

Association between autoimmune inflammatory rheumatic diseases and COVID-19 infectivity and outcomes: a Korean nationwide cohort

Running head: Autoimmune inflammatory rheumatic diseases and COVID-19

Seung Won Lee, MD, PhD,^{1*} Youn Ho Shin, MD, PhD,^{2*} Sung Yong Moon, BS,¹ Hyun Young Jin, BS,¹ So Young Kim, MD,³ Jee Myung Yang, MD, PhD,⁴ Seong Ho Cho, MD,⁵ Sungeun Kim, BS,⁶ Minho Lee, MS,⁶ Youngjoo Park, MS,⁶ Min Seo Kim, MD,^{7, 8} Hong-Hee Won, PhD,⁸ Sung Hwi Hong, MD, MPH,^{6, 9} Andreas Kronbichler, MD, PhD,¹⁰ Ai Koyanagi, MD, PhD,^{11,12} Louis Jacob, PhD,^{11, 13} Lee Smith, PhD,¹⁴ Keum Hwa Lee, MD,¹⁵ Dong In Suh, MD, PhD,¹⁶ Jae Il Shin, MD, PhD,^{15*} Dong Keon Yon, MD,^{16 *}

¹ Department of Data Science, Sejong University College of Software Convergence, Seoul, Republic of Korea

² Department of Pediatrics, CHA Gangnam Medical Center, CHA University School of Medicine, Seoul, Republic of Korea

³ Department of Otorhinolaryngology-Head & Neck Surgery, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Republic of Korea

⁴ Department of Ophthalmology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

20 ⁵ Division of Allergy-Immunology, University of South Florida Morsani College of Medicine,
21 Tampa, FL, USA

22 ⁶ Yonsei University College of Medicine, Seoul, Republic of Korea

23 ⁷ Korea University College of Medicine, Seoul, Republic of Korea

24 ⁸ Genomics and Digital Health, Samsung Advanced Institute for Health Sciences and
25 Technology (SAIHST), Sungkyunkwan University, Seoul, Republic of Korea

26 ⁹ Department of Global Health and Population, Harvard TH Chan School of Public Health,
27 Boston, USA

28 ¹⁰ Department of Internal Medicine IV (Nephrology and Hypertension), Medical University of
29 Innsbruck, Innsbruck, Austria

30 ¹¹ Research and Development Unit, Parc Sanitari Sant Joan de Déu, CIBERSAM, Barcelona,
31 Spain

32 ¹² ICREA (Catalan Institution for Research and Advanced Studies), Barcelona, Spain

33 ¹³ Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-
34 Bretonneux, France

35 ¹⁴ The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University,
36 Cambridge, UK

37 ¹⁵ Department of Pediatrics, Severance Hospital, Yonsei University College of Medicine, Seoul,
38 Republic of Korea

39 ¹⁶ Department of Pediatrics, Seoul National University Children's Hospital, Seoul National
40 University College of Medicine, Seoul, Republic of Korea

41

42 * Seung Won Lee, Youn Ho Shin, Jae Il Shin, and Dong Keon Yon contributed equally as first
43 and corresponding authors

44

45 ***Corresponding author**

46 Seung Won Lee, MD, PhD

47 Department of Data Science, Sejong University College of Software Convergence, 209

48 Neungdong-ro, Gwangjin-gu, Seoul, 05006, South Korea

49 Phone: +82-2-6935-2476

50 Fax: +82-504-478-0201

51 Email: swlsejong@sejong.ac.kr

52

53 Youn Ho Shin, MD, PhD

54 Department of Pediatrics, CHA Gangnam Medical Center, CHA University School of Medicine,

55 566 Nonhyeon-ro, Gangnam-gu, Seoul 06135, South Korea

56 Phone: +82-2-3468-3032

57 Fax: +82-2-3468-3697

58 E-mail: epirubicin13@gmail.com

59

60 Jae Il Shin, MD, PhD

61 Department of Pediatrics, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-
62 gu, Seoul 03722, South Korea

63 Phone: +82-2-2228-2050

64 Fax: +82-2-393-9118

65 E-mail: shinji@yuhs.ac.

66

67 Dong Keon Yon, MD, FACAAI

68 Department of Pediatrics, Seoul National University College of Medicine, 103 Daehak-ro,
69 Jongno-gu, Seoul, 03080, South Korea

