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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 1.47, 95% CI 1.05–2.03; p=0.022), severe COVID-19 outcomes (1.76, 1.06–2.96; p=0.031), and COVID-19-related death (1.69, 1.01–2.84; p=0.046). Similar results were observed in patients with connective tissue disease (adjusted OR 1.19, 95% CI 1.03–1.40; p=0.026), severe COVID-19 outcomes (1.26, 1.02–1.59; p=0.041), and COVID-19-related death (1.69, 1.01–2.84; p=0.046). 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=0.022), severe COVID-19 outcomes (1.76, 1.06–2.96; p=0.031), and COVID-19-related death (3.34, 1.23–9.80; p=0.017).

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 in 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,7–8 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-19.9 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,
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 Korea Centers for Disease Control and Prevention (KCDCP). We evaluated using the appropriate International Classification of Diseases, tenth revision (ICD-10), codes, as reported previously. 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. 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. Information on age, sex, 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. 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. 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. 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. Information on age, sex,
See Online for appendix

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.20,21

**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 1:3 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).7

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
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); 4,365 (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 8,222 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 1.02–1.38; p=0.040). Compared to those without inflammatory arthritis, the risk of COVID-19-related death in patients with autoimmune inflammatory rheumatic diseases stratified by DMARD and systemic corticosteroid use 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 cohort B; n=27,933) and participants without versus those with connective tissue disease (matched cohort C; n=7,437) 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 1.26, 95% CI 1.01–1.59; p=0.041), severe COVID-19 (1.71, 1.06–2.71; p=0.025), and COVID-19-related death (3.34, 1.23–8.90; p=0.017). DMARDs were 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. For DAGitty see http://www.dagitty.net

Table 1: Baseline covariates of patients who underwent SARS-CoV-2 testing and received general health examination in the nationwide cohort
results. Second, we did minimal selected matching by the 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; 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. 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. 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 or positive association 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, which is consistent with our main findings. The reason for this adverse association of COVID-19 with Asian ethnicity might be due to higher
ACE2 expression, cross-reactive immunity—eg, due to past exposure to infections (eg, malaria), regional temperature, and humidity—which can affect virus survival and the host immune response.26

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

Data are n (%) unless otherwise indicated. 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.

angiotensin-converting enzyme (ACE) concentrations and lower androgen concentrations, which lead to increased ACE2 expression, cross-reactive immunity—eg, due to
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.\(^2\) 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.\(^3\) Corticosteroids might reduce ACE2 expression levels,\(^4\) 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),\(^5\) 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.\(^6\) 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.\(^7\) 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 homoeostasis) 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.\(^7\) 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 diseases\(^8\) and chronic inflammatory diseases,\(^9\) 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 inflammatory diseases.
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 definitions\(^1\) 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 accurate data on the individual viral loads and contact-reliability of our results. Third, because we did not have driven propensity score matching to ensure the prevalence-induced bias, our study was done with a general population. Although there exists potential for prevalence-induced bias, 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.

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### Patients/total (%) Adjusted odds ratio (95% CI) p value

| Test                          | 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) | 121/3419 (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 (1.23–9.00)            | 0.017   |

**Table 6** 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)
professionals treating patients with COVID-19 in South Korea as well as the Ministry of Health and Welfare and the Health Insurance Review and Assessment Service of Korea for sharing invaluable national health insurance claims data.

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