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Association between rheumatoid arthritis and interstitial lung disease and impact of serologic status: a large-scale longitudinal study

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Interstitial lung disease (ILD) leads to worse outcomes in subjects with rheumatoid arthritis (RA). Few large-scale longitudinal studies have provided comprehensive data on the incidence and risk of ILD in RA compared with non-RA populations. We compare the risk of incident ILD in subjects with RA and matched controls, while also evaluating the impact of RA serologic status. Using the Korean National Health Insurance Service Data between 2010 and 2017, we identified 52,325 individuals with RA and 261,625 without RA. During a median follow-up period of 4.4 years, 3.7% of the RA cohort and 0.5% of the matched cohort developed ILD, with incidence rates of 8.30 and 1.01 per 1,000 person-years. Compared to controls, the risk of incident ILD was significantly higher in the RA cohort (adjusted hazard ratio [aHR] 7.84 [7.29–8.44]), and seropositive and seronegative RA exhibited aHRs of 9.00 (8.34–9.72) and 4.81 (4.25–5.44). Although the risk of ILD was higher in seropositive RA than seronegative RA, the risk of developing ILD was also higher in subjects with seronegative RA than in matched controls, suggesting that close monitoring for ILD should be performed in this population.

Keywords Rheumatoid arthritis, Interstitial lung disease, Epidemiology, Risk

Abbreviations

BMI	Body mass index
CI	Confidence interval
DM	Diabetes mellitus
DMARD	Disease-modifying antirheumatic drug
HR	Hazard ratio
ICD-10	International Classification of Disease 10th revision
ILD	Interstitial lung disease

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NHIS	National Health Insurance Service
RA	Rheumatoid arthritis
RID	Rare intractable disease
SD	Standard deviation
SNRA	Seronegative rheumatoid arthritis
SPRA	Seropositive rheumatoid arthritis

Rheumatoid arthritis (RA) is the most common inflammatory arthritis disease and is characterized by systemic inflammation that progressively damages joints, particularly the small joints in the wrists, hands, and feet, often resulting in severe disability[1]. RA is associated with various extra-articular manifestations, including interstitial lung disease (ILD), which is a serious condition linked to increased morbidity and mortality rates[1–3]. Furthermore, ILD in subjects with RA is correlated with a decline in quality of life, limitations in functional abilities, and increased utilization of healthcare services, leading to higher costs[4,5]. The heterogeneity and variable course of ILD in subjects with RA present an ongoing challenge for clinicians.

Due to the clinical importance of ILD in RA patients, numerous previous studies have focused on its prevalence, incidence, and associated risk factors[2,6–8]. The prevalence of ILD ranges from approximately 4–8% in surveyed RA populations[2,6–8]and the incidence varies widely from 1.8 to 7.1 per 1,000 person-years[8]. Despite ongoing efforts, there remains a shortage of large-scale longitudinal studies that provide comprehensive data on the incidence and risk of ILD, especially in comparison to the non-RA population[2]. This is primarily because most prior studies did not include a control group. While one study did compare the risk of ILD between RA and non-RA populations, it had a relatively small sample size and did not fully adjust for potential confounders[2]. Therefore, to accurately assess the risk of ILD in the RA population relative to controls, further longitudinal cohort studies that thoroughly address these factors are essential.

Seropositivity for rheumatoid factor (RF) or anti-cyclic citrullinated peptide antibodies (anti-CCP) indicates high disease activity and thereby increases the risk of extra-articular manifestations[9,10]. The development of ILD was found to be related to RF or anti-CCP positivity in previous studies[9,11–13]. Given that confirmation of seropositivity is a standard practice at RA diagnosis, data on the association between seropositivity and ILD risk would be clinically very informative. However, few studies have conducted additional analyses to determine differences in the incidence and risk factors of ILD based on serological status.

Therefore, the objective of this study was to compare the incidence and risk of ILD between a cohort of individuals with RA and age- and sex-matched controls drawn from a large, nationally representative longitudinal database in Korea. Additionally, to assess whether RA serologic status affects the risk of developing incident ILD, we compared ILD risk between seropositive and seronegative populations with RA and compared these groups with the non-RA population.

Results

Baseline characteristics

The mean age of the study population was 58.5 years (standard deviations [SD], 10.0 years) and 24.5% were male. The proportions of pulmonary and extra-pulmonary comorbidities were higher in the RA cohort than the matched cohort ($p < 0.001$ for all), except for diabetes mellitus ($p = 0.288$). Additionally, compared to the matched cohort, there were fewer never-smokers, alcohol drinkers, and regular exercisers in the RA cohort ($p < 0.001$). Body mass index (BMI) was lower in the RA cohort than in the matched cohort ($p < 0.001$).

The seropositive rheumatoid arthritis (SPRA) group had a higher proportion of males, was younger, and had fewer never-smokers than subjects with seronegative rheumatoid arthritis (SNRA) ($p < 0.001$ for all). Additionally, subjects with SPRA consumed more alcohol, engaged in regular exercise more frequently, and had a higher BMI than those with SNRA ($p < 0.001$ for all). All comorbidities, except for myocardial infarction ($p = 0.150$), airway diseases ($p = 0.242$), and tuberculosis were more frequently observed in individuals with SPRA than those with SNRA. However, tuberculosis was more common in subjects with SNRA compared to those with SPRA ($p = 0.005$) (Table 1).

