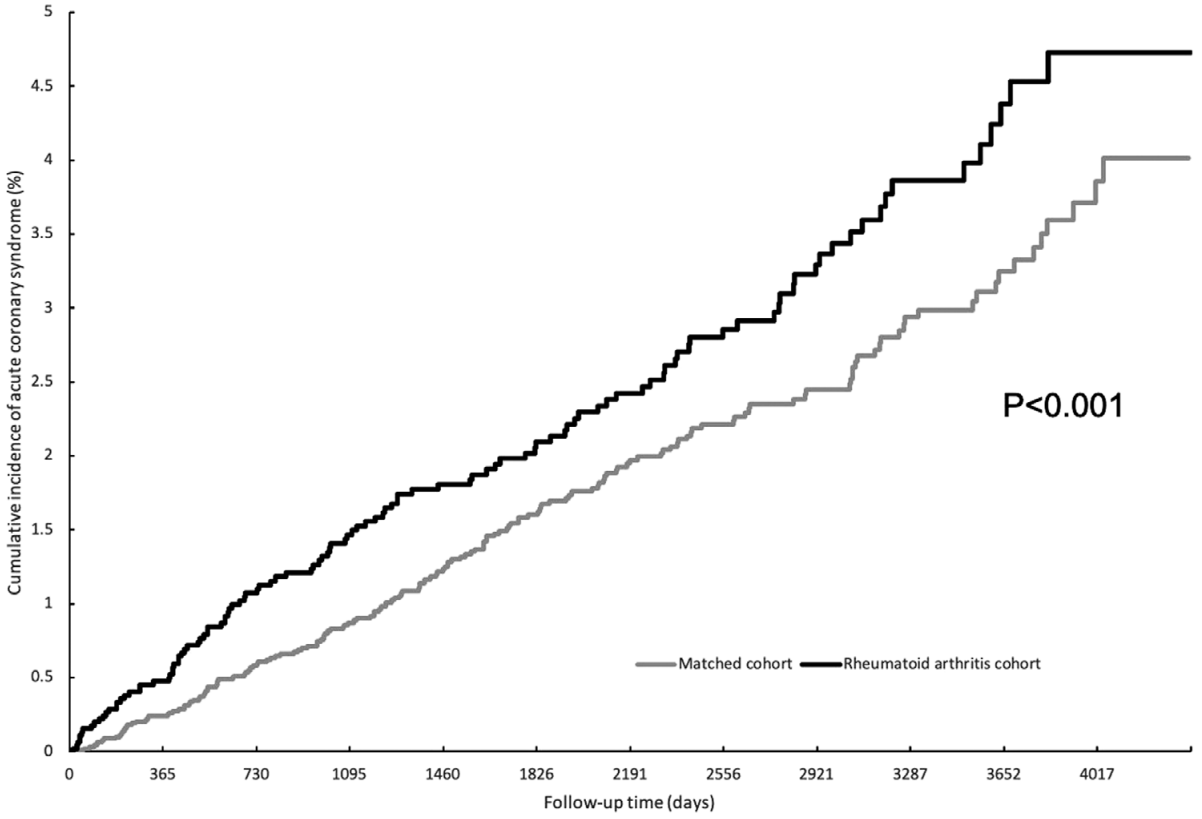

Figure 2. Cumulative incidence of acute coronary syndrome during follow-up.

Table 2. Cumulative Incidence (%) of Acute Coronary Syndrome (ACS) and Atrial Fibrillation (AF) During Different Cumulative Time Frames