70 Phone: +82-2-6935-2476

71 Fax: +82-504-478-0201

72 Email: yonkkang@gmail.com

73

74 **Contributors**

75 Dr DKY had full access to all of the data in the study and took responsibility for the integrity
76 of the data and the accuracy of the data analysis. All authors approved the final version before
77 submission. *Study concept and design:* SWL, YHS, JIS, and DKY; *Acquisition, analysis, or*

interpretation of data: LSW, JIS, and DKY; *Drafting of the manuscript:* YHS, SK, ML, YP, MSK, JIS, and DKY; *Critical revision of the manuscript for important intellectual content:* all authors; *Statistical analysis:* LSW, SYM, SK, ML, YP, MSK, JIS, and DKY; *Study supervision:* DKY. DKY is guarantor for this study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of interests

We declare no competing interests.

Sources of funding for the research

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (NRF2019R1G1A109977912). The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

94 **Background:** Real-world evidence and ethnic differences on the association between
95 autoimmune inflammatory rheumatic diseases (AIRDs), AIRDs-related drug use, and COVID-
96 19 are inconsistent. This study aimed to investigate the potential association between AIRD
97 and COVID-19 early in the COVID-19 pandemic in the context of AIRDs.

98 **Methods:** We performed an exposure-driven propensity score-matched study using a Korean
99 nationwide cohort linked to general health examination records. We analyzed all Korean
100 patients aged >20 years who underwent severe acute respiratory syndrome coronavirus 2
101 (SARS-CoV-2) testing from January 1 to May 30, 2020 (n=133,609). Positive SARS-CoV-2
102 testing, severe COVID-19 illness, and COVID-19-related death were the main outcomes.

103 **Findings:** After matching, patients with AIRD showed an increased likelihood of SARS-
104 CoV-2 infectivity (adjusted odds ratio [aOR], 1.19; 95% CI, 1.03–1.40), severe COVID-19
105 outcomes (aOR, 1.26; 95% CI, 1.02–1.59), and COVID-19-related death (aOR, 1.69; 95%
106 CI, 1.01–2.84). Similar positive results were observed in patients with connective tissue
107 diseases and inflammatory arthritis. Patients with AIRD who were treated with any doses of
108 systemic steroids or disease-modifying antirheumatic drugs (DMARDs) were not associated
109 with COVID-19-related outcomes, but those receiving high dose (≥ 10 mg/day) of systemic
110 steroids had an increased likelihood of positive SARS-CoV-2 testing (aOR, 1.50; 95% CI,
111 1.05–2.15), severe COVID-19 outcomes (aOR, 1.95; 95% CI, 1.13–3.35), and COVID-19-
112 related death (aOR, 3.26; 95% CI, 1.20–8.28). Similar patterns of association were found
113 between different sensitivity analyses.

Interpretation: Early in the COVID-19 pandemic, AIRD contribute to an increased likelihood of positive SARS-CoV-2 testing, worse clinical outcomes of COVID-19 as well as COVID-19-related deaths in South Korea. A high dose of systemic corticosteroid, but not DMARDs, showed an adverse effect on COVID-19 infectivity and COVID-19-related clinical outcomes.

Funding National Research Foundation of Korea

Word count: 280

Keywords

Autoimmune inflammatory rheumatic disease; COVID-19; SARS-CoV-2; Steroid; Connective tissue disease, Inflammatory arthritis; Disease-modifying antirheumatic drugs.

Abbreviations

ACE, angiotensin-converting enzyme; AIRD, autoimmune inflammatory rheumatic disease; aOR, adjusted odds ratio; CI, confidence interval; COVID-19, coronavirus disease; CTD, connective tissue disease; DMARD, disease-modifying antirheumatic drug; IA, inflammatory arthritis; ICD-10, International Classification of Disease 10th revision; ICU, intensive care unit; KCDC, Korea Centers for Disease Control; KNHIS, Korean National Health Insurance Service; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SMDs, standardized mean differences; TNF, tumor necrosis factor.