Incidence and risk of ILD according to the presence or absence of RA

During the median follow-up period of 4.4 (interquartile range, 2.6–6.4) years, 3.7% ($n = 1{,}921/52{,}325$) of the RA cohort and 0.5% ($n = 1{,}197/261{,}625$) of the matched cohort developed ILD, with incidence rates of 8.30 and 1.01 per 1,000 person-years, respectively ($p < 0.001$ for both). Even after adjusting for potential confounders, the risk of incident ILD was also significantly higher in the RA cohort than in the matched cohort: unadjusted hazard ratio (HR) 8.25, 95% confidence interval [CI] 7.68–8.87; adjusted HR in Model 1 8.19, 95% CI 7.62–8.81; adjusted HR in Model 2 7.97, 95% CI 7.41–8.58; subdistribution HR [sHR] in Model 3 7.84, 95% CI 7.29–8.44). Similarly, the cumulative incidence plot depicts a significantly higher incidence of ILD in the RA cohort than in the matched cohort (log-rank $p < 0.001$; Fig. 1A).

Incidence and risk of ILD according to RA serologic status

When RA was classified according to serologic status, 2.1% ($n = 323/15{,}094$) of the SNRA cohort and 4.3% ($n = 1{,}598/37{,}231$) of the SPRA cohort developed ILD, with incidence rates of 4.88 and 9.66 per 1,000 person-years, respectively ($p < 0.001$ for both) (Table 2). In model 3, both SNRA (sHR 4.81, 95% CI, 4.25–5.44) and SPRA cohorts (sHR 9.00, 95% CI, 8.34–9.72) were at higher risk of developing ILD compared to matched controls. When the risk of ILD was compared between SPRA and SNRA cohorts, the SPRA cohort exhibited higher risk of ILD than the SNRA cohort (sHR 1.90, 95% CI, 1.68–2.14) (Table 2). Figure 1B shows the cumulative incidence plot according to RA serologic status.

Variables	Total (n = 313,950)	RA status			Serologic status		
		No (n = 261,625)	Yes (n = 52,325)	p -value	SNRA (n = 15,094)	SPRA (n = 37,231)	p-value
Male sex	76,866 (24.5)	64,055 (24.5)	12,811 (24.5)	> 0.999	8,783 (23.6)	4,028 (26.7)	< 0.001
Age, years	58.5 ± 10.0	58.5 ± 10.0	58.5 ± 10.0	> 0.999	58.8 ± 10.1	57.8 ± 10.0	< 0.001
40–64	225,078 (71.7)	187,565 (71.7)	37,513(71.7)	> 0.999	26,295 (70.6)	11,218 (74.3)	< 0.001
≥ 65	88,872 (28.3)	74,060 (28.3)	14,812(28.3)		10,936 (29.4)	3,876 (25.7)	
Low income	73,652 (23.5)	61,362 (23.5)	12,290(23.5)	0.868	8,899 (23.9)	3,391 (22.5)	< 0.001
Smoking				< 0.001			< 0.001
Never smoker	250,645 (79.8)	209,476 (80.1)	41,169(78.7)		29,396 (79.0)	11,773 (78.0)	
Ex-smoker (< 20 PY)	18,028 (5.7)	14,953 (5.7)	3,075(5.9)		1,960 (5.3)	1,115 (7.4)	
Ex-smoker (≥ 20 PY)	12,304 (3.9)	9,866 (3.8)	2,438(4.7)		1,659 (4.5)	779 (5.2)	
Current smoker (< 20 PY)	16,592 (5.3)	13,935 (5.3)	2,657(5.1)		1,910 (5.1)	747 (5.0)	
Current smoker (≥ 20 PY)	16,381 (5.2)	13,395 (5.1)	2,986(5.7)		2,306 (6.2)	680 (4.5)	
Alcohol drinking	88,214 (28.1)	75,808 (29.0)	12,406(23.7)	< 0.001	8,608 (23.1)	3,798(25.2)	< 0.001
Regular exercise	63,521 (20.2)	53,881 (20.6)	9,640(18.4)	< 0.001	6,645 (17.9)	2,995(19.8)	< 0.001
BMI, kg/m^2				< 0.001			< 0.001
< 18.5	9,021 (2.9)	7,055 (2.7)	1,966 (3.8)		1,480(4.0)	486(3.2)	
18.5–23.0	121,658 (38.8)	100,036 (38.2)	21,622 (41.3)		15,723(42.2)	5,899(39.1)	
23.0–25.0	79,284 (25.3)	66,507 (25.4)	12,777 (24.4)		9,063(24.3)	3,714(24.6)	
≥ 25.0	103,987 (33.1)	88,027 (33.7)	15,960 (30.5)		10,965(29.5)	4,995(33.1)	
Comorbidities							
Diabetes mellitus	41,638 (13.3)	34,623 (13.2)	7,015 (13.4)	0.288	4,834 (13.0)	2,181(14.5)	< 0.001
Hypertension	122,173 (38.9)	100,275 (38.3)	21,898 (41.9)	< 0.001	15,202 (40.8)	6,696 (44.4)	< 0.001
Dyslipidemia	104,307 (33.2)	86,407 (33.0)	17,900 (34.2)	< 0.001	12,238 (32.9)	5,662 (37.5)	< 0.001
CKD	22,371 (7.1)	17,889 (6.8)	4,482 (8.6)	< 0.001	3,037 (8.2)	1,445 (9.6)	< 0.001
MI	1,900 (0.6)	1,343 (0.5)	557 (1.1)	< 0.001	381 (1.0)	176 (1.2)	0.150
Airway diseases	53,130 (16.9)	40,439 (15.5)	12,691 (24.3)	< 0.001	9,082 (24.4)	3,609 (23.9)	0.242
Tuberculosis	646 (0.2)	353 (0.1)	293 (0.6)	< 0.001	230 (0.6)	63 (0.4)	0.005

