

Autoimmune inflammatory rheumatic diseases and COVID-19 outcomes in South Korea: a nationwide cohort study



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Summary

Background Real-world evidence on the association between autoimmune inflammatory rheumatic diseases, therapies related to these diseases, and COVID-19 outcomes are inconsistent. We aimed to investigate the potential association between autoimmune inflammatory rheumatic diseases and COVID-19 early in the COVID-19 pandemic.

Methods We did an exposure-driven, propensity score-matched study using a South Korean nationwide cohort linked to general health examination records. We analysed all South Korean patients aged older than 20 years who underwent SARS-CoV-2 RT-PCR testing between Jan 1 and May 30, 2020, and received general health examination results from the Korean National Health Insurance Service. We defined autoimmune inflammatory rheumatic diseases (inflammatory arthritis and connective tissue diseases) based on the relevant ICD-10 codes, with at least two claims (outpatient or inpatient) within 1 year. The outcomes were positive SARS-CoV-2 RT-PCR test, severe COVID-19 (requirement of oxygen therapy, intensive care unit admission, application of invasive ventilation, or death), and COVID-19-related death. Adjusted odds ratios (ORs) with 95% CIs were estimated after adjusting for the potential confounders.

Findings Between Jan 1 and May 30, 2020, 133 609 patients (70 050 [52·4%] female and 63 559 [47·6%] male) completed the general health examination and were tested for SARS-CoV-2; 4365 (3·3%) were positive for SARS-CoV-2, and 8297 (6·2%) were diagnosed with autoimmune inflammatory rheumatic diseases. After matching, patients with an autoimmune inflammatory rheumatic disease showed an increased likelihood of testing positive for SARS-CoV-2 (adjusted OR 1·19, 95% CI 1·03–1·40; $p=0\cdot026$), severe COVID-19 outcomes (1·26, 1·02–1·59; $p=0\cdot041$), and COVID-19-related death (1·69, 1·01–2·84; $p=0\cdot046$). Similar results were observed in patients with connective tissue disease and inflammatory arthritis. Treatment with any dose of systemic corticosteroids or disease-modifying antirheumatic drugs (DMARDs) were not associated with COVID-19-related outcomes, but those receiving high dose (≥ 10 mg per day) of systemic corticosteroids had an increased likelihood of a positive SARS-CoV-2 test (adjusted OR 1·47, 95% CI 1·05–2·03; $p=0\cdot022$), severe COVID-19 outcomes (1·76, 1·06–2·96; $p=0\cdot031$), and COVID-19-related death (3·34, 1·23–8·90; $p=0\cdot017$).

Interpretation Early in the COVID-19 pandemic, autoimmune inflammatory rheumatic diseases were associated with an increased likelihood of a positive SARS-CoV-2 PCR test, worse clinical outcomes of COVID-19, and COVID-19-related deaths in South Korea. A high dose of systemic corticosteroid, but not DMARDs, showed an adverse effect on SARS-CoV-2 infection and COVID-19-related clinical outcomes.

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Introduction

COVID-19 has become a global pandemic that has affected more than 160 million people worldwide.^{1,4} South Korea was one of the first countries to be affected by COVID-19; the first confirmed case was reported on Jan 20, 2020. As of June 8, 2021, there have been 144 637 confirmed cases of COVID-19 in South Korea, resulting 1974 deaths (see the WHO Coronavirus (COVID-19) Dashboard).

Patients with autoimmune inflammatory rheumatic diseases are considered to be at risk of developing serious infections because of lowered immunity resulting from their underlying conditions and use of immune-modulating therapies.^{5,6} Although several

studies have reported the associations between autoimmune inflammatory rheumatic diseases and SARS-CoV-2 infection, COVID-19 outcomes, or COVID-19-related mortality,^{5–10} the conclusions have been inconsistent, mainly ascribed to non-hypothesis-driven analysis, sampling bias, or measurement bias. Furthermore, studies have shown that ethnicity might be important in the context of COVID-19.¹¹ However, to the best of our knowledge, no studies have so far reported COVID-19 outcomes in patients with autoimmune inflammatory rheumatic diseases of Asian ethnicity. Hence, we aimed to determine the risk of SARS-CoV-2 infection, severe COVID-19 outcomes, and

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For the WHO Coronavirus (COVID-19) Dashboard see <https://covid19.who.int/>

Research in context

Evidence before this study

We searched PubMed, MEDLINE, Embase (Ovid), and Google Scholar on Oct 26, 2020, for studies published in English describing susceptibility to SARS-CoV-2 infection and clinical outcomes of COVID-19 in patients with autoimmune inflammatory rheumatic diseases, using the search terms “COVID-19”, “SARS-CoV-2”, “coronavirus”, “rheumatoid”, “connective tissue disease”, “rheumatic disease”, “severe acute respiratory syndrome”, “mortality”, and their variants. Although several studies reported the relationships between autoimmune inflammatory rheumatic diseases and SARS-CoV-2 infectivity, COVID-19 outcomes, or mortality, the conclusions have been inconsistent, mainly ascribed to non-hypothesis-driven analysis, sampling bias, or measurement bias. Furthermore, real-world evidence on the association between autoimmune inflammatory rheumatic diseases, immunomodulatory therapies, and COVID-19 is scarce.

Added value of this study

Using a South Korean nationwide cohort, we determined the potential association of autoimmune inflammatory rheumatic diseases with the risk of SARS-CoV-2 infection, COVID-19 severity, and COVID-19-related deaths in 133 609 patients who underwent SARS-CoV-2 testing early in the COVID-19 pandemic, between Jan 1 and May 30, 2020. We found that patients with an autoimmune inflammatory

rheumatic diseases—namely, inflammatory arthritis and connective tissue diseases—have an increased risk of testing positive for SARS-CoV-2, severe COVID-19, and COVID-19-related death. Patients with an autoimmune inflammatory rheumatic disease treated with any dose of systemic corticosteroid or disease-modifying antirheumatic drugs did not have an increased risk of any of the aforementioned COVID-19 outcomes; however, those receiving a high dose of a systemic corticosteroid (≥ 10 mg per day) had an increased risk of SARS-CoV-2 positivity, COVID-19 severity, and COVID-19-related death.

