



OPEN Rheumatoid arthritis and risk of pancreatitis: a nationwide cohort study

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We aimed to assess whether patients with rheumatoid arthritis (RA) have a higher risk of developing acute and chronic pancreatitis compared to individuals without RA. We identified 54,910 individuals with RA between 2010 and 2017. After exclusion, they were matched in a 1:3 ratio based on age and gender to control population without RA. Cox regression analyses were performed to estimate hazard ratio. During a median follow-up of 5.5 years, 0.18% of the patients with RA and 0.14% of the matched control developed acute pancreatitis. The risk acute pancreatitis was higher in the RA cohort compared to matched control (adjusted hazard ratio [aHR] 1.33; 95% confidence interval [CI] 1.02–1.74). In the case of chronic pancreatitis, 0.11% of patients with RA and 0.09% of the matched control developed chronic pancreatitis. Patients with RA appear to have a marginally elevated risk of chronic pancreatitis compared to matched controls (aHR 1.25, 95% CI 0.90–1.74), though this increase did not achieve statistical significance. The risk of acute pancreatitis is slightly higher in individuals with RA than in matched controls. The risk of chronic pancreatitis did not show statistical significance, but it tended to increase marginally in patients with RA.

Keywords Rheumatoid arthritis, Acute pancreatitis, Chronic pancreatitis

Rheumatoid arthritis (RA) is an autoimmune disorder marked by widespread inflammation throughout the body, affecting both the joints and various extra-articular regions. Numerous studies demonstrated its association with cardiovascular disease¹, stroke², Parkinson disease³, and interstitial lung disease⁴.

Acute or chronic pancreatitis also involves inflammation as its main pathophysiological mechanism, and it is plausible that RA may increase the risk of these diseases. Apart from several earlier case reports^{5–7}, only a few studies examined the association between RA and acute or chronic pancreatitis (Supplementary Table 1). A population-based cohort study conducted in Taiwan indicated that patients with RA have an increased risk of acute pancreatitis (adjusted hazard ratio [aHR] 1.62, 95% CI 1.43–1.83). However, that study specifically focused on the occurrence of acute pancreatitis, and the occurrence of pancreatitis based on serological status of RA was not examined⁸. Another cross-sectional study conducted in the US suggested that RA may be an independent risk factor for pancreatic manifestations including acute pancreatitis (OR 2.41, 95% CI 2.41–2.60) and chronic pancreatitis (OR 2.97, 95% CI 2.70–3.26). This study benefited from its large sample size, including over 500,000 Western individuals. However, considering the cross-sectional nature of the database, establishing a timeline and the duration of treatment exposure is not possible. Moreover, there may be limitations in diagnostic accuracy since it was evaluated using diagnosis codes from electronic medical records⁹. Ultimately, there a few long-term

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studies observing the occurrence of pancreatitis, encompassing both acute and chronic forms, in relation to RA when tracked from the time of RA diagnosis.

In the present study, we investigated the association between RA and subsequent pancreatitis risk including both acute and chronic form using a nation-wide population-based cohort in South Korea, excluding well-known risk factors of pancreatitis, adjusting for underlying diseases or behavioral factors that, to the best of our knowledge, were not considered in previous studies.

Methods

Data source and study setting

In this cohort study, we used data from the National Health Insurance Service (NHIS), which is a single insurer managed by the Korean government and provides a mandatory social insurance program that covers 97% of the Korean population. In addition, administration for the remaining 3% (the Medical Aid population, with the lowest income) are also managed by NHIS. Therefore, the NHIS has information on the whole Korean population and their demographic characteristics, health care use, and diagnostic codes from the International Classification of Diseases, Tenth Revision (ICD-10), medical treatment information.

Additionally, the NHIS provides free biennial national health examination programs for the public, and adults are recommended to undergo a check-up at least once every 2 years¹⁰. This health screening program data comprise anthropometric measurements, self-administered questionnaires on health behavior, which were developed for national health screening purposes, and laboratory results. All these resources retained by the NHIS have been utilized to create cohort data for various epidemiologic studies, including investigations of disease risk in patients with RA^{3,11–13}. This study was conducted according to the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Samsung Medical Center (#SMC 2024-07-196). The IRB has approved a waiver of the requirement to obtain informed consent because the NHIS database is available to researchers and is supplied as anonymized data.