Cumulative time frame	ACS		AF	
	Matched cohort	RA cohort	Matched cohort	RA cohort
1 year	0.22 (0.14–0.35)	0.46 (0.29–0.71)	0.37 (0.26–0.52)	0.49 (0.31–0.75)
2 years	0.55 (0.40–0.73)	0.90 (0.64–1.23)	0.69 (0.53–0.90)	0.93 (0.66–1.28)
3 years	0.70 (0.67–1.08)	1.32 (0.99–1.73)	1.02 (0.81–1.27)	1.26 (0.94–1.66)
4 years	1.01 (0.80–1.27)	1.65 (1.27–2.11)	1.43 (1.17–1.73)	1.70 (1.31–2.17)
5 years	1.35 (1.09–1.66)	1.92 (1.50–2.43)	1.79 (1.49–2.13)	2.04 (1.60–2.57)
6 years	1.74 (1.43–2.10)	2.27 (1.79–2.84)	2.09 (1.75–2.47)	2.27 (1.79–2.84)
7 years	1.95 (1.61–2.33)	2.68 (2.14–3.33)	2.55 (2.16–2.99)	2.69 (2.14–3.33)
8 years	2.24 (1.85–2.67)	3.16 (2.52–3.90)	3.06 (2.60–3.57)	3.32 (2.67–4.09)
9 years	2.58 (2.14–3.09)	3.60 (2.87–4.45)	3.24 (2.75–3.78)	3.50 (2.84–4.31)
10 years	2.86 (2.35–3.44)	4.04 (3.18–5.03)	3.62 (3.06–4.25)	3.60 (2.88–4.44)
11 years	3.24 (2.63–3.94)	4.41 (3.43–5.55)	4.12 (3.42–4.91)	4.16 (3.24–5.25)

Groups were matched 1:2 on follow-up time and propensity score was calculated by multivariable-adjusted Cox proportional hazard model with predictors listed in Table 1. RA, rheumatoid arthritis.

the study as controls for another RA patient. Additionally, 28 RA patients were excluded due to a less than 1:2 propensity score-matching ratio (**Figure 1**). Finally, a total of 4,217 incident RA patients and their 8,434 matched controls comprised the incident RA cohort and the matched cohort, respectively, in this study. Mean follow-up time was 5.90 (±3.41) and 5.89 (±3.42) years, generating 74,635 and 74,467 person-years for the analyses of ACS and AF, respectively. During follow-up, a total of 240 ACS and 288 AF cases were identified.

Table 1 shows the baseline characteristics of the cohorts. Mean age was 66.4 years and 72.9% were female. Covariate distribution between cohorts was similar in that the highest STD was 6.8% for CCI. There was no significant difference in hypertension, diabetes, dyslipidemia, and CCI between groups. Comparison of cumulative incidence for

Table 3. Effects of Incident Rheumatoid Arthritis (RA) on Acute Coronary Syndrome (ACS) and Atrial Fibrillation (AF)

	ACS		AF	
	Matched cohort	RA cohort	Matched cohort	RA cohort
n	8,434	4,217	8,434	4,217
No. of events	141	99	99	189
Person-years	49,992	24,642	49,804	24,662
Incidence rate (95% CI)*	282 (239–333)	402 (330–489)	379 (329–437)	401 (329–489)
Hazard ratio (95% CI)	1	1.43 (1.10–1.84)§	1	1.06 (0.83–1.35)

*Events per 100,000 person-years. §P=0.007. Groups were matched 1:2 on follow-up time and propensity score was calculated by multivariable-adjusted Cox proportional hazard model with predictors listed in Table 1. CI, confidence interval.

ACS showed a statistically significant difference (P for stratified log-rank test <0.001) between cohorts (**Figure 2**). During 10 years of follow-up, cumulative incidence of ACS was 4.04% (95% CI, 3.18–5.03) for the RA cohort and 2.86% (95% CI, 2.35–3.44) for the matched cohort (**Table 2**). Regarding density of incidence, 99 ACS cases were identified during 24,642 person-years (IR 402 per 100,000 person-years, 95% CI 330–489) among the RA cohort. In the matched cohort, 141 ACS cases were identified during 49,992 person-years (IR 282 per 100,000 person-years, 95% CI 239–333). This difference indicated that incident RA patients were 1.43-fold more likely to develop ACS than their matched controls (HR 1.43, 95% CI 1.10–1.84). Results for the Fine and Gray subdistribution hazard models were similar to those of the cause-specific model.

Contrary to the increased risk for ACS, our results failed to show an effect of RA on the development of AF (HR 1.06, 95% CI 0.83–1.35). Among the RA cohort, the IR of AF was 401 per 100,000 person-years (95% CI 329–489) (**Table 3**).

Discussion

In the NHIS-Senior cohort data of South Korea, the incidence and risk of new-onset ACS and AF in patients with RA was compared with matched controls for a 10-year follow-up using risk-set analysis. Our main findings were as follows: (1) there was a higher risk of developing ACS in senior patients with RA compared with that of the matched controls, and (2) the risk of developing AF in senior patients with RA was similar to that of the matched controls.