Implications of all the available evidence

Our study advances the understanding of the relationship between autoimmune inflammatory rheumatic diseases, and treatment, and the pathogenesis of COVID-19. Clinicians and patients should be aware that those with autoimmune inflammatory rheumatic diseases might have an increased risk of SARS-CoV-2 infection, severe COVID-19, and COVID-19-related death. Patients with an autoimmune inflammatory rheumatic disease receiving a high dose of a systemic corticosteroid should be considered as particularly vulnerable to SARS-CoV-2 infection and developing severe disease; therefore, clinicians should be cautious in determining care for such patients amid the COVID-19 pandemic.

COVID-19-related death in autoimmune inflammatory rheumatic diseases using a South Korean nationwide cohort linked to general health examination records early in the COVID-19 pandemic.

Methods

Study design and participants

The dataset for this nationwide cohort study was obtained from a South Korean national health insurance claims-based database. Briefly, our large-scale nationwide cohort included all individuals aged older than 20 years who underwent SARS-CoV-2 testing between Jan 1 and May 30, 2020, in South Korea via the services expedited by the Korean National Health Insurance Service, the Korea Centers for Disease Control, and the Ministry of Health and Welfare, South Korea. The dataset links general health examination records from the Korean National Health Insurance Service and national COVID-19-related register from the Korea Centers for Disease Control. Therefore, the dataset in this study comprised records of personal data, health-care records of inpatients and outpatients, pharmaceutical prescriptions, general health examination results, COVID-19-associated clinical outcomes, and death documents in the past 3 years (Jan 1, 2018, to July 30, 2020). All patient-associated medical documents used in this study were kept confidential. The study protocol was approved by the Institutional Review Board of Sejong

University (Seoul, South Korea; SJU-HR-E-2020-003). The requirement for written informed consent was waived by the ethics committee due to the urgent medical needs to be met amid the COVID-19 pandemic and the use of routinely collected health data.

SARS-CoV-2 infection was confirmed by a positive result on a real-time RT-PCR assay of nasal or pharyngeal swabs according to WHO guidelines.^{12–14} For each patient, the cohort entry date (individual index date) was the date of the first SARS-CoV-2 test. Patients' medical history was evaluated using the appropriate International Classification of Diseases, tenth revision (ICD-10), codes, as reported previously.^{12–15} Current use of medications (aspirin, metformin, statins, systemic corticosteroids, and disease-modifying antirheumatic drugs [DMARDs; methotrexate, leflunomide, azathioprine, sulfasalazine, antimalarials, anti-tumour necrosis factor (TNF) agents, and other biologics]) was defined based on the medications received within 3 months before the individual index date.¹⁴ Anti-TNF agents available in South Korea were infliximab, adalimumab, etanercept, certolizumab, and golimumab. Other biologics available were tocilizumab, rituximab, abatacept, ustekinumab, ixekizumab, and secukinumab. The region of residence was classified as Seoul Capital Area, Daegu/Gyeongbuk area, or other area, as previously reported.^{16–19} Information on age, sex, household income, and residency of a nursing facility was

obtained from insurance eligibility data. Body-mass index, smoking habits, frequency of alcohol consumption, and sufficient aerobic activity (>500 metabolic equivalent task min per week) were obtained from the general health examination by personal medical interview.

Exposure

We identified patients with an autoimmune inflammatory rheumatic disease (inflammatory arthritis or connective tissue disease) based on ICD-10 codes (appendix p 44) who had at least two claims within 1 year during the study period. Inflammatory arthritis was defined as rheumatoid arthritis, psoriatic arthritis, or spondyloarthritis based on ICD-10 codes.^{20,21} Connective tissue disease was defined as systemic lupus erythematosus, Sjogren's syndrome, systemic sclerosis, polymyalgia rheumatica, mixed connective tissue disease, dermatomyositis or polymyositis, polyarteritis nodosa, or vasculitis, based on ICD-10 codes.^{20,21}

Outcomes

The endpoints of this study were a positive SARS-CoV-2 RT-PCR test result, severe COVID-19 (requirement of oxygen therapy, intensive care unit [ICU] admission, application of invasive ventilation, or death), and COVID-19-related death.^{12–15}

Statistical analysis

We generated 12 matched cohort studies to determine the robustness (or reliability) of our main findings. First, we used exposure-driven propensity score matching to adjust for the baseline covariates of the two groups (ie, patients with and without autoimmune inflammatory rheumatic diseases) and to minimise potential confounding factors from the predicted probability of patients with an autoimmune inflammatory rheumatic disease versus those without (matched cohort A), patients with inflammatory arthritis versus those without (matched cohort B), and patients with connective tissue disease versus those without (matched cohort C). Each matching was done in a 3:1 ratio using a greedy nearest-neighbour algorithm. The variables used for matching each cohort are in the appendix (pp 3–5). Second, we implemented three additional exposure-driven propensity score matching strategies based on the nationwide cohort study without linking the general health examination records (matched cohorts D–F; appendix pp 25–26). Finally, to avoid overmatching bias, we selected the matched covariates by using the directed acyclic graph approach (appendix pp 39–40) and matched six additional cohorts (matched cohorts G–L) based on matched cohort A–F. We used a directed acyclic graph approach to confirm adequate potential mediators and thus provide a visualisation of the causal relationship between autoimmune inflammatory rheumatic disease (exposure) and the risk of COVID-19 (outcome).¹⁷