Study population

The current study included patients newly diagnosed with RA between 2010 and 2017 who are 40 years or older. Seropositive rheumatoid arthritis (SPRA) patients were defined by the following criteria: (1) had a registered diagnostic code for RA (ICD-10 M05), (2) received a prescription for any disease-modifying anti-rheumatic drugs (DMARDs) for 270 days or more, and (3) were enrolled in the rare and intractable disease (RID) program. The RID program in Korea offers substantial reductions in copayment for various rare and intractable diseases (5% of copayment vs. typical 30% for other common diseases), including RA. Enrollment in this program as RA requires official certification of diagnosis by a physician, typically a rheumatologist, which is issued when a patient fulfilled 4 or more American College of Rheumatology criteria with positive results from rheumatoid factor or anti-cyclic citrullinated peptide antibody. Seronegative rheumatoid arthritis (SNRA) patients were defined by the following criteria: (1) had a registered diagnostic code for RA (ICD-10 M06 except M06.1 and M06.4), and (2) received a prescription for any DMARDs for 270 days¹⁴. The date of RID program registration for SPRA and the first administration of RA ICD-10 code for SNRA were considered as the index date. This operational definition was considered highly valid¹⁵ and was repeatedly used in many epidemiological studies conducted in Korea¹⁶.

The study enrolled 92,336 individuals diagnosed with RA between 2010 and 2017, including 66,493 with SPRA and 25,840 with SNRA. Of the 92,336 identified cases of RA, we selected 54,910 patients who had undergone a national health screening within 2 years prior to RA diagnosis to obtain covariate information. This allowed us to gather medical and health behavior information from the health screening results. After that, we excluded heavy drinkers ($n = 1,577$), a common risk factor for both acute and chronic pancreatitis, and those whose records were missing any information ($n = 1,925$). After these exclusions, a total of 51,318 patients with RA remained (Fig. 1).

Subsequently, we applied different exclusion criteria considering the risk factors associated with each outcome, resulting in the final study populations being defined differently. Specifically, for the analyses of the risk of acute pancreatitis, we excluded 1) individuals who had triglyceride (TG) levels exceeding 400 mg/dl ($n = 312$), those with a history of chronic pancreatitis ($n = 572$), those with a history of prior gall stones ($n = 3,239$), those who had previously been diagnosed with acute pancreatitis before RA diagnosis ($n = 1,646$), and those who were diagnosed with acute pancreatitis within 1 year after the index date (called 1-year lag period) ($n = 382$). After these exclusions, patients with RA and individuals without RA were matched (1:3) to RA cases based on age, sex, and index date.

For the analyses of chronic pancreatitis, we excluded individuals with a history of prior acute pancreatitis ($n = 2,286$), those who had previously been diagnosed with chronic pancreatitis before RA diagnosis ($n = 411$), and those who were diagnosed with chronic pancreatitis within 1 year after the index date (called 1-year lag period) ($n = 418$). After these exclusions, patients with RA and individuals without RA were matched (1:3) to RA cases based on age, sex, and index date. The study participants were followed from 1 year after RA diagnosis or corresponding index date to the date of acute or chronic pancreatitis diagnosis, death, or the end of the follow-up period (until December 31, 2019), whichever came first.

Study outcome and follow-up

The end point of the study was newly diagnosed acute pancreatitis or chronic pancreatitis using the ICD-10 code. To mitigate possible reverse causality, the participants were followed from 1 year after the index date (1-year of lag period) to the date of acute or chronic pancreatitis diagnosis, death, or the end of the follow-up period (until December 31, 2019), whichever came first. While there was no formal validation study for the use of ICD 10 codes to identify acute or chronic pancreatitis in our study setting, it is unlikely that these