Table 1. Baseline characteristics of study participants. Data are presented as mean ± SD or number (percentage). *RA* Rheumatoid arthritis; *SNRA* Seronegative rheumatoid arthritis; *SPRA* Seropositive rheumatoid arthritis; *PY* Pack-years; *BMI* Body mass index; *CKD* Chronic kidney disease; *MI* Myocardial infarction.

Subgroup analysis

Sex, age, and smoking status had significant interactions with the association between RA and ILD development (p for interaction < 0.001 for all). The association between RA and ILD was more prominent in females compared to males (adjusted HR 9.37, 95% CI 8.52–10.30 vs. 6.24, adjusted HR 95% CI 5.57–7.00) and in younger individuals compared to older individuals (adjusted HR 11.0, 95% CI 9.91–12.20 vs. adjusted HR 5.62, 95% CI 5.06–6.24). Regarding smoking status and ILD risk, the risk of ILD was especially high in never-smokers (adjusted HR 8.78; 95% CI, 8.03–9.60) and current smokers (adjusted HR 8.37; 95% CI, 6.18–11.33 and adjusted HR 6.99; 95% CI, 5.62–8.69) compared to ex-smokers (adjusted HR 5.87, 95% CI 4.50–7.64 for < 20 pack-years (PY) and adjusted HR 5.42, 95% CI 4.23–6.93 for ≥ 20 PY) (p for interaction < 0.001). Income, alcohol drinking, regular exercise, BMI, and tuberculosis did not have significant effect modifications on the association between RA and ILD development (Table 3)**.** Similar results were observed in both SPRA and SNRA cohorts (**Supplementary Table 1**).

Discussion

This study is the largest comprehensive study to evaluate the incidence of ILD in individuals with RA compared with a non-RA population using national cohort data. Furthermore, we conducted additional analyses by subdividing the cohort into SPRA and SNRA groups. Individuals with RA had an ILD incidence rate of 8.30 per 1,000 person-years, which is approximately 8-fold higher than those without RA. Additionally, the increased risk of developing ILD was significant in both SPRA and SNRA, although it was especially high in SPRA. Sex, age, and smoking status had significant interactions with the association between RA and ILD development.

Since ILD is a serious extra-articular manifestation of RA related to increased morbidity and mortality[14], previous epidemiological studies have focused on ILD incidence and related risk factors. One recent population-based study in Germany (n= 40,686 in 2007 to 85,175 in 2020) investigated the prevalence and incidence of ILD in RA patients between 2007 and 2020. They reported that incident ILD ranged from 0.13 to 0.21% per year (0.17% in SPRA and 0.07% in SNRA in 2020)[6]. One recent Canadian RA population-based study (n= 184,400) using repeated cross-sectional analyses from 2000 to 2018 reported that ILD incidence rose from 1.6 (95% CI