Subsequently, we used a logistic regression model with minimal adjustment for age (20–39, 40–59, and ≥60 years)

and sex and full adjustment for age; sex; region of residence (Seoul Capital Area, Daegu/Gyeongbuk area, and other areas); residency of a skilled nursing facility; a history of diabetes, cardiovascular disease, cerebrovascular

See Online for appendix

	Entire cohort (n=133 609)	Autoimmune inflammatory rheumatic disease (n=8297)	Inflammatory arthritis (n=7140)*	Connective tissue disease (n=1953)*
Age, years				
20–39	37 125 (27.8%)	782 (9.4%)	623 (8.7%)	255 (13.1%)
40–59	48 278 (36.1%)	2595 (31.3%)	2207 (30.9%)	719 (36.8%)
≥60	48 206 (36.1%)	4920 (59.3%)	4310 (60.4%)	979 (50.1%)
Sex				
Male	63 559 (47.6%)	3048 (36.7%)	2618 (36.7%)	625 (32.0%)
Female	70 050 (52.4%)	5249 (63.3%)	4522 (63.3%)	1328 (68.0%)
Region of residence				
Seoul Capital Area	59 632 (44.6%)	3640 (43.9%)	3073 (43.0%)	928 (47.5%)
Daegu/Gyeongbuk area	25 820 (19.3%)	1625 (19.6%)	1467 (20.5%)	310 (15.9%)
Other area	48 157 (36.0%)	3032 (36.5%)	2600 (36.4%)	715 (36.6%)
Resident of a skilled nursing facility	6616 (5.0%)	606 (7.3%)	517 (7.2%)	117 (6.0%)
Comorbidities, history of				
Diabetes	29 699 (22.2%)	3441 (41.5%)	3004 (42.1%)	752 (38.5%)
Cardiovascular disease	25 637 (19.2%)	3134 (37.8%)	2681 (37.5%)	744 (38.1%)
Cerebrovascular disease	15 905 (11.9%)	1881 (22.7%)	1640 (23.0%)	393 (20.1%)
Chronic obstructive pulmonary disease	16 706 (12.5%)	2006 (24.2%)	1714 (24.0%)	482 (24.7%)
Hypertension	29 443 (22.0%)	3146 (37.9%)	2735 (38.3%)	700 (35.8%)
Chronic kidney disease	45 781 (34.3%)	4654 (56.1%)	4047 (56.7%)	1015 (52.0%)
Current use of aspirin	11 891 (8.9%)	1210 (14.6%)	1045 (14.6%)	282 (14.4%)
Current use of metformin	13 807 (10.3%)	1260 (15.2%)	1115 (15.6%)	235 (12.0%)
Current use of a statin	31 208 (23.4%)	3230 (38.9%)	2837 (39.7%)	659 (33.7%)
Household income				
Low (0–39 percentile)	40 632 (30.4%)	2978 (35.9%)	2573 (36.0%)	686 (35.1%)
Middle (40–79 percentile)	54 934 (41.1%)	2851 (34.4%)	2461 (34.5%)	673 (34.5%)
High (80–100 percentile)	38 043 (28.5%)	2468 (29.7%)	2106 (29.5%)	594 (30.4%)
Smoking				
Never smoker	87 771 (65.7%)	5955 (71.8%)	5130 (71.8%)	1468 (75.2%)
Ex-smoker	22 031 (16.5%)	1339 (16.1%)	1132 (15.9%)	299 (15.3%)
Current smoker	23 807 (17.8%)	1003 (12.1%)	878 (12.3%)	186 (9.5%)
Alcohol consumption, days per week				
<1	83 130 (62.2%)	6347 (76.5%)	5507 (77.1%)	1486 (76.1%)
1–2	41 590 (31.1%)	1495 (18.0%)	1240 (17.4%)	383 (19.6%)
3–4	6585 (4.9%)	306 (3.7%)	258 (3.6%)	62 (3.2%)
≥5	2304 (1.7%)	149 (1.8%)	135 (1.9%)	22 (1.1%)
Body-mass index, kg/m ²				
<25	86 641 (64.8%)	5298 (63.9%)	4508 (63.1%)	1374 (70.4%)
25–30	39 081 (29.3%)	2493 (30.0%)	2189 (30.7%)	491 (25.1%)
≥30	7887 (5.9%)	506 (6.1%)	443 (6.2%)	88 (4.5%)
Sufficient aerobic activity†	62 418 (46.7%)	4105 (49.5%)	3527 (49.4%)	984 (50.4%)
Current use of a systemic corticosteroid	16 268 (12.2%)	2446 (29.5%)	1977 (27.7%)	859 (44.0%)

(Table 1 continues on next page)

	Entire cohort (n=133 609)	Autoimmune inflammatory rheumatic disease (n=8297)	Inflammatory arthritis (n=7140)*	Connective tissue disease (n=1953)*
(Continued from previous page)				
Current use of a DMARD				
Methotrexate– leflunomide– azathioprine	8149 (6.1%)	3519 (42.4%)	3048 (42.7%)	1313 (67.2%)
Sulfasalazine	487 (0.4%)	439 (5.3%)	432 (6.1%)	80 (4.1%)
Antimalarials	7781 (5.8%)	1692 (20.4%)	1491 (20.9%)	727 (37.2%)
Anti-tumour necrosis factor agent	852 (0.6%)	489 (5.9%)	452 (6.3%)	124 (6.3%)
Other biologics	1413 (1.1%)	348 (4.2%)	327 (4.6%)	72 (3.7%)

Data are n (%). Percentages might not sum to 100% due to rounding. DMARD=disease-modifying antirheumatic drug.
*Includes 796 patients who had both inflammatory arthritis and connective tissue disease. †More than 500 metabolic equivalent task min per week.