Research in context

Evidence before this study

We searched PubMed, MEDLINE, Embase (Ovid), and Google Scholar on October 26, 2020, for studies published in English describing AIRDs and susceptibility to and clinical outcomes of COVID-19, using the search ‘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 (AIRDs) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infectivity, COVID-19 outcomes, or mortality, the conclusions have been inconsistent, mainly ascribed to non-hypothesis-driven analysis, sampling bias, and/or measurement bias. Furthermore, real-world evidence and ethnic differences on the association between autoimmune inflammatory rheumatic diseases (AIRDs), AIRDs-related drug use, and COVID-19 are lacking.

Added value of this study

Using a Korean nationwide cohort, we determined the potential association of AIRDs 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. We found that patients with AIRD, namely, inflammatory arthritis and connective tissue disease, have an increased risk of SARS-CoV-2 infectivity, severe COVID-19 outcomes, and mortality. Patients with AIRDs treated with any dose of systemic corticosteroid or disease-modifying

antirheumatic drugs (DMARDs) were not associated with an increased risk of any of the
aforementioned COVID-19 outcomes; however, those with AIRDs receiving a high dose of
systemic corticosteroid (≥ 10 mg/day) had an increased risk of SARS-CoV-2 infection, COVID-
19 severity, and COVID-19-related deaths.

Implications of all the available evidence

AIRD has contributed to an increased likelihood of SARS-CoV-2 infection and worse clinical
outcomes of COVID-19 as well as COVID-19-related deaths in South Korea early in the
COVID-19 pandemic. A high dose of systemic corticosteroid, but not DMARDs, showed an
adverse effect on COVID-19 infectivity and COVID-19-related clinical outcomes. Our study
provides an advanced understanding of the relationship between AIRD, including its treatment,
and the pathogenesis of COVID-19. Clinicians and patients should be aware that those with a
history of AIRDs might have an increased risk of SARS-CoV-2 infection, severe COVID-19
outcomes, and mortality.

INTRODUCTION

In December 2019, a novel respiratory infection due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in Wuhan, China, and the virus-related illness, called coronavirus disease (COVID-19), has resulted in a rapidly spreading pandemic.^{1,2} With the rapid increase in the number of patients with COVID-19 and related deaths, immediate reporting of information on the disease's clinical progression, epidemiological evidence, and patient prognosis is crucial, which could, in turn, expedite the advancement of hospital guidelines and strategies to control SARS-CoV-2 infection.³

Autoimmune inflammatory rheumatic diseases (AIRDs) are a heterogeneous class of conditions associated with the stimulation of the host's immune system.⁴ Although several studies reported the relationships between AIRDs and SARS-CoV-2 infectivity, COVID-19 outcomes, or mortality,⁴⁻⁶ the conclusions have been inconsistent mainly ascribed to non-hypothesis-driven analysis, sampling bias, and/or measurement bias. Furthermore, recently published papers have shown that ethnicity data may be important in the context of COVID-19.⁷ However, to the best of our knowledge, no studies have so far reported the exact effect of Asian ethnicity on COVID-19 in the context of AIRDs, which may offer a vital scientific understanding on the relatively undetermined pulmonary consequences of COVID-19 in patients with AIRDs and on the influence of COVID-19 in the course and management of AIRDs. Hence, we aimed to determine the association of SARS-CoV-2 infectivity, severe COVID-19 outcomes, and COVID-19-related death with AIRDs using a Korean nationwide cohort linked to general health examination records early in the COVID-19 pandemic.

METHODS

Korean nationwide cohort

The dataset in this study was obtained from a Korean national health insurance claims-based database. Briefly, this large-scale nationwide cohort included all subjects who underwent SARS-CoV-2 testing between January 1 and May 30, 2020, in the Republic of Korea via the services expedited by the Korean National Health Insurance Service (KNHIS), the Korea Centers for Disease Control (KCDC), and the Ministry of Health and Welfare, Republic of Korea. The dataset links general health examination results from the KNHIS and national COVID-19-related register from the KCDC. Therefore, the dataset in this study comprises records of personal data, healthcare records of in- and outpatients, pharmaceutical visits, general health examination results, COVID-19-associated clinical consequences, and death documents in the past 3 years (January 1, 2018 to July 30, 2020). All subject-associated medical documents utilized in this study were kept confidential. The study protocol was approved by the Institutional Review Board of Sejong University (SJU-HR-E-2020-003).