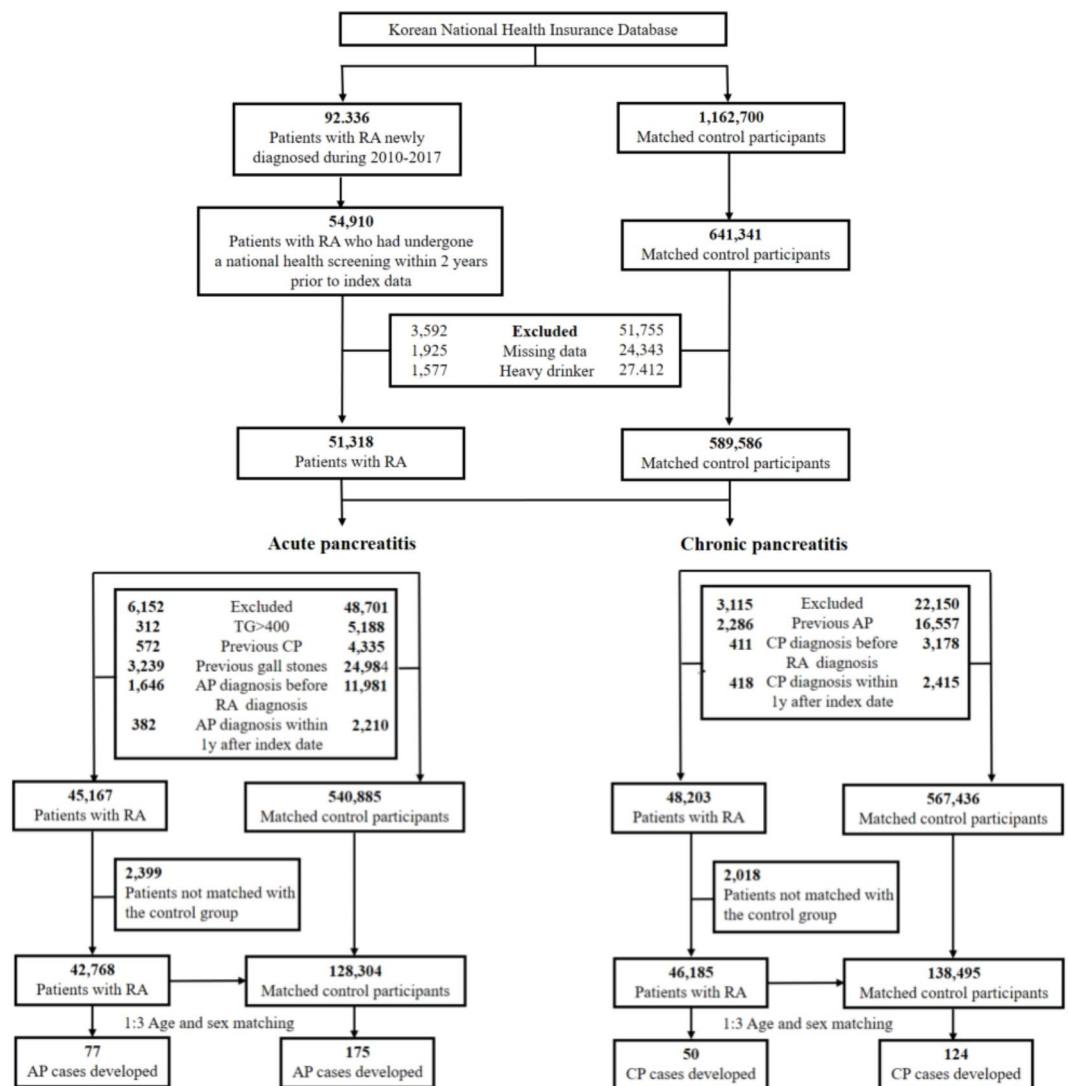


Fig. 1. Flow chart of study populations. Abbreviations: RA, rheumatoid arthritis; AP, acute pancreatitis; CP, chronic pancreatitis; TG, triglyceride.

codes were administered solely for administrative or billing purpose without clinical conditions. Moreover, prior population-based cohort studies using claims data related to pancreatitis incidence have utilized ICD codes^{8,17}.

Covariates

We collected data on baseline characteristics including age, sex, body mass index (BMI), smoking status, alcohol use, physical activity, income level, and comorbidities from the dataset. Personal behaviors, such as smoking status, alcohol consumption, and physical activity, were assessed using a self-reported questionnaire. Smoking status was classified into never smoker, ex-smoker, and current smoker. Alcohol intake was divided into none, mild to moderate (< 30 g of alcohol/day), and intake. Regular exercise was defined as moderate exercise for more than 5 days a week or vigorous exercise for more than 3 days a week¹⁸. Household income was divided into quartiles according to insurance premium levels, as in Korea, insurance premiums are based on income. Those receiving Medical Aid (poorest 3%) were included in the lowest income quartile. The lowest income quartile was labeled as “low income”¹⁹. BMI was calculated by dividing weight (kg) by height (m) squared. Definitions of comorbidities such as diabetes mellitus, hypertension, dyslipidemia, and chronic kidney were based on ICD-10 codes as previously described^{3,11,18}.

Statistical analysis

The baseline characteristics of the study participants were compared based on the presence of RA and the serologic status of RA. Continuous variables were presented as mean (SD) and categorical variables were presented as number and percentage. The incidence rates of acute or chronic pancreatitis were presented per 1,000 person-years. The cumulative incidence of pancreatitis, based on RA status was estimated using the Kaplan-Meier method. Log-rank tests were applied to evaluate differences among the groups. We conducted Cox regression

analyses to calculate adjusted hazard ratios (aHR) and 95% confidence intervals (CIs) for the risk of pancreatitis. A multivariable-adjusted proportional hazard model was applied: (1) model 1 was non-adjusted; (2) model 2 was adjusted for age, sex; (3) model 3 was further adjusted for smoking, alcohol drinking, physical activity, low income; (4) model 4 included model 3 plus diabetes, hypertension, hyperlipidemia, chronic kidney disease. Schoenfeld residuals were used to assess the proportional hazards (PH) assumption in Cox regression models. For Model 4, we performed an additional analysis with the Fine-Gray competing risk model as a sensitivity analysis. Statistical analyses were performed in May 2023 using SAS version 9.4 (SAS Institute Inc.), and 2-sided $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of study participant

Table 1 presents the baseline characteristics of the study participants for the analysis of acute pancreatitis according to the presence of RA and the serologic status of RA. Among a total of 171,072 study participants at the index date, 38,136 individuals (22.3%) were male, and the mean (SD) age was 58.0 (9.9) years. Alcohol consumption, even in small amounts, was significantly higher in those without RA compared to those with RA (26.4% vs. 21.3%), while current smoking was significantly lower in those without RA compared to those with RA (8.8% vs. 9.6%). The levels of TG were significantly higher in those without RA at 105.7 mg/dl compared to 102.1 mg/dl in patients with RA.