Table 1: Baseline covariates of patients who underwent SARS-CoV-2 testing and received general health examination in the nationwide cohort

disease, chronic obstructive pulmonary disease, hypertension, or chronic kidney disease; household income (low, middle, and high); smoking (never, ex, and current); frequency of alcohol consumption (<1, 1–2, 3–4, and ≥5 days per week); body-mass index (<25 kg/m², 25–30 kg/m², and ≥30 kg/m²); sufficient aerobic activity; and current use of aspirin, metformin, and a statin. To investigate the association of COVID-19-related outcomes by current treatment, we did subgroup analyses stratified by DMARDs and systemic corticosteroids. Adequacy of the matching was established by comparing exposure-driven propensity score densities and standardised mean differences (appendix pp 27–38). Adjusted odds ratios (ORs) with 95% CIs were estimated after adjusting for the potential confounders.

Statistical analyses were done with SAS software (version 9.4) and R software (version 3.6.1). Directed acyclic graphics were presented with DAGitty (version 2.3). A two-sided p value of less than 0.05 was considered to be significant.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The demographics and clinical characteristics of the 133 609 people (female 70 050 [52.4%] and 63 559 [47.6%] male) who completed the general health examination and underwent SARS-CoV-2 testing between Jan 1 and May 30, 2020, were analysed (table 1); 4365 (3.3%) had a positive SARS-CoV-2 test. 8297 (6.2%) patients were diagnosed with autoimmune inflammatory rheumatic diseases: 7140 (5.3%) patients were diagnosed with inflammatory arthritis and 1953 (1.5%) patients with

connective tissue disease. Of the 8297 patients with an autoimmune inflammatory rheumatic disease, 796 (9.6%) patients had both inflammatory arthritis and connective tissue disease (figure; table 1).

After exposure-driven propensity score matching of participants (matched cohort A; n=31 905; figure), no major asymmetries in the baseline covariates evaluated by standardised mean difference between groups were found (table 2). 365 (4.4%) of 8222 patients with autoimmune inflammatory rheumatic diseases and 891 (3.8%) of 23 683 participants without autoimmune inflammatory rheumatic diseases had a positive SARS-CoV-2 test (fully adjusted OR 1.19, 95% CI 1.03–1.40; p=0.026; table 3). Patients with autoimmune inflammatory rheumatic diseases were more likely to develop severe COVID-19 (fully adjusted OR 1.26, 95% CI 1.02–1.59; p=0.041) and had a higher risk of COVID-19-related death (1.69, 1.01–2.84; p=0.046).

After propensity score matching of participants without versus those with inflammatory arthritis (matched cohort B; n=27 933) and participants without versus those with connective tissue disease (matched cohort C; n=7437) no asymmetries in baseline covariates were noted (table 2). Patients with inflammatory arthritis had an increased risk of testing positive for SARS-CoV-2 (fully adjusted OR 1.20, 95% CI 1.03–1.40; p=0.020), severe COVID-19 (1.27, 1.01–1.63; p=0.049), and COVID-19-related death (1.81, 1.02–3.18; p=0.040), compared to those without inflammatory arthritis. Connective tissue disease was associated with an increased risk of testing positive for SARS-CoV-2 (fully adjusted OR 1.33, 95% CI 1.02–1.74; p=0.036) and severe COVID-19 (1.71, 1.06–2.71; p=0.025), but not associated with an increased likelihood of COVID-19-related death (1.87, 0.71–4.85; p=0.20).

Table 4 shows the subgroup analysis of SARS-CoV-2 positivity, severe COVID-19, and COVID-19-related death in the context of autoimmune inflammatory rheumatic diseases stratified by DMARD and systemic corticosteroid use. Treatment with any dose of systemic corticosteroid was not associated with the odds of testing positive for SARS-CoV-2, severe COVID-19, or COVID-19-related death in patients with autoimmune inflammatory rheumatic diseases; however, patients taking ≥10 mg per day of systemic corticosteroid had an increased odds of a positive SARS-CoV-2 test (fully adjusted OR 1.47, 95% CI 1.05–2.03; p=0.022), severe COVID-19 (1.76, 1.06–2.96; p=0.031), and COVID-19-related death (3.34, 1.23–8.90; p=0.017). DMARDs were not associated with the risk of testing positive for SARS-CoV-2, severe COVID-19, or COVID-19-related death, in patients with autoimmune inflammatory rheumatic diseases.

We did several sensitivity analyses (appendix pp 3–5). First, we did additional exposure-driven propensity score-matching in the cohort without linking the general health examination results (matched cohorts D-F; appendix pp 6–12), and the findings were consistent with our main results. Second, we did minimal selected matching by the

For DAGitty see
<http://www.dagitty.net>

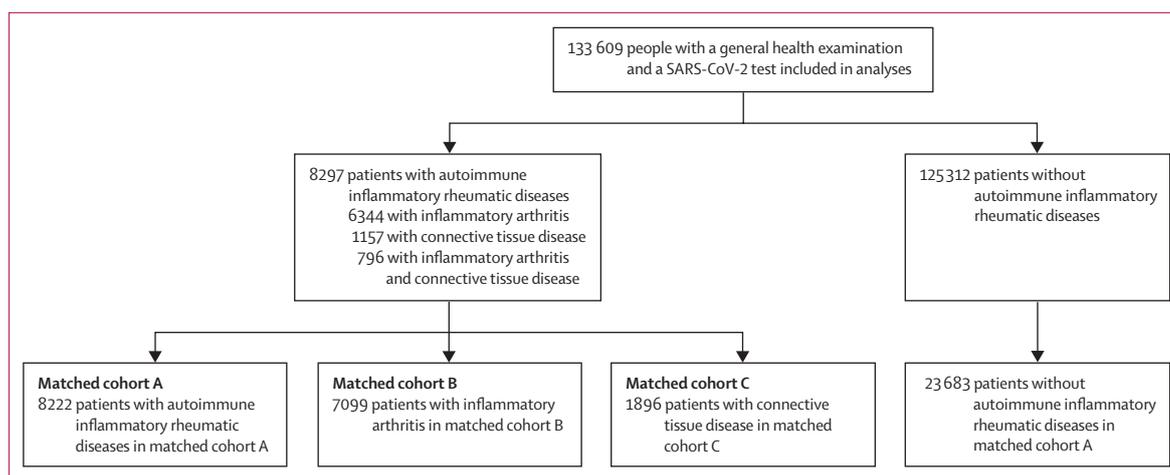


Figure: Disposition of patients in the South Korean nationwide cohort linked to the general health examination records