Study population

We analyzed all subjects aged >20 years who had SARS-CoV-2 testing in the Republic of Korea from January 1, 2020 to May 30, 2020 by medical or KCDC referral (n=133,609). SARS-CoV-2 infection was confirmed by a positive result on a real-time reverse transcriptase–polymerase chain reaction assay of nasal or pharyngeal swabs according to the World Health Organization guideline.⁸⁻¹⁰ For each subject, the cohort entry data (individual index data) was the date of the first SARS-CoV-2 testing. Patient’s medical history was

evaluated using the appropriate International Classification of Disease 10th revision (ICD-10) codes, as reported previously.⁸⁻¹⁰ Current use of medications (aspirin, metformin, statin, systemic steroid, and disease-modifying antirheumatic drugs [DMARDs; methotrexate–leflunomide–azathioprine, sulfasalazine, anti-tumor necrosis factor (TNF)- α agent, and other biologics]) was defined based on the medications received within 3 month before the individual index date.¹⁰ Anti-TNF- α 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.¹¹⁻¹⁴ 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, sufficient aerobic activity (more than 500 metabolic equivalent task min/week) were obtained from the general health examination by personal medical interview.

Exposure

Inflammatory arthritis (IA) was defined as rheumatoid arthritis, psoriatic arthritis, or spondyloarthritis based on the ICD-10 code, with at least two claims within 1 year.^{15,16} Connective tissue disease (CTD) was defined as systemic lupus erythematosus, Sjogren's syndrome, systemic sclerosis, polymyalgia rheumatica, mixed connective tissue disease, dermatomyositis/polymyositis, polyarteritis nodosa, or vasculitis, based on the ICD-10 code.^{15,16} Patients with AIRD were those with IA or CTD. We defined rheumatic disease based on the ICD-10 code. IA and CTD were overlapping in some patients.

Outcomes

The endpoints of this study were a positive laboratory test result, severe COVID-19 (intensive care unit [ICU] admission, application of invasive ventilation, or death), and COVID-19-related death.⁸⁻¹⁰

Statistical analysis

In the nationwide cohort, pre-existing AIRD was defined as the “exposure;” a positive SARS-CoV-2 test result or severe COVID-19 outcomes were defined as the “outcomes.” We generated 12 matched cohort studies to demonstrate the robustness (or reliability) of our main findings. Firstly, exposure-driven propensity score matching was performed to adjust the baseline covariates of the two groups (i.e., patients with and without AIRDs) and to minimize potential confounding factors from the predicted probability of 1) patients with AIRD vs. those without AIRD (matched cohort A), 2) patients with IA vs. those without IA (matched cohort B); and 3) patients with CTD vs. those without CTD (matched cohort C). Each matching was commenced in a 3:1 ratio using a “greedy nearest-neighbor” algorithm. Secondly, 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; Figure S1 and S2). Finally, to avoid overmatching bias, we selected the matched covariates by using the directed acyclic graph approach (Figure S15 and S16) and performed six additional matching (matched cohorts G-L) based on matched cohort A-F. A directed acyclic graph approach was used to confirm adequate potential mediators and thus provided a visualization of the causal relationship between AIRD (“exposure”) and the risk of COVID-19 (“outcome”).¹² The observation

period was between January 1, 2015, and July 31, 2020.

Subsequently, we utilized 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 mellitus, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, hypertension, or chronic kidney disease; household income (low, middle, and high); smoking (never, ex-, and current); alcoholic drinks (<1 , 1–2, 3–4, ≥ 5 days per week); body mass index (< 25 , 25–30, and ≥ 30 kg/m²); sufficient aerobic activity; and current use of aspirin, metformin, and/or statin. Adequacy of the matching was established by comparing exposure-driven propensity score densities and standardized mean differences (SMDs; Figure S3-S14). Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were estimated after adjusting for the potential confounders.

Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC) and R software version 3.6.1 (R Foundation, Vienna, Austria). Directed acyclic graphics were presented using DAGitty (version 2.3; <http://www.dagitty.net/>). A two-sided *P* value < 0.05 was considered statistically significant.

RESULTS

Descriptive overview

The demographics and clinical characteristics of the 133,609 patients (age groups: 27.8% [20–39 years], 36.1% [40–59 years], and 36.1% [≥ 60 years]; male 70,050 [52.4%]) who underwent SARS-CoV-2 testing were analyzed (Table 1). A total of 8297 patients (6.2%) were diagnosed with AIRDs; specifically, 7140 patients (5.3%) were diagnosed with IA and 1953 patients (1.5%) with CTDs (Figure 1 and 2).