Table 2 describes the baseline characteristics of the study participants for the analysis of chronic pancreatitis according to the presence of RA and the serologic status of RA. The mean (SD) age of study participants

	Total	RA status			Serological status of RA		
		Non-RA	RA	P-value	SPRA	SNRA	p-value
Acute pancreatitis							
Participants, No	171,072	128,304	42,768		30,565	12,203	
Sex, Male	38,136 (22.3)	28,602 (22.3)	9,534 (22.3)	> 0.99	6,617 (21.7)	2,917(23.9)	<0.0001
Age	58.0 ± 9.9	58.0 ± 9.9	58.0 ± 9.9	> 0.99	58.3 ± 9.9	57.4 ± 9.9	<0.0001
40–59	98,784 (57.7)	74,088 (57.7)	24,696 (57.7)	> 0.99	17,365 (56.8)	7,331(60.1)	<0.0001
≥ 60	72,288 (42.3)	54,216 (42.3)	18,072 (42.3)		13,200 (43.2)	4,872 (39.9)	
Income				0.030			<0.0001
< 25%	38,296 (22.4)	28,695 (22.4)	9,601 (22.5)		6,910 (22.6)	2,691 (22.1)	
Smoking status				< 0.0001			<0.0001
Never	140,498 (82.1)	105,975 (82.6)	34,523 (80.7)		24,701 (80.8)	9,822 (80.5)	
Former	15,167 (8.9)	11,024 (8.6)	4,143 (9.7)		2,753 (9.0)	1,390 (11.4)	
Current	15,407 (9.0)	11,305 (8.8)	4,102 (9.6)		3,111 (10.2)	991 (8.1)	
Alcohol consumption				< 0.0001			<0.0001
None	128,102 (74.9)	94,431 (73.6)	33,671 (78.7)		24,223 (79.3)	9,448 (77.4)	
< 30 g/day	429,70 (25.1)	33,873(26.4)	9,097 (21.3)		6,342 (20.8)	2,755 (22.6)	
Physical activity							
Regular	344,02 (20.1)	26,591 (20.7)	7,811 (18.3)	< 0.0001	5,438 (17.8)	2,373 (19.5)	<0.0001
Body mass index				< 0.0001			<0.0001
< 18.5	4,994 (2.9)	3,326 (2.6)	1,668 (3.9)		1,261 (4.1)	407 (3.3)	
18.5–23	68,176 (39.9)	50,112 (39.1)	18,064 (42.2)		13,201 (43.2)	4,863 (39.9)	
23–25	42,846 (25.1)	32,406 (25.3)	10,440 (24.4)		7,448 (24.4)	2,992 (24.5)	
25–30	48,742 (28.5)	37,578 (29.3)	11,164 (26.1)		7,748 (25.4)	3,416 (28.0)	
≥ 30	6,314 (3.7)	4,882 (3.8)	1,432 (3.4)		907 (3.0)	525 (4.3)	
Diabetes mellitus	20,628 (12.1)	15,593 (12.2)	5,035 (11.8)	0.0365	3,513 (11.5)	1,522 (12.5)	0.0046
Hypertension	63,426 (37.1)	46,840 (36.5)	16,586 (38.8)	< 0.0001	11,448 (37.5)	5,138 (42.1)	<0.0001
Dyslipidemia	55,131 (32.2)	41,380 (32.3)	13,751 (32.2)	0.7044	9,406 (30.8)	4,345 (35.6)	<0.0001
Chronic kidney disease	11,648 (6.8)	8,294 (6.5)	3,354 (7.8)	< 0.0001	2,259 (7.4)	1,095 (9.0)	<0.0001
Lipid profile							
*TG	104.8 (104.6-105.1)	105.7 (105.4–106.0)	102.0 (101.6-102.5)	< 0.0001	100.8 (100.2-101.3)	105.6 (104.6-106.5)	<0.0001
Acute pancreatitis	252 (0.15)	175 (0.14)	77 (0.18)	0.0415	56 (0.18)	21 (0.17)	0.8064
F/U duration							
Mean ± SD	5.6 ± 2.3	5.6 ± 2.3	5.5 ± 2.3	< 0.0001	5.6 ± 2.3	5.5 ± 2.2	0.1394
Median (Q1-Q3)	5.5 (3.7–7.5)	5.5 (3.7–7.5)	5.4 (3.6–7.4)	< 0.0001	5.4 (3.6–7.5)	5.5 (3.7–7.3)	0.087

Table 1. Baseline characteristics of study participants for the analysis of acute pancreatitis. RA, Rheumatoid arthritis; SPRA, seropositive rheumatoid arthritis; SNRA, seronegative rheumatoid arthritis; TG, triglyceride; SD, standard deviation.