directed acyclic graph approach in the original cohort (matched cohorts G–I; appendix pp 15–20, 40) and the cohort without linking the general health examination results (matched cohorts J–L; appendix pp 21–24). The results from these six matched cohorts yielded results similar to our primary findings. Third, analyses using the matched cohort D also indicated a significantly increased odds of a positive SARS-CoV-2 test, severe COVID-19, and COVID-19-related death in patients with autoimmune inflammatory rheumatic diseases taking ≥ 10 mg per day of systemic corticosteroid (appendix pp 13–14). Finally, the use of the same analysis in the fully unmatched cohort without linking the general health examination results also showed that patients with autoimmune inflammatory rheumatic diseases had an increased risk of a positive SARS-CoV-2 test, severe COVID-19, and COVID-19-related death in either crude and adjusted models, a finding similar to our matched results (appendix pp 41–43).

Discussion

We found that patients with autoimmune inflammatory rheumatic diseases—*inflammatory arthritis* or *connective tissue disease*—have an increased risk of testing positive for SARS-CoV-2, severe COVID-19, and COVID-19-related death. Notably, patients with autoimmune inflammatory rheumatic diseases taking a dose of a systemic corticosteroid ≥ 10 mg per day had a higher risk of testing positive for SARS-CoV-2, severe COVID-19, and COVID-19-related death than those not taking systemic corticosteroids. Patients with autoimmune inflammatory rheumatic disease receiving DMARDs did not have any increased risk of these outcomes.

A previous meta-analysis suggested that patients with autoimmune inflammatory rheumatic diseases have an increased risk of SARS-CoV-2 infection;²² however, the results were limited because the study mainly included hospitalised patients and had a small sample size, skewed

clinic-based data, selection bias (ie, not all patients had laboratory-confirmed COVID-19), and insufficient confounding adjustment.²² In our study, we used nationwide data and used exposure-driven propensity score matching with sufficient confounding adjustment. Our results showed that patients with autoimmune inflammatory rheumatic diseases have an increased risk of testing positive for SARS-CoV-2, a finding that corresponds well with a previous meta-analysis.²² However, to our knowledge, no study has shown a difference in the odds of testing positive for SARS-CoV-2 between patients with inflammatory arthritis and those with connective tissue diseases compared with the general population. We believe this is the first study to show that patients with inflammatory arthritis and connective tissue diseases are at increased risk of testing positive for SARS-CoV-2 independently. Furthermore, we found no association between connective tissue disease and COVID-19-related death, but these findings might be due to the small number of patients with connective tissue disease, which calls for further large-scale and international studies.

Previous studies have suggested no association^{23,24} or positive association¹⁰ between autoimmune inflammatory rheumatic disease and COVID-19 severity and COVID-19-related deaths in European and North American cohorts. Our findings from a South Korean nationwide cohort support European and North American studies that showed that patients with autoimmune inflammatory rheumatic diseases have an increased risk of SARS-CoV-2 infection, severe COVID-19, and COVID-19-related death. A previous epidemiological study also reported that Asian ethnicity compared with White ethnicity is associated with higher intensive care admission and COVID-19-related mortality rates,²⁵ which is consistent with our main findings. The reason for this adverse association of COVID-19 with Asian ethnicity might be due to higher angiotensin-converting enzyme (ACE)