RA appears to have a common pathophysiology for developing CVD, including AF, compared with the general population, because it triggers a non-articular inflammatory cascade that has been shown to mainly influence the development of CVD in RA patients with DRARD.[1,2] Previous studies have demonstrated that RA is associated with the development of CVD, including only AMI, and its poor prognosis in Western general populations.[4,6,7] McCoy et al[6] demonstrated that AMI in patients with RA had a higher rate of death in the short term compared with controls (12% vs. 6%), although it did not reach statistical significance. However, long-term mortality was higher in the senior patients with RA than in the controls. The study was limited by its small population used and the short time frame with a classical analytic method. Mantel et al also analyzed a European national database to compare the outcomes of AMI in RA with a matched group, and showed a higher short-term mortality rate for patients with RA than for the matched controls.[7] However, Francis et al[5] and Elbadawi et al[8] showed lower in-hospital mortality rates in their RA patients with AMI compared with the controls using a classical analytic method. A previous study[2] almost demonstrated a direct relationship between AMI or stable coronary artery disease within CVD and RA for comparative analysis, but progressive pro-inflammatory cytokines, such as tumor necrosis factor-α, interleukin-6, C-reactive protein and inflammatory cells such as macrophages and T-cell accumulation are reported to induce endothelial dysfunction, atherosclerotic plaque and oxidative stress in ACS and AF.[29] Therefore, based on their common pathophysiology with RA, ACS and AF of the general CVD could be more likely to develop in the RA cohort, and the present study could be more representative of specific fatal CVDs in the Asian population than previous studies that assert differences in incidence and risk for each CVD and ethnic disparity by analyzing risk-set propensity matching. Interestingly, the present study demonstrated that senior RA patients significantly developed ACS, which significantly increased in the 10-year time frame compared with the matched controls (**Table 3**, **Figure 2**). In addition, the present study showed that the occurrence and risk of new-onset AF in the senior patients with RA was similar to that in the matched controls, which unexpectedly contradicted the pathophysiology. The reason for a similar effect of incidence and risk for new-onset AF might be the limited close surveillance of heart rhythm, which may be underdiagnosed in the national database. Further investigations are needed to determine this potential underdiagnosis.

Study Limitations and Strengths

First, information bias may remain. Some important variables (e.g., severity of RA, smoking status and family history) were not included in the national database. Therefore, residual confounding factors may remain, even after propensity score-matching analysis. As administrative claims data, the diagnostic codes may not represent each patient's true disease. Second, disease codes listed as inclusion criteria may not represent a patient's true disease status, which is an inherent limitation of insurance databases. However, the incidence of RA, ACS, and AF in this study could be well identified because nearly all types of hospitals follow the fee-for-service system and all treatment procedures and prescriptions must be claimed.

This study has some strengths. First, the NHIS-Senior cohort is a large sample, with a relatively low rate of follow-up loss over 13 years of follow-up, due to the nature of the national administration data. Second, the NHIS-Senior cohort represents the entire South Korean population over

60 years of age. As such, RA patients in this study could represent the entire South Korean RA patient population older than 65 years of age. Although there are limitations, the present study is the first to report a causal relationship between RA and CVD using contemporary risk-set propensity analysis in a nationwide large senior population, mimicking a prospective design despite the retrospective nature of the study, and could contribute to improved evidence in the setting of Asian RA patients. Our study results suggest that RA patients with cardiovascular risk factors should be closely monitored for timely collaboration with cardiology specialists and a recommendation for proper management is needed to reduce the risk of occurrence for CVD in these elderly RA patients.

Conclusions

This risk-set matched analysis of a national database demonstrated a higher incidence and risk of ACS and a similar risk of AF in senior RA patients compared with matched controls.

Acknowledgments

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This study was based on data from the Korean National Health Insurance Service (research administration no. NHIS-2018-2-261), and the results of the study are not related to the National Health Insurance Service.

Disclosures

The authors declare no conflicts of interest.

IRB Information

The Institutional Review Board number: EMC EUIRB2018-27 at Eulji University.

Data Availability

The deidentified participant data will not be shared.

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