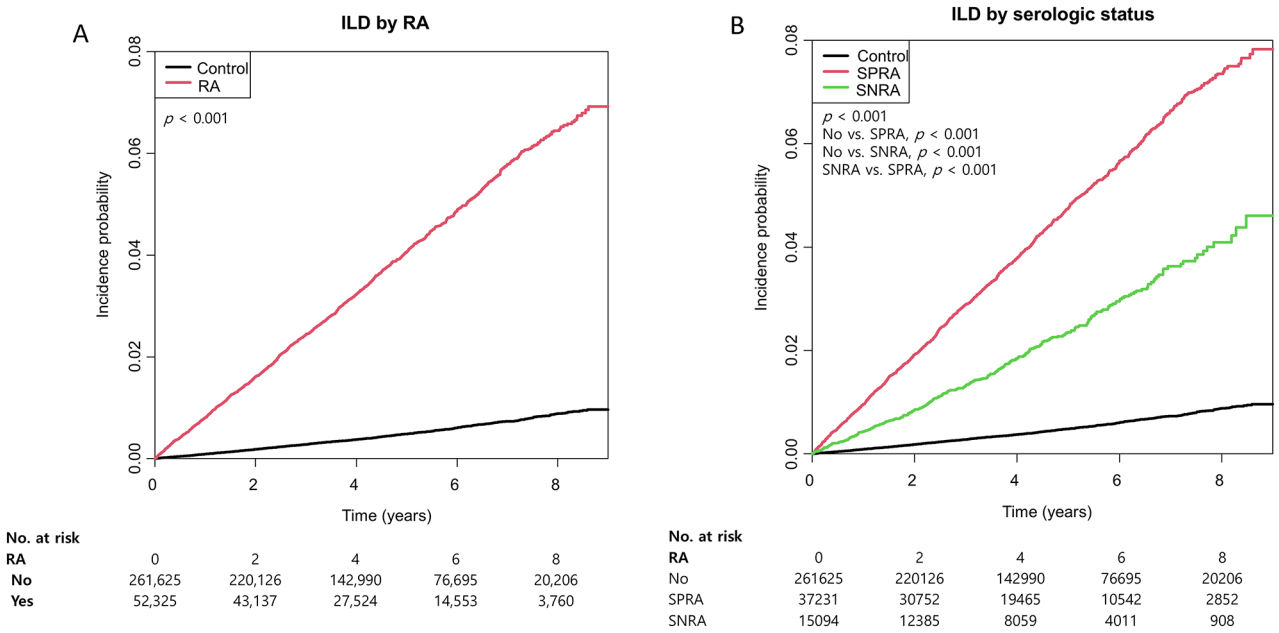


Fig. 1. Cumulative incidence of ILD according to (**A**) rheumatoid arthritis status and (**B**) serologic status of rheumatoid arthritis. *ILD* interstitial lung disease; *RA* Rheumatoid arthritis; *SNRA* Seronegative rheumatoid arthritis; *SPRA* Seropositive rheumatoid arthritis.

	Participants No.	ILD	Duration (PY)	Incident rate (/1,000 PY) with 95% CI	Unadjusted HR (95% CI)	Model 1 aHR (95% CI)	Model 2 aHR (95% CI)	Model 3 sHR (95% CI)
By RA status								
Control	261,625	1,197	1,189,075.5	1.01 (0.95–1.07)	Reference	Reference	Reference	Reference
RA	52,325	1,921	231,535.6	8.30 (7.93–8.68)	8.25 (7.68–8.87)	8.19 (7.62–8.81)	7.97 (7.41–8.58)	7.84 (7.29–8.44)
By RA status and seropositivity								
Control	261,625	1,197	1,189,075.5	1.01 (0.95–1.07)	Reference	Reference	Reference	Reference
SNRA	15,094	323	66,178.0	4.88 (4.36–5.44)	4.86 (4.30–5.49)	4.94 (4.36–5.58)	4.83 (4.27–5.47)	4.81 (4.25–5.44)
SPRA	37,231	1,598	165,357.6	9.66 (9.20–10.15)	9.61 (8.91–10.35)	9.47 (8.78–10.21)	9.19 (8.52–9.91)	9.00 (8.34–9.72)
By seropositivity								
SNRA	15,094	323	66,178.0	4.88 (4.36–5.44)	Reference	Reference	Reference	Reference
SPRA	37,231	1,598	165,357.6	9.66 (9.20–10.15)	1.98 (1.76–2.23)	1.94 (1.72–2.18)	1.92 (1.70–2.16)	1.90 (1.68–2.14)

Table 2. Risk of ILD according to RA status and serologic status of RA. **Model 1** was adjusted for age, sex, low income, smoking, alcohol drinking, physical activity, and body mass index. **Model 2** was further adjusted for diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, myocardial infarction, airway diseases, and tuberculosis. **Model 3** used the Fine-Gray Competing risk model. **Model 3** was also adjusted for age, sex, low income, smoking, alcohol drinking, physical activity, body mass index, diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, myocardial infarction, airway diseases, and tuberculosis. *ILD* interstitial lung disease; *RA* rheumatoid arthritis; *PY* person-years; *HR* hazard ratio; *CI* confidence interval; *aHR* adjusted hazard ratio; *sHR* subdistribution hazard ratio; *SNRA* seronegative RA; *SPRA* seropositive RA.

1.3–2.0) to 3.3 (95% CI 3.0–3.6) per 1,000 RA patients during the study period[7]. Another study with nationwide longitudinal data from the USA from 2008 to 2017 (n=509,787) reported that the incidence rate of ILD was 7.14 (95% CI 7.02–7.26) per 1,000 person-years among subjects with RA[8]. Although many studies have been conducted, these previous studies have limitations with due to the lack of a control group. Thus, the relative risk of ILD in individuals with RA versus those without RA could not be adequately evaluated.

To the best of our knowledge, only one USA population-based study (subjects with RA, n=582; subjects without RA, n=603) compared RA and non-RA cohorts, and reported that the risk of developing ILD was 7.7%