COVID-19 and AIRD

After exposure-driven propensity score matching of the study subjects (matched cohort A; $n=31,905$), no major asymmetries in the baseline covariates evaluated by SMD between groups were found (Table 2; all SMDs <0.08). The SARS-CoV-2 positive result rate was 4.4% (365/8222) in subjects with AIRDs and 3.8% (891/23,683) in those without AIRDs (fully aOR, 1.19; 95% CI, 1.03–1.40). Subjects with AIRDs were more likely to develop severe clinical outcomes of COVID-19 (fully aOR, 1.26; 95% CI, 1.02–1.59) and were more likely to have a higher risk of COVID-19-related deaths (fully aOR, 1.69; 95% CI, 1.01–2.84).

After another propensity score matching (matched cohort B; $n=27,933$; patients without vs. those with IA and matched cohort C; $n=7437$; patients without vs. those with CTD), no asymmetries in baseline covariates were noted (Table 2; all SMDs <0.08). Patients with IA had an increased risk of SARS-CoV-2 infectivity (fully aOR, 1.20; 95% CI, 1.03–1.40), severe COVID-19 illness (fully aOR, 1.27; 95% CI, 1.01–1.63), and COVID-19-related deaths (fully aOR, 1.81; 95% CI, 1.02–3.18). Patients with CTD were associated with

increased SARS-CoV-2 infectivity (fully aOR, 1.33; 95% CI, 1.02–1.74), severe COVID-19 (fully aOR, 1.71; 95% CI, 1.06–2.71), but not associated with COVID-19-related deaths (fully aOR, 1.87; 95% CI, 1.71–4.85).

Subgroup analysis stratified by use of DMARDs and systemic steroid

Table 3 shows the subgroup analysis of SARS-CoV-2 infectivity, severe COVID-19, and COVID-19-related deaths in the context of AIRDs stratified by DMARD and systemic steroid use. Subjects with AIRDs treated with any dose of systemic corticosteroid were not associated with a likelihood of SARS-CoV-2 infectivity, severe COVID-19, or COVID-19-related deaths; however, those with AIRDs treated with high dose (≥ 10 mg/day) of systemic corticosteroid had an increased likelihood of SARS-CoV-2 infectivity (fully aOR, 1.47; 95% CI, 1.05–2.03), severe COVID-19 (fully aOR, 1.76; 95% CI 1.06–2.96), and COVID-19-related deaths (fully aOR, 3.34; 95% CI, 1.23–8.90). Patients with AIRDs treated with DMARD showed no association with the risk of SARS-CoV-2 infection, severe COVID-19, and COVID-19-related mortality.

Sensitivity analysis

We conducted several sensitivity analyses (Table S1). First, we performed the additional exposure-driven propensity score-matching in the cohort without linking the general health examination results (matched cohorts D-F; Table S2 and S3), and the findings were consistent with our main results. Second, we conducted minimal selected matching by the directed acyclic graph approach in the original cohort (matched cohorts G-I; Table S5) and the cohort without linking the general health examination results (matched cohorts J-L; Table S6). The results from six matched cohorts yielded results comparable to our primary findings. Third, analyses using the matched cohort D also indicated a significantly increased likelihood of

SARS-CoV-2 infectivity, severe COVID-19 and COVID-19-related deaths in patients with AIRDs treated with a high dose of systemic steroid (≥ 10 mg/day) (Table S4). Finally, the use of the same analysis in the fully unmatched cohort also showed that patients with AIRDs had an increased risk of SARS-CoV-2 infectivity, severe COVID-19, and COVID-19-related deaths in either crude and adjusted models, a finding comparable to our matched results (Figure S17-S19).

DISCUSSION

Using a Korean nationwide cohort, we determined the potential association of AIRDs 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. We found that patients with AIRDs, IAs, or CTDs have an increased risk of SARS-CoV-2 infection and severe COVID-19 outcomes. Those with AIRDs and IAs were associated with an increased likelihood of COVID-19-related mortality. Interestingly, patients with AIRDs treated with high dose of a systemic corticosteroid had a higher SARS-CoV-2 infectivity, severe COVID-19 outcomes, and COVID-19-related mortality. Patients with AIRD receiving DMARDs were not associated with an increased risk of any of the aforementioned COVID-19 outcomes. Similar patterns of association were found between different sensitivity analyses from matched cohorts D-L.