(*n* = 184,660) at the index date was 58.3 (9.9) years; 22.7% were male. The patients with RA were more likely to be current smokers (9.7% vs. 9.0%), consume less alcohol (21.2% vs. 26.1%), and were less likely to be overweight (BMI ≥ 25) or obese (BMI ≥ 30) (29.9% vs. 33.4%).

Risk of acute pancreatitis according to the presence of RA

During a median (IQR) follow-up of 5.5 (3.7–7.5) years after a 1-year lag period, 252 participants (77 in the RA group and 175 in the control group) were newly diagnosed with acute pancreatitis. Compared with the control group, patients with RA showed a higher risk for acute pancreatitis (aHR, 1.33 [95%CI, 1.02–1.74], *P* = 0.032) (Table 2). By serological status, patients with SPRA are at a higher risk (aHR 1.36, 95% CI 1.01–1.84) compared to matched controls, whereas patients with SNRA showed no significant difference in risk (aHR 1.26, 95% CI 0.80–1.98). However, the comparison between SPRA and SNRA showed no significant difference (SPRA vs. SNRA, aHR 1.10, 95% CI 0.66–1.81). (Table 3; Fig. 2A). When the Fine-Gray model was applied, acute pancreatitis did not show a significant association (aHR 1.29, 95% CI 0.99–1.69, *P* = 0.061); however, the results were generally consistent with the main analyses using the Cox model.

Risk of chronic pancreatitis according to the presence of RA

During a median (Interquartile Range [IQR]) follow-up of 5.47(3.67–7.46) years after a 1-year lag period, 174 participants (50 in the RA group and 124 in the control group) were newly diagnosed with chronic pancreatitis (Fig. 2B). Patients with RA tend to have slightly higher risk of developing chronic pancreatitis (aHR 1.25, 95% CI 0.90–1.74, *P* = 0.189) than a matched control, although it did not reach predefined statistical significance (Table 2). By serological status, patients with SPRA tended to have marginally higher risk (aHR 1.36, 95% CI

	Total	RA status		P-value	Serological status of RA		
		Non-RA	RA		SPRA	SNRA	p-value
Participants, No	184,660	138,495	46,165		32,185	13,350	
Sex, Male	41,972 (22.7)	31,479 (22.7)	10,493 (22.7)		7,247 (22.1)	3,246 (24.3)	<0.0001
Age	58.3 ± 9.9	58.3 ± 9.9	58.3 ± 9.9		58.5 ± 9.9	57.7 ± 10.0	<0.0001
40–59	104,852 (56.8)	78,639 (56.8)	26,213 (56.8)		18,316 (55.8)	7,897 (59.2)	
≥ 60	79,808 (43.2)	59,856 (43.2)	19,952 (43.2)		14,499 (44.2)	5,453 (40.9)	
Income							
< 25%	41,383 (22.4)	31,011 (22.4)	10,372 (22.5)	0.046	7,399 (22.6)	2,973 (22.3)	0.0002
Smoking status				<0.0001			<0.0001
Never	151,098 (81.8)	113,985 (82.3)	37,113 (80.4)		26,409 (80.5)	10,704 (80.2)	
Former	16,670 (9.03)	12,090 (8.7)	4,580 (9.9)		3,036 (9.3)	1,544 (11.6)	
Current	16,892 (9.2)	12,420 (9.0)	4,472 (9.7)		3,370 (10.3)	1,102 (8.3)	
Alcohol consumption				<0.0001			<0.0001
None	138,681 (75.1)	102,289 (73.9)	36,392 (78.8)		26,031 (79.3)	10,361 (77.6)	
< 30 g/day	45,979 (24.9)	36,206 (26.1)	9,773 (21.2)		6,784 (20.7)	2,989 (22.4)	
Physical activity							
Regular	37,273 (20.2)	28,825 (20.8)	8,448 (18.3)	<0.0001	5,850 (17.8)	2,598 (19.5)	<0.0001
Body mass index				<0.0001			<0.0001
< 18.5	5,363 (2.9)	3,594 (2.6)	1,769 (3.8)		1,331 (4.1)	438 (3.3)	
18.5–23	73,021 (39.5)	53,727 (38.8)	19,294 (41.8)		14,027 (42.8)	5,267 (39.5)	
23–25	46,110 (25.0)	34,841 (25.2)	11,269 (24.4)		8,003 (24.4)	3,266 (24.5)	
25–30	53,163 (28.8)	40,917 (29.5)	12,246 (26.5)		8,454 (25.8)	3,792 (28.4)	
≥ 30	7,003 (3.8)	5,416 (3.9)	1,587 (3.4)		1,000 (3.1)	587 (4.4)	
Diabetes mellitus	23,018 (12.5)	17,311 (12.5)	5,707 (12.4)	0.4396	3,949 (12.0)	1,758 (13.2)	<0.0001
Hypertension	69,670 (37.7)	51,433 (37.1)	18,237 (39.5)	<0.0001	12,519 (38.2)	5,718 (42.8)	<0.0001
Dyslipidemia	60,416 (32.7)	45,209 (32.6)	15,207 (33.0)	0.2381	10,317 (31.4)	4,890 (36.6)	<0.0001
Chronic kidney disease	12,858 (7.0)	9,150 (6.6)	3,708 (8.0)		2,473 (7.5)	1,235 (9.3)	
Lipid profile							
*TG	106.3 (106.0–106.6)	107.2 (107.0–107.8)	103.4 (102.9–103.9)	<0.0001	102.0 (101.4–102.5)	107.1 (106.2–108.0)	<0.0001
Chronic pancreatitis	174 (0.09)	124 (0.09)	50 (0.11)	0.2549	39 (0.12)	11(0.08)	0.2803
F/U duration							
Mean ± SD	5.6 ± 2.3	5.6 ± 2.25	5.5 ± 2.3	<0.0001	5.5 ± 2.3	5.5 ± 2.2	0.1486
Median (Q1–Q3)	5.5 (3.7–7.5)	5.5 (3.7–7.5)	5.4 (3.6–7.4)	<0.0001	5.4 (3.6–7.5)	5.4 (3.6–7.3)	0.0378