	Matched cohort A			Matched cohort B			Matched cohort C		
	No autoimmune inflammatory rheumatic disease (n=23 683)	Autoimmune inflammatory rheumatic disease (n=8222)	Standardised mean difference	No inflammatory arthritis (n=20 834)	Inflammatory arthritis (n=7099)	Standardised mean difference	No connective tissue disease (n=5541)	Connective tissue disease (n=1896)	Standardised mean difference
Age, years	0.008	0.002	0.018
20–39	2131 (9.0%)	765 (9.3%)	..	1766 (8.5%)	617 (8.7%)	..	662 (11.9%)	225 (11.9%)	..
40–59	7384 (31.2%)	2560 (31.1%)	..	6543 (31.4%)	2189 (30.8%)	..	1984 (35.8%)	695 (36.7%)	..
≥60	14 168 (59.8%)	4897 (59.6%)	..	12 525 (60.1%)	4293 (60.5%)	..	2895 (52.2%)	976 (51.5%)	..
Sex	0.037	0.022	0.003
Male	9206 (38.9%)	3048 (37.1%)	..	7908 (38.0%)	2618 (36.9%)	..	1819 (32.8%)	625 (33.0%)	..
Female	14 477 (61.1%)	5174 (62.9%)	..	12 926 (62.0%)	4481 (63.1%)	..	3722 (67.2%)	1271 (67.0%)	..
Region of residence	0.002	0.005	0.037
Seoul Capital Area	10 284 (43.4%)	3597 (43.7%)	..	8921 (42.8%)	3045 (42.9%)	..	2614 (47.2%)	899 (47.4%)	..
Daegu/Gyeongbuk area	4734 (20.0%)	1604 (19.5%)	..	4208 (20.2%)	1458 (20.5%)	..	946 (17.1%)	299 (15.8%)	..
Other area	8665 (36.6%)	3021 (36.7%)	..	7705 (37.0%)	2596 (36.6%)	..	1981 (35.8%)	698 (36.8%)	..
Resident of a skilled nursing facility	1700 (7.2%)	606 (7.4%)	0.008	1526 (7.3%)	517 (7.3%)	0.002	345 (6.2%)	116 (6.1%)	0.004
Comorbidities, history of									
Diabetes	9656 (40.8%)	3426 (41.7%)	0.020	8563 (41.1%)	2993 (42.2%)	0.023	2043 (36.9%)	735 (38.8%)	0.039
Cardiovascular disease	8393 (35.4%)	3095 (37.6%)	0.050	7391 (35.5%)	2659 (37.5%)	0.045	1932 (34.9%)	710 (37.4%)	0.054
Cerebrovascular disease	5092 (21.5%)	1874 (22.8%)	0.035	4573 (21.9%)	1631 (23.0%)	0.028	1069 (19.3%)	388 (20.5%)	0.029
Chronic obstructive pulmonary disease	5028 (21.2%)	1940 (23.6%)	0.062	4351 (20.9%)	1674 (23.6%)	0.071	1246 (22.5%)	458 (24.2%)	0.039
Hypertension	13 082 (55.2%)	4630 (56.3%)	0.022	11 666 (56.0%)	4031 (56.8%)	0.016	2798 (50.5%)	987 (52.1%)	0.031
Chronic kidney disease	3808 (16.1%)	1436 (17.5%)	0.042	3337 (16.0%)	1221 (17.2%)	0.036	911 (16.4%)	368 (19.4%)	0.077
Current use of aspirin	3274 (13.8%)	1206 (14.7%)	0.027	2913 (14.0%)	1045 (14.7%)	0.023	715 (12.9%)	269 (14.2%)	0.038
Current use of metformin	3652 (15.4%)	1260 (15.3%)	0.003	3254 (15.6%)	1115 (15.7%)	0.002	701 (12.7%)	235 (12.4%)	0.008
Current use of a statin	9077 (38.3%)	3207 (39.0%)	0.015	7993 (38.4%)	2825 (39.8%)	0.031	1826 (33.0%)	647 (34.1%)	0.025
Household income	0.015	0.012	0.039
Low (0–39 percentile)	8208 (34.7%)	2944 (35.8%)	..	7298 (35.0%)	2554 (36.0%)	..	1845 (33.3%)	666 (35.1%)	..
Middle (40–79 percentile)	8393 (35.4%)	2825 (34.4%)	..	7374 (35.4%)	2449 (34.5%)	..	1940 (35.0%)	645 (34.0%)	..
High (80–100 percentile)	7082 (29.9%)	2453 (29.8%)	..	6162 (29.6%)	2096 (29.5%)	..	1756 (31.7%)	585 (30.9%)	..
Smoking	0.007	0.002	0.054
Never smoker	16 938 (71.5%)	5885 (71.6%)	..	14 971 (71.9%)	5096 (71.8%)	..	4248 (76.7%)	1416 (74.7%)	..
Ex-smoker	3748 (15.8%)	1336 (16.2%)	..	3304 (15.9%)	1128 (15.9%)	..	762 (13.8%)	296 (15.6%)	..
Current smoker	2997 (12.7%)	1001 (12.2%)	..	2559 (12.3%)	875 (12.3%)	..	531 (9.6%)	184 (9.7%)	..
Alcohol consumption, days per week	<0.001	0.005	0.054
<1	18 001 (76.0%)	6281 (76.4%)	..	15 960 (76.6%)	5471 (77.1%)	..	4282 (77.3%)	1440 (75.9%)	..
1–2	4417 (18.7%)	1486 (18.1%)	..	3818 (18.3%)	1235 (17.4%)	..	1053 (19.0%)	373 (19.7%)	..
3–4	896 (3.8%)	306 (3.7%)	..	733 (3.5%)	258 (3.6%)	..	136 (2.5%)	61 (3.2%)	..
≥5	369 (1.6%)	149 (1.8%)	..	323 (1.6%)	135 (1.9%)	..	70 (1.3%)	22 (1.2%)	..
Body mass index, kg/m ²	0.012	0.022	0.028
<25	15 175 (64.1%)	5242 (63.8%)	..	13 281 (63.7%)	4481 (63.1%)	..	3856 (69.6%)	1324 (69.8%)	..
25–30	7155 (30.2%)	2477 (30.1%)	..	6408 (30.8%)	2179 (30.7%)	..	1455 (26.3%)	484 (25.5%)	..
≥30	1353 (5.7%)	503 (6.1%)	..	1145 (5.5%)	439 (6.2%)	..	230 (4.2%)	88 (4.6%)	..
Sufficient aerobic activity*	11 673 (49.3%)	4062 (49.4%)	0.002	10 211 (49.0%)	3503 (49.3%)	0.007	2862 (51.7%)	957 (50.5%)	0.024

Data are n (%) unless otherwise indicate. Percentages might not sum to 100% due to rounding. A standardised mean difference of less than 0.1 indicates no major imbalance. All standardised mean difference values were less than 0.08 in the propensity score-matched cohort. *More than 500 metabolic equivalent task min per week.