Subgroups	RA	No.	ILD	Duration (person-years)	IR per 1,000 person-years	Adjusted HR*
Sex						
Male	No	64,055	538	277,277.5	1.94	Reference
	Yes	12,811	678	53,130.0	12.76	6.24 (5.57–7.00)
Female	No	197,570	659	911,798.0	0.72	Reference
	Yes	39,514	1,243	178,405.6	6.97	**9.37 (8.52–10.30)**
p for interaction						< 0.001
Age, years						
40–64	No	187,565	518	871,523.7	0.59	Reference
	Yes	37,513	1,168	171,358.7	6.82	**11.0 (9.91–12.20)**
≥ 65	No	74,060	679	317,551.9	2.14	Reference
	Yes	14,812	753	60,176.9	12.51	5.62 (5.06–6.24)
p for interaction						< 0.001
BMI						
<18.5	No	7,055	39	30,333.9	1.29	Reference
	Yes	1,966	73	8,278.8	8.82	6.98 (4.73–10.30)
18.5–23.0	No	100,036	443	455,318.2	0.97	Reference
	Yes	21,622	798	96,566.7	8.26	8.21 (7.30–9.22)
23.0–25.0	No	66,507	299	304,883.9	0.98	Reference
	Yes	12,777	501	56,990.3	8.79	8.69 (7.53–10.03)
≥25.0	No	88,027	416	398,539.5	1.04	Reference
	Yes	15,960	549	69,699.7	7.88	7.28 (6.40–8.27)
p for interaction						0.256
Low income						
No	No	200,263	926	913,967.8	1.01	Reference
	Yes	40,035	1,511	179,099.3	8.44	7.98 (7.35–8.67)
Yes	No	61,362	271	27,5107.7	0.99	Reference
	Yes	12,290	410	52,436.3	7.82	7.94 (6.81–9.26)
p for interaction						0.956
Smoking						
Never smoker	No	209,476	781	963,380.6	0.81	Reference
	Yes	41,169	1,342	185,255.3	7.24	**8.78 (8.03–9.60)**
Ex-smoker (< 20 PY)	No	14,953	101	62,751.0	1.61	Reference
	Yes	3,075	122	12,742.6	9.57	5.87 (4.50–7.64)
Ex-smoker (≥ 20 PY)	No	9,866	112	41,763.3	2.68	Reference
	Yes	2,438	146	9,798.5	14.90	5.42 (4.23–6.93)
Current smoker (< 20 PY)	No	13,935	69	61,088.3	1.13	Reference
	Yes	2,657	107	11,169.4	9.58	**8.37 (6.18–11.33)**
Current smoker (≥ 20 PY)	No	13,395	134	60,092.4	2.23	Reference
	Yes	2,986	204	12,569.8	16.23	**6.99 (5.62–8.69)**
p for interaction						< 0.001
Alcohol drinking						
No	No	185,817	862	852,010.1	1.01	Reference
	Yes	39,919	1,482	178,025.5	8.32	7.97 (7.32–8.67)
Yes	No	75,808	335	337,065.4	0.99	Reference
	Yes	12,406	439	53,510.1	8.20	7.98 (6.92–9.21)
p for interaction						0.980
Regular exercise						
No	No	207,744	939	946,774.2	0.99	Reference
	Yes	42,685	1,567	189,382.8	8.27	8.06 (7.42–8.74)
Yes	No	53,881	258	242,301.3	1.06	Reference
	Yes	9,640	354	42,152.8	8.40	7.65 (6.51–8.98)
p for interaction						0.571
Tuberculosis						
No	No	261,272	1,193	1,187,628.1	1.00	Reference
	Yes	52,032	1,906	230,253.6	8.28	7.99 (7.43–8.60)

Continued

Subgroups	RA	No.	ILD	Duration (person-years)	IR per 1,000 person-years	Adjusted HR*
Yes	No	353	4	1,447.4	2.76	Reference
	Yes	293	15	1,282.0	11.70	3.71 (1.23–11.17)
p for interaction						0.174

Table 3. Stratified analysis of ILD risk according to RA status. *Data are presented as hazard ratio (95% confidence interval). Hazard ratios were adjusted for age, sex, low income, smoking, alcohol drinking, physical activity, body mass index, diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, myocardial infarction, airway diseases, and tuberculosis. *ILD* interstitial lung disease; *RA* rheumatoid arthritis; *PY* pack-years; *BMI* body mass index.

for subjects with RA and 0.9% for those without, showing an approximately 9-fold increase in risk[2]. However, the number of subjects with RA and controls was relatively small (about 600 in each group), and only age, sex, and smoking status were adjusted for in this study. Additionally, RA was not analyzed by serologic status. After addressing these limitations by including a larger study population and adjusting for potential biases, our study demonstrated that patients with RA have approximately 8-fold higher risk of developing ILD than those without RA, which is consistent with the results of the abovementioned study[2]. Our study also has the advantage of performing subgroup analysis according to seropositivity.

Similar to our results showing higher risk of ILD in SPRA than in SNRA, previous studies showed that RF or anti-CCP positivity was related to the development of ILD[9,11–13]. For example, the Veterans Affairs Rheumatoid Arthritis prospective registry (n=2,328) reported that higher concentrations of RF and anti-CCP were independently associated with the presence of RA-ILD[13]. In addition, a Canadian cohort study (n=184,400) found trends toward an association between RF seropositivity and ILD, although the results did not achieve statistical significance[7]. Supporting this, translational research reported higher concentrations of anti-CCP in bronchoalveolar lavage fluid in individuals with RA with lung abnormalities, and suggested that RA-related autoantibodies are produced in the lungs and may promote ILD-related inflammation.

While it is well established that the risk of ILD is higher in SPRA than in SNRA[13], it remains largely unclear whether the risk of ILD in SNRA is higher compared to the non-RA population. In previous studies, individuals with SNRA were used as controls to estimate the risk of ILD in individuals with SPRA. Another previous study that evaluated the risk of ILD in individuals with RA versus controls did not subdivide RA into SPRA and SNRA[2]. Overcoming these limitations by comparing the relative risk of ILD in RA to matched controls according to seropositivity, we were able to determine that SNRA carries approximately 5-fold higher risk of developing ILD compared to age- and sex-matched controls.