Table 2. Baseline characteristics of study participants for the analysis of chronic pancreatitis. RA, Rheumatoid arthritis; SPRA, seropositive rheumatoid arthritis; SNRA, seronegative rheumatoid arthritis; TG, triglyceride; SD, standard deviation.

					Cause-specific model				Fine and Gray model
RA status	No	Events, No	Duration, PY	Incidence rate (per 1000 PY)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)	Model 4 HR (95% CI)
Acute pancreatitis									
Control	128,304	175	722,722.2	0.24 (0.21–0.28)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
RA	42,768	77	237,132.0	0.32 (0.26–0.41)	1.34 (1.03–1.76)	1.36 (1.04–1.78)	1.35 (1.03–1.77)	1.33 (1.02–1.74)	1.29 (0.99–1.69)
P value					0.031	0.024	0.038	0.032	0.061
Control	128,304	175	722,722.2	0.24 (0.21–0.28)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
SPRA	30,565	56	169,785.0	0.33 (0.25–0.43)	1.36 (1.01–1.84)	1.38 (1.02–1.86)	1.37 (1.01–1.85)	1.36 (1.01–1.84)	1.31 (0.97–1.77)
SNRA	12,203	21	67,346.9	0.31 (0.2–0.48)	1.29 (0.82–2.03)	1.32 (0.84–2.08)	1.32 (0.84–2.07)	1.26 (0.80–1.98)	1.25 (0.79–1.96)
P value					0.096	0.077	0.087	0.109	0.169
SPRA	30,565	56	169,785.0	0.33 (0.25–0.43)	1.06 (0.64–1.74)	1.04 (0.63–1.72)	1.03 (0.62–1.71)	1.10 (0.66–1.81)	1.07 (0.64–1.77)
SNRA	12,203	21	67,346.9	0.31 (0.2–0.48)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
P value					0.831	0.877	0.905	0.726	0.791
Chronic pancreatitis									
Control	138,495	124	776,047.4	0.16 (0.13–0.19)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
RA	46,165	50	254,482.3	0.20 (0.15–0.26)	1.23 (0.89–1.71)	1.25 (0.90–1.74)	1.26 (0.91–1.75)	1.25 (0.90–1.74)	1.21 (0.87–1.69)
P value					0.214	0.182	0.170	0.189	0.264
Control	138,495	124	776,047.4	0.16 (0.13–0.19)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
SPRA	32,815	39	181,211.2	0.22 (0.16–0.29)	1.35 (0.94–1.93)	1.36 (0.95–1.96)	1.37 (0.95–1.96)	1.36 (0.95–1.96)	1.31 (0.91–1.89)
SNRA	13,350	11	73,271.1	0.15 (0.08–0.27)	0.94 (0.51–1.75)	0.97 (0.52–1.79)	0.99 (0.53–1.83)	0.96 (0.52–1.78)	0.95 (0.51–1.77)
P value					0.244	0.223	0.228	0.228	0.204
SPRA	32,815	39	181,211.2	0.22 (0.16–0.29)	1.44 (0.74–2.82)	1.42 (0.73–2.77)	1.40 (0.72–2.75)	1.45 (0.74–2.84)	1.41 (0.71–2.81)
SNRA	13,350	11	73,271.1	0.15 (0.74–2.82)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
P value					0.284	0.308	0.324	0.283	0.332

Table 3. Risk of acute pancreatitis and chronic pancreatitis according to the presence of rheumatoid arthritis and serologic status. PY, person-years; RA, rheumatoid arthritis; SPRA, seropositive RA; SNRA, seronegative RA. *Model 1 was non-adjusted; model 2 was adjusted for age, sex; model 3 was adjusted additionally smoking, alcohol drinking, physical activity, low income; model 4 was adjusted additionally diabetes, hypertension, hyperlipidemia, chronic kidney disease.