Table 2: 3:1 propensity score-matched covariates in patients with autoimmune inflammatory rheumatic diseases, inflammatory arthritis, or connective tissue disease

concentrations and lower androgen concentrations, (eg, malaria), regional temperature, and humidity—which lead to increased ACE2 expression, cross-reactive immunity—eg, due to past exposure to infections which can affect virus survival and the host immune response.²⁶

	Matched cohort A			Matched cohort B			Matched cohort C		
	No autoimmune inflammatory rheumatic disease (n=23 683)	Autoimmune inflammatory rheumatic disease (n=8222)	p value	No inflammatory arthritis (n=20 834)	Inflammatory arthritis (n=7099)	p value	No connective tissue disease (n=5541)	Connective tissue disease (n=1896)	p value
SARS-CoV-2-positive PCR test	891 (3.8%)	365 (4.4%)	..	796 (3.8%)	327 (4.6%)	..	188 (3.4%)	84 (4.4%)	..
Minimally adjusted odds ratio* (95% CI)	1 (ref)	1.18 (1.05-1.35)	0.0098	1 (ref)	1.19 (1.03-1.38)	0.020	1 (ref)	1.32 (1.02-1.72)	0.037
Fully adjusted odds ratio† (95% CI)	1 (ref)	1.19 (1.03-1.40)	0.026	1 (ref)	1.20 (1.03-1.40)	0.020	1 (ref)	1.33 (1.02-1.74)	0.036
Severe COVID-19	285 (1.2%)	127 (1.5%)	..	234 (1.1%)	103 (1.5%)	..	51 (0.9%)	30 (1.6%)	..
Minimally adjusted odds ratio* (95% CI)	1 (ref)	1.28 (1.04-1.60)	0.024	1 (ref)	1.28 (1.02-1.62)	0.036	1 (ref)	1.73 (1.09-2.73)	0.019
Fully adjusted odds ratio† (95% CI)	1 (ref)	1.26 (1.02-1.59)	0.041	1 (ref)	1.27 (1.01-1.63)	0.049	1 (ref)	1.71 (1.06-2.71)	0.025
COVID-19-related death	40 (0.2%)	24 (0.3%)	..	32 (0.2%)	20 (0.3%)	..	11 (0.2%)	7 (0.4%)	..
Minimally adjusted odds ratio* (95% CI)	1 (ref)	1.74 (1.04-2.88)	0.033	1 (ref)	1.84 (1.06-3.22)	0.031	1 (ref)	1.85 (0.72-4.82)	0.21
Fully adjusted odds ratio† (95% CI)	1 (ref)	1.69 (1.01-2.84)	0.046	1 (ref)	1.81 (1.02-3.18)	0.040	1 (ref)	1.87 (0.71-4.85)	0.20

Data are n (%) unless otherwise indicate. *Minimally adjusted for age and sex. †Fully adjusted for age; sex; region of residence; resident of a skilled nursing facility; history of diabetes, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, hypertension, and chronic kidney disease; household income; smoking status; alcohol consumption; body-mass index; sufficient aerobic activity; and current use of aspirin, metformin, and statins.

Table 3: Propensity score-matched analysis of adjusted odds ratio (95% CI) for positive SARS-CoV-2 test, severe COVID-19 outcomes, or COVID-19-related death in patients with autoimmune inflammatory rheumatic diseases, inflammatory arthritis, or connective tissue disease

The use of DMARDs was not associated with any COVID-19-related endpoints in our study. There is conflicting evidence of an association between corticosteroid use and severe COVID-19 outcomes. One study reported no relationship between inhaled corticosteroid use and COVID-19-related death among people with asthma or chronic obstructive pulmonary disease.²⁷ Our results suggest that patients with autoimmune inflammatory rheumatic disease receiving any dose of systemic corticosteroids do not have an increased risk of a positive SARS-CoV-2 test, severe COVID-19, or COVID-19-related death. However, the patients with autoimmune inflammatory rheumatic disease receiving a high dose of systemic corticosteroids have an increased risk of testing positive for SARS-CoV-2, severe COVID-19, COVID-19-related death. Our results support those from a previous cohort study of patients with autoimmune inflammatory rheumatic disease that showed that a high dose of systemic corticosteroids is associated with higher odds of hospitalisation for COVID-19 than not taking corticosteroids.²⁸ Corticosteroids might reduce ACE2 expression levels,²⁹ which might lead to altered SARS-CoV-2 susceptibility either beneficially (ie, reduced SARS-CoV-2 entry) or adversely (ie, reduced beneficial effect of ACE2 on hyperinflammation),³⁰ thereby suggesting a potential dichotomous effect of systemic corticosteroids.

Researchers should exercise caution when interpreting data regarding systemic corticosteroid use in patients with COVID-19 in the context of autoimmune

inflammatory rheumatic diseases. First, proinflammatory cytokines implicated in most rheumatic diseases, such as interleukin-6, TNF, and interleukin-1, have been reported as the pathogenic factors produced by macrophages after T lymphocytes bearing T-cell receptors recognise SARS-CoV-2 bound to the surface of cells, and these cytokines might be culpable for the tissue destruction in various organs in patients with severe COVID-19.³¹ It is plausible that rheumatic disorders and COVID-19 could affect each other at the pathogenic level, which ultimately results in decline in patients' conditions. Second, the immunological abnormalities due to rheumatic disease affect most circulating T cells, which evolve from an early stage in the rheumatic disease course.³² T-cell dynamics in patients with autoimmune inflammatory rheumatic disease (ie, lack of T-cell receptor rearrangement excision circle-positive cells and abnormalities in T-cell homeostasis) suggests that the ability of patients with autoimmune inflammatory rheumatic diseases to react to novel antigens, such as during SARS-CoV-2 infection, is compromised.³² Third, ACE2 receptor and transmembrane serine protease 2 have an important role in the entry of SARS-CoV-2 and are highly expressed in autoimmune diseases³³ and chronic inflammatory diseases,³⁴ suggesting that patients with autoimmune inflammatory rheumatic diseases might be at a higher risk of poor COVID-19 outcomes, which is consistent with our findings. Hence, we conjectured that SARS-CoV-2 could potentially aggravate autoimmune