In our study, the association between RA and ILD was especially prominent among females, younger individuals, and never- or current smokers. The reasons for these phenomena could not be fully explained considering the observational nature of our study. One consideration is RA disease severity, which is significantly associated with increased risk of ILD. Studies have shown that RA disease activity measures are worse in females than in males and in patients with younger disease onset[15,16]. However, due to lack of data on disease activity other than seropositivity, we could not adjust for disease severity. Interestingly, smoking status also had a significant influence on the relationship between RA and the risk of ILD. This association was more prominent among never-smokers and current smokers compared to among ex-smokers. Smoking is not only a risk factor of idiopathic ILD, including idiopathic pulmonary fibrosis[17,18], but is also an important risk factor for developing ILD in RA[19]. Therefore, it would be plausible for the risk of ILD to be higher in currently smoking RA individuals compared to ex-smokers, since quitting smoking could attenuate the risk of ILD[20]. However, unexpectedly, the risk of ILD in never-smokers was as high as that in current smokers. Currently, it is difficult to provide plausible explanations for these phenomena, and thus, future prospective studies, including genetics, are needed.

Our study results provide valuable insights for clinicians and basic researchers. First, the higher risk of ILD not only in SPRA but also SNRA versus matched controls suggests that monitoring for ILD should be considered even in SNRA patients. Unfortunately, there is no standard method used for the early screening of ILD in patients with RA. Chest imaging (CT or lung ultrasonography), pulmonary function tests (e.g., spirometry and diffusion capacity of carbon monoxide), or some biomarkers (e.g., matrix metalloproteinase, pulmonary, activation-regulated chemokine, surfactant protein D, or KL-6) might be helpful for the early detection of ILD[21,22]. Future studies are needed. Second, our study results could be helpful for researchers exploring the pathogenesis of RA-ILD, especially in those with SNRA. While most studies have evaluated the role of anti-CCP in the pathogenesis of RA-ILD, there is a large area of uncertainty regarding how ILD develops in SNRA.

Our study has some limitations. First, since this study was conducted with a Korean dataset, studies performed in other countries or ethnicities are needed to generalize our study results. Also, healthy user bias can occur by including only individuals with health screening data in our analyses. Second, although we used a validated definition of RA based on International Classification of Disease 10th revision (ICD-10) codes and medications, ICD-10 code-based definition of RA may over- or underestimate RA. Similarly, other comorbidities were determined using ICD-10 codes, so there might be over- or underestimations of diagnosis. For ILD, the definition of ILD has evolved over time with various patterns of ILD including interstitial lung abnormality and interstitial pneumonia with autoimmune features. Such patterns of ILD have not been included in the ICD-10 codes used in our study. This could have affected the incidence of ILD in our study. Third, due to lack of laboratory, pulmonary function, and radiologic data, we could not incorporate these factors into our analyses.

We also did not have clinical data to determine the severity of RA and ILD, so we were unable to conduct an analysis that reflected disease severity. Future studies are needed to incorporate these data. Fourth, unlike previous studies showing a male predominance in RA-ILD, in our study, the risk of developing RA-ILD was higher in females than in males. This might be attributable to environmental or ethnic influences; however, we could not verify this.

In conclusion, we determined the incidence of ILD in patients with RA based on a nationwide dataset. The incidence of ILD in individuals with RA was higher than in individuals without RA. Although the risk of ILD was higher in individuals with SPRA than SNRA, the risk of developing ILD was also significantly higher in individuals with SNRA than in matched controls, suggesting that close monitoring for ILD should be performed in the RA population as a whole.

Methods

Data source

This is a retrospective cohort study. For this study we used a dataset provided by the Korean National Health Insurance Service (NHIS), a universal insurance provider managed by the government that covers 97% of the Korean population, approximately 50 million people. The NHIS dataset includes information on socioeconomics, demographic variables, healthcare utilization, health screening examination findings, disease diagnosis based on ICD-10 codes, and medical treatment and procedures[23]. The NHIS database includes a variety of medical and health information and has been widely used in various epidemiologic studies to identify risk factors for diseases[24–29].

Data from annual or biennial health screening examination programs for all adults, offered free of charge by the Ministry of Health and Welfare, constitute the health screening database. Commencing in 2009, the health screening examination encompasses anthropometric measurements like BMI, questionnaires pertaining to smoking, alcohol consumption, and physical activity, blood tests including lipid levels, and chest radiographs. With a current participation rate of 70–80%, the health screening examinations are representative of the Korean population. Furthermore, the Korean government furnishes anonymized health examination data to researchers[23].

Our study protocol was approved by the Institutional Review Board of Samsung Medical Center (IRB No. SMC 2022-06-141). The requirement for informed consent was waived by the IRB of Samsung Medical Center because the NHIS database uses an anonymous patient identification system. Our study complied with the Declaration of Helsinki and is reported according to the STROBE reporting guidelines for epidemiologic studies.