0.95–1.96) than the matched control, while patients with SNRA did not differ in their risk (aHR 0.96, 95% CI 0.52–1.78). Patients with SPRA tended to have higher risk than patients with SNRA (aHR 1.45, 95% CI 0.74–2.84), although this was not statistically significant (Table 3; Fig. 2B). When the Fine-Gray model was applied, chronic pancreatitis did not show a significant association (aHR 1.21, 95% CI 0.87–1.69, $P=0.264$), generally consistent with the main analyses using the Cox model.

Discussion

In this nationwide cohort study, we observed that patients with RA had a 1.33-fold higher risk of developing acute pancreatitis compared to those without RA, and we also observed a slight increase in developing chronic pancreatitis among patients with RA, although this was not statistically significant.

Our results showing 1.33-fold risk of developing acute pancreatitis in the RA group compared to the matched control participants aligns with the previous research, although the estimates are lower than findings of previous research from Taiwan (aHR=1.62) or the US (OR=2.51)^{8,9}. The specific biological mechanisms connecting RA and acute pancreatitis have not yet been fully understood. However, there is no doubt that an inflammatory immune mechanism likely plays a pivotal role in its development. The pathogenesis of RA involves many immune cells, cytokines growth and differentiation factors, and transcription factors, which induce inflammatory response²⁰. Patients with acute pancreatitis also show increased serum levels of pro-inflammatory or inflammatory cytokines^{21,22}. Examining the pathogenesis of RA and acute pancreatitis reveals similarities in the release of cytokines and chemokines, which fuels systemic hyper-inflammation reactions caused by the activation of NF-κB, transcription factors and the inflammatory reaction resulting from the accumulation of the

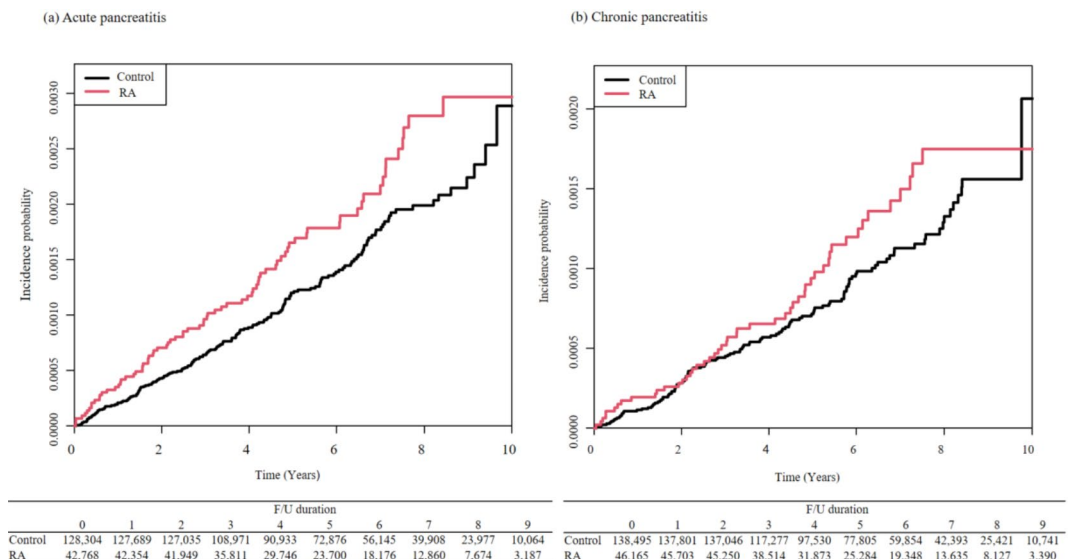


Fig. 2. Cumulative incidence of pancreatitis according to rheumatoid arthritis. (A) Acute pancreatitis, (B) Chronic pancreatitis.

NLRP3 inflammasome, a critical producer of IL-1 and IL-18^{21–27}. In both RA and acute pancreatitis patients, the production of IL-1 and IL-18 by the NLRP3 inflammasome is increased, and these cytokines are already known to play a crucial role in the pathogenesis of both diseases^{20,21,25}.

Our study showed no significant difference in acute pancreatitis between SPRA and SNRA patients. Although SNRA did not show significant difference compared to matched control patients, it appears to be due to the small sample size, rather than true lack of association. Consequently, while the results should be interpreted with caution due to the limited sample size, the potential clinical relevance cannot be dismissed.