	Patients/total (%)	Adjusted odds ratio (95% CI)	p value
Positive SARS-CoV-2 PCR test			
No DMARD treatment	140/3021 (4.6%)	1 (ref)*	..
DMARDs	225/5201 (4.3%)	0.90 (0.70-1.17)	0.43
No systemic corticosteroid treatment	244/5803 (4.2%)	1 (ref)†	..
Systemic corticosteroids (any dose)	121/2419 (5.0%)	1.18 (0.92-1.51)	0.19
Systemic corticosteroids (≥10 mg per day)	49/802 (6.1%)	1.47 (1.05-2.03)	0.022
Severe COVID-19			
No DMARD treatment	45/3021 (1.5%)	1 (ref)*	..
DMARDs	82/5201 (1.6%)	1.01 (0.69-1.50)	0.96
No systemic corticosteroid treatment	82/5803 (1.4%)	1 (ref)†	..
Systemic corticosteroids (any dose)	45/2419 (1.9%)	1.34 (0.92-1.95)	0.13
Systemic corticosteroids (≥10 mg per day)	20/802 (2.5%)	1.76 (1.06-2.96)	0.031
COVID-19-related death			
No DMARD treatment	8/3021 (0.3%)	1 (ref)*	..
DMARDs	16/5201 (0.3%)	1.19 (0.52-2.74)	0.69
No systemic corticosteroid treatment	13/5803 (0.2%)	1 (ref)†	..
Systemic corticosteroids (any dose)	11/3419 (0.3%)	2.02 (0.89-4.56)	0.091
Systemic corticosteroids (≥10 mg per day)	6/802 (0.7%)	3.34 (1.23-8.90)	0.017

DMARD=disease-modifying antirheumatic drug. *Adjusted for age; sex; region of residence; resident of a skilled nursing facility; history of diabetes, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, hypertension, and chronic kidney disease; household income; smoking status; alcohol consumption; body-mass index; sufficient aerobic activity; and current use of aspirin, metformin, a statin, and a systemic corticosteroid. †Adjusted for age; sex; region of residence; resident of a skilled nursing facility; history of diabetes, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, hypertension, and chronic kidney disease; household; smoking status; alcohol consumption; body-mass index; sufficient aerobic activity; and current use of aspirin, metformin, and statins and DMARDs.

Table 4: Propensity score-matched subgroup analysis of adjusted odds ratio (95% CI) of positive SARS-CoV-2 RT-PCR test, severe COVID-19 outcomes, or COVID-19-related death in patients with an autoimmune inflammatory rheumatic disease stratified by DMARD and systemic corticosteroid (matched cohort A)

inflammatory rheumatic diseases, which could, in turn, exacerbate viral infection and result in devastating COVID-19 sequelae. This indicates a complex biopathological mechanism wherein underlying autoimmune inflammatory rheumatic diseases could adversely affect the pathogenesis of COVID-19.

The main strengths of our study include the use of a nationwide cohort with a large sample size (219 959 patients), several strict exposure-driven propensity score matching approaches (12 matched cohorts), and adjustment for various potential confounders by linking the general health examination records (ie, household income, body-mass index, smoking habits, frequency of alcohol consumption, and sufficient aerobic activity). Our study provides potential evidence of the contribution of autoimmune inflammatory rheumatic disease to an increased risk of testing positive for SARS-CoV-2 and severe clinical consequences of COVID-19. We also reported the harmful association of a high dose of systemic corticosteroid in patients with autoimmune inflammatory rheumatic diseases on COVID-19.

This study has some limitations. First, the diagnosis of autoimmune inflammatory rheumatic diseases was based on ICD-10 codes, which can be imprecise;

however, numerous previous studies have also used these definitions²¹ and the results of our cohort study were supported by those of our several additional matched cohorts. Second, as our database included people who underwent SARS-CoV-2 tests, the characteristics of our cohort might vary from those of the general population. Although there exists potential for prevalence-induced bias, our study was done with a large population-established cohort and with exposure-driven propensity score matching to ensure the reliability of our results. Third, because we did not have accurate data on the individual viral loads and contact-tracing results, we need to be careful about the interpretation of SARS-CoV-2 test positive results despite the large-scale and national-level dataset. Finally, COVID-19 outcomes have improved in accordance with physician experience and management strategies for COVID-19.³⁵ Because we used the dataset that reflected the initial period of the pandemic in South Korea, caution should be exercised when generalising our results to the current situation.

Autoimmune inflammatory rheumatic diseases contribute to an increased likelihood of testing positive for SARS-CoV-2, worse clinical outcomes of COVID-19 and COVID-19-related death in South Korea. Patients with inflammatory arthritis and connective tissue disease have an increased risk of testing positive for SARS-CoV-2 and worse clinical outcomes of COVID-19. In addition, autoimmune inflammatory rheumatic disease treatment with a high dose of systemic corticosteroids was associated with SARS-CoV-2 test positivity, severe COVID-19, and COVID-19-related death; treatment with DMARDs was not associated with an increased risk of worse clinical outcomes. Similar patterns of association were found between different sensitivity analyses from 12 matched cohorts. Thus, our study advances the understanding of the relationship between autoimmune inflammatory rheumatic disease, including its treatment, and the pathogenesis of COVID-19.

Contributors

DKY and SWL had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version before submission. SWL, YHS, JIS, and DKY contributed to study concept and design. SWL, JIS, and DKY were involved in acquisition, analysis, or interpretation of data. YHS, SK, ML, YP, MSK, JIS, and DKY drafted the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content. SWL, HYJ, SYM, SK, ML, YP, MSK, JIS, and DKY did the statistical analysis. DKY supervised the study and is guarantor for this study.

Declaration of interests

We declare no competing interests.

Data sharing

Data from the Korean National Health Insurance Service COVID-19 study is available on application (see the Data Sharing Service).

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