Study population and characteristics

To establish the RA cohort, from among 119,788 individuals diagnosed with RA between 2010 and 2017, we initially included 64,457 individuals who were diagnosed with RA and had health screening examination data within 2 years before RA diagnosis or follow-up between 2010 and 2017 for comprehensive analyses considering various confounders (e.g., BMI, personal habits including smoking status, alcohol consumption, or physical activity). We exclude those with other rheumatic diseases ($n=213$) and those with missing health screening examination data ($n=2,321$). Since the development of RA-ILD is relatively rare in young individuals[30,31], and health screening examinations were only offered to individuals aged 40 years or older prior to 2019[23], we excluded those younger than 40 years ($n=5,489$). After further excluding those who had previously been diagnosed with cystic fibrosis ($n=18$) or ILD ($n=2,253$) and those who were diagnosed with ILD within 1 year after RA diagnosis ($n=1,072$) to minimize the risk of reverse causality, we identified 53,091 individuals for the RA cohort. Of these, 52,325 individuals were eligible for 1:5 age- and sex-matching.

To establish age- and sex-matched controls, of the 1,207,831 individuals who were approximately 1:10 age- and sex-matched to the 119,788 individuals with RA, we included 677,322 who underwent health screening examinations in the same year that matched RA patients received health screening examinations. After excluding (1) 193,902 individuals aged < 40 years and 30,705 with missing health screening examination data, (2) 51 individuals with cystic fibrosis, (3) 20 individuals with other rheumatic diseases, (4) 2,084 individuals diagnosed with ILD before the index date, and (5) 2,529 individuals diagnosed with ILD within 1 year after the index date, 448,031 individuals remained in the matched controls. Of these, 261,625 individuals were eligible for 1:5 age and sex matching for the RA cohort (Fig. 2).

Study exposure

The exposure of this study was RA, which included both SPRA and SNRA. To identify subjects with SPRA and SNRA, a separate operational definition was applied to each group[32–35]. The NHIS operates the Rare and Intractable Disease (RID) program for patients with certain diseases, which provides beneficial cost reduction for relevant medical expenses. For subjects with RA, SPRA are eligible to be registered in the RID program only if the following requirements are satisfied: a positive result of RF or anti-CCP and a clinician's official document certifying that the patient meets the classification criteria for RA. SPRA patients were defined based on whether their claim records included the ICD-10 diagnostic code M05, the RID registration code V223, and a record of prescriptions for any disease-modifying anti-rheumatic drugs (DMARDs), including conventional synthetic DMARDs (methotrexate, hydroxychloroquine, leflunomide, sulfasalazine, tacrolimus, cyclosporine, D-penicillamine, bucillamine, azathioprine, minocycline, or mizoribine), biologic DMARDs (adalimumab, etanercept, infliximab, golimumab, rituximab, abatacept, tocilizumab), or targeted synthetic DMARDs (tofacitinib) for at least 180 days. For SNRA, subjects who visited the hospitals with diagnostic codes of ICD-10 M06, except M06.1 and M06.4, and had a prescription record of DMARDs for ≥ 180 days were defined as patients with newly diagnosed SNRA[32–35]. The index date was defined as when the RA-related diagnostic code was first registered.

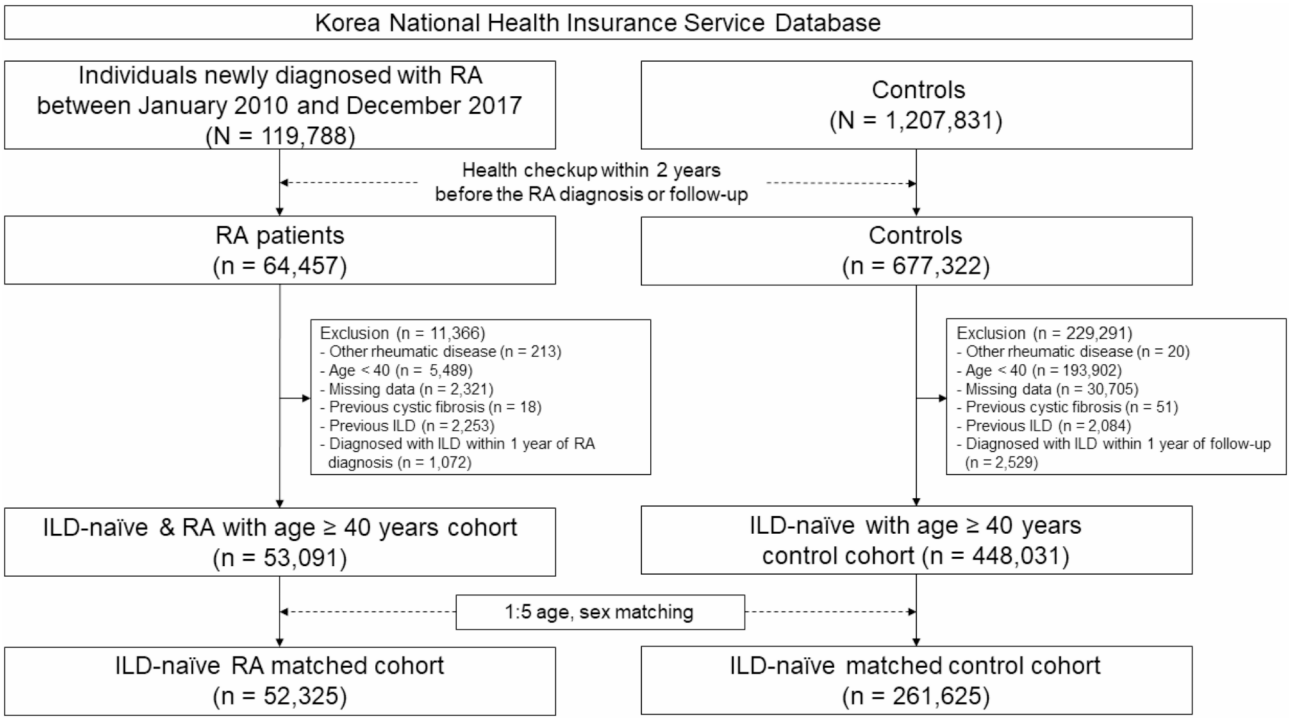


Fig. 2. Flow chart of the study population. *ILD* interstitial lung disease; *RA* Rheumatoid arthritis.