In the case of chronic pancreatitis, while the limited sample size did not yield statistically significant results, a small increase in chronic pancreatitis was noted among patients with RA. When examined by serological status, it seemed that only SPRA is associated with chronic pancreatitis, although caution is needed for the interpretation because of the small number of events. The mechanism linking RA and chronic pancreatitis remains unclear. However, since chronic pancreatitis is a condition characterized by fibrosis resulting from recurrent episode of acute inflammation, it can be considered similar to RA in terms of chronic inflammation²⁵. Additionally, a pathological study found that in patients with RA, pancreatic tissue evaluation revealed ischemia due to vasculitis, which was accompanied by reactive inflammation and regressive changes in the pancreatic gland²⁸. When examined by serological status, it seemed that only SPRA is associated with chronic pancreatitis, although caution is needed in the interpretation because of the small number of events. Additionally, autoimmune pancreatitis, a form of chronic pancreatitis characterized by lymphocyte infiltration and inflammation²⁹, may have been included in the chronic pancreatitis group. Autoimmune pancreatitis is known to be associated with autoimmune diseases such as Sjögren's syndrome, rheumatoid arthritis, primary biliary cirrhosis, and primary sclerosing cholangitis and so on^{30,31}.

In patients with RA, gastrointestinal (GI) manifestations can arise from various causes, such as bowel infarction, bowel perforation, pan-colitis or appendicitis³². This study suggests that it may be necessary to consider acute or chronic pancreatitis as a differential diagnosis in cases of GI manifestations. Conversely, if acute or chronic pancreatitis develops in patients with RA, it is important to consider a possible association with RA as a potential cause.

The present study has several methodological advantages over previous ones. First, we applied a more accurate definition of the diagnosis of RA and examined the occurrence of both acute and chronic pancreatitis according to serologic status of RA. While previous studies depended on disease code only⁹ or prescriptions of DMARDs⁸ to identify patients with RA, our study used a combination of disease codes, RID program enrollment, and prescription of DMARDs for sufficient amounts of time to define RA, thereby reducing the likelihood of misclassification. Second, we adjusted various socioeconomic, metabolic, and behavioral factors in the multivariate-adjusted model, which were not considered in previous studies^{8,9}, and we found consistent results across all adjustments. This implies RA is an independent risk factor for pancreatitis development.

Several limitations of the present study should also be mentioned. First, due to the nature of claims data, the inability to access RA disease activity led to a restricted assessment of RA severity. Second, although it may be important to consider whether chronic pancreatitis is autoimmune-related when examining its association with RA, the incidence of autoimmune pancreatitis among the cases of chronic pancreatitis was not separately investigated because they are included under the same ICD-10 code. However, the proportion of autoimmune pancreatitis cases within those of chronic pancreatitis is 1–2% and is unlikely to have significantly influenced the results of this study. Nonetheless, considering the potential connection between the mechanisms of RA and autoimmune pancreatitis, further studies that investigate them separately would be valuable³³. Third, the

number of pancreatitis cases was not large enough to conduct an analysis of the association with DMARDs administration. Fourth, even though our models were adjusted for various potential confounders, information on other potential confounders like family history and genetic information was not available^{34,35}. Moreover, we were unable to adjust for medications and procedures such as post-endoscopic retrograde cholangiopancreatography that could potentially influence pancreatitis^{36,37}. Fifth, retrospective studies typically encounter surveillance bias, where individuals diagnosed with RA may receive more frequent health care service, potentially leading to a higher likelihood of obtaining a pancreatitis diagnosis. However, diagnosis of acute pancreatitis is very unlikely to have been affected or increased by frequent hospital visits for check-up or other reasons, since acute pancreatitis usually manifests with acute severe pain, requiring a visit to the hospital. Lastly, our study participants were restricted to those undergoing health screenings and may have been healthier and more committed to a healthy lifestyle compared to the general population.

Conclusion

In conclusion, this nationwide cohort study found an association between RA and an increased risk of acute pancreatitis and also possibly chronic pancreatitis. Therefore, as shown in the present study, a diagnosis of acute or chronic pancreatitis should not be overlooked and included as one of the differential diagnosis when patients with RA present with abdominal pain or discomfort.

Data availability

The data can be accessed on the Korean National Health Insurance homepage (<http://nhiss.nhis.or.kr>), but restrictions apply to the availability of the data, which was used with permission for the current study and therefore not publicly available. The data is available from the corresponding author upon reasonable request and with permission of KNHIS. Applications to use the KNHIS data will be reviewed by the inquiry committee of research support and, once approved, raw data will be provided to the applicant with a fee.

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Author contributions

D.W.S., H.K. and J.P. contributed study concept and design, analysis and interpretation, drafting and critical revision of the manuscript. J.H.J. and K.H. designed statistical analysis. Y.E., S.K., S.K. and J.J.H. critically revised the manuscript. All authors reviewed the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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