Study outcome

The outcome of this study was the incidence of ILD. ILD was defined as claims under the ICD-10 diagnosis code J84[36–38]. The study participants were followed from 1 year after RA diagnosis (or corresponding index date for matched controls) to the date of ILD diagnosis, censored date, or 31 December 2019.

Covariates

Data for basal characteristics of age, sex, BMI, smoking status, alcohol status, physical activity, income status, and comorbidities were collected from the dataset. Household income was categorized into quartiles based on insurance premium levels (in Korea, insurance premiums are determined by income level), with those covered by Medical Aid (poorest 3%) being merged into the lowest income quartile[39,40]. The lowest income quartile group was defined as "low income". Personal behaviors, including smoking status, alcohol consumption, and physical activity were determined based on a self-reported questionnaire. Smoking status was divided into never, ex-, and current smoker[41], and subjects with a history of smoking were subdivided into groups based on 20 PY. Alcohol consumption was divided into none, 1–2 times a week, 3–4 times a week, and almost every day. "Regular exercise" was defined as a moderate-intensity exercise for more than 5 days per week or vigorous exercise for more than 3 days per week[26,42,43]. BMI was calculated as body weight divided by the square of height (kg/m^2) and classified into four groups as follows: low (< 18.5 kg/m^2), normal (18.5–22.9 kg/m^2), overweight (23.0–24.9 kg/m^2), obese (≥ 25 mg/k^2)[44–46]. The definitions of comorbidities (diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, ischemic heart disease, and airway diseases [asthma or chronic obstructive pulmonary disease]) were based on ICD-10 codes as previously described[47–56]. Additionally, tuberculosis and other rheumatic diseases, including systemic sclerosis, systemic lupus erythematosus, dermatomyositis, mixed connective tissue diseases, and polymyalgia rheumatica, were defined using ICD-10 codes as well as registration with the national RID supporting program[25,27,29,33–35,39,47,57] (**Supplementary Table 2**).

Statistical analysis

Descriptive statistics are presented as number (percentage) for categorical variables and mean ± SD for continuous variables. We compared the two groups using the $\chi 2$ test for categorical variables, and t-tests for continuous variables. The incidence rates of ILD were calculated by dividing the number of incident events by the total follow-up period (1,000 person-years). A cumulative incidence plot was used to compare the incidence of ILD between the RA and matched cohorts, and a log-rank test was used to evaluate significant differences between the groups.

The risk of incident ILD in the RA cohort compared to the matched cohort was estimated using univariable and multivariable Cox proportional hazards regression analyses. In multivariable models, potential variables that may affect the development of RA as well as ILD were adjusted; model 1 was adjusted for age, sex, low income, smoking, alcohol drinking, physical activity, and body mass index that can be obtained from health screening examination. Model 2 was further adjusted for common medical comorbid conditions (diabetes mellitus,

hypertension, dyslipidemia, chronic kidney disease, myocardial infarction, airway diseases, and tuberculosis). Model 3 used a fine gray competitive risk model, calibrating all the variables that were adjusted in Model 2.

Stratified analyses were performed by basal demographics (sex, age, body mass index [BMI], and income status), personal habits (smoking, alcohol drinking, and regular exercise), and tuberculosis. Additionally, all these analyses were performed in equally divided groups according to RA serologic status. A two-sided p-value < 0.05 was considered statistically significant. All statistical analyses were performed using Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, NC, USA. http://www.sas.com).

Ethical approval and consent to participate The study protocol was approved by the Institutional Review Board of Samsung Medical Center (IRB No. SMC 2022-06-141). The requirement for informed consent was waived by the IRB of Samsung Medical Center because the NHIS database uses an anonymous patient identification system.

Data availability

The data that support the findings of this study are available from the Korean National Health Insurance Service. Restrictions apply to the availability of these raw data, which were used under license for the current study, and so are not publicly available. Data are however available from the corresponding authors upon reasonable request and with permission of the Korean National Health Insurance Service.

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Author contributions

H.K. and D.W.S. are the guarantors of the manuscript and take responsibility for the content of the manuscript, including the data and analysis.B.-G.K., H.L., K.H., H.K., and D.W.S. contributed to the conception and design of the study.B.-G.K., H.L., Y.E., K.H., J.-H.J., H.C., H.K., and D.W.S. were involved in the collection and interpretation of the data.K.H. and J.-H.J. were involved in statistical analyses.B.-G.K. and H.L. were major contributors to writing the manuscript.All authors read and approved the final manuscript.

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Declarations

Consent for publication

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Competing interests

The authors declare no competing interests.

Additional information

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