SARS-CoV-2 infectivity

A previous meta-analysis suggested that patients with AIRDs have an increased risk of SARS-CoV-2 infection;¹⁷ however, the results are limited in that the study mainly included hospitalized patients and had a small sample size, skewed clinic-based data, selection bias (i.e., not all patients were laboratory-confirmed cases), and insufficient confounding adjustment.¹⁷ In our study, we used nationwide data and employed a sophisticated statistical technique (exposure-driven propensity score matching with sufficient confounding adjustment). Our results showed that patients with AIRDs have an increased risk of SARS-CoV-2 infection, a finding that corresponds well with a previous meta-analysis.¹⁷ However, no study has shown the different infectivity to SARS-CoV-2 infection between patients with IA and those with

CTD. We believe this is the first study to demonstrate that patients with IA and CTD are at increased risk of SARS-CoV-2 infection independently.

COVID-19 severity and mortality

Previous studies have suggested no association^{18,19} or positive association²⁰ between AIRD and COVID-19 severity and COVID-19-related deaths in Western cohorts. Our findings from a Korean nationwide cohort support studies showed that patients with AIRDs have an increased likelihood of COVID-19 infectivity, severe COVID-19 outcomes, and COVID-19-related mortality. A previous epidemiologic study also reported that Asian ethnicity is associated with higher ICU admission and COVID-19-related mortality rates,²¹ which is consistent with our main findings. The reason for such adverse association of COVID-19 with Asian ethnicity may be due to higher angiotensin-converting enzyme (ACE) level and lower androgen level which lead to increased ACE2 expression, cross-immunity such as past exposure to infections (i.e. malaria), regional temperature and humidity which can influence virus survival and host immune response.²² Further, we found no association between CTDs and COVID-19-related death, but these findings may be due to the small number of subjects with CTDs, which calls for further large-scaled and international studies.

DMARDs, systemic steroid, and COVID-19

The use of DMARD was not associated with any COVID-19-related endpoints in the nationwide cohort study. The relationship of systemic steroid use in patients with AIRDs in the context of COVID-19 outcomes has preliminary evidence, but the supporting evidence remains lacking. First, researcher should have caution when interpreting the the systemic steroid use results in patients with AIRDs, which can be influenced by unmeasured confounding factors in observational studies. A previous study reported no relationship

between inhaled steroid use and severe COVID-19, although the hazard ratio was statistically significant (hazard ratio, 1.39; 95% CI, 1.10–1.76).²³ The present results of a nationwide cohort study suggest that patients with AIRD receiving any dose of systemic steroids do not have an increased risk of SARS-CoV-2 infectivity, COVID-19-related outcomes, or its mortality. However, the subjects with AIRD receiving a high dose of systemic steroids have an increased risk of SARS-CoV-2 infectivity and COVID-19-related outcomes and mortality, which corresponds well with a well-designed cohort study that demonstrated that a high dose of systemic steroid might have a higher odds of hospitalization for COVID-19²⁴. In addition, we advanced our knowledge on the SARS-CoV-2 by showing the novel results that patients on a high dose of systemic steroids have a higher risk for SARS-CoV-2 infection. A corticosteroid may reduce ACE2 expression levels²⁵, which may lead to altered SARS-CoV-2 susceptibility either beneficially (i.e., reduced SARS-CoV-2 entry) or adversely (i.e., reduced beneficial effect of ACE2 from hyperinflammation)²⁶, thereby suggesting an unknown effect of systemic corticosteroids. Researchers should exercise caution when interpreting data regarding systemic steroid use in patients with COVID-19 in the context of AIRDs.

Basic mechanisms in AIRD and COVID-19

First, proinflammatory cytokines, such as IL-6, TNF- α , and IL-1, which have been reported as the pathogenic factors produced by macrophages after T lymphocytes bearing T-cell receptors recognize SARS-CoV-2 bound to the surface of cells in most rheumatic diseases, may be culpable for the tissue destruction in various organs in patients with COVID-19.²⁷ It is plausible that rheumatic disorders and COVID-19 could influence each other at the pathogenic level, which ultimately results in the fatal decline of patients' condition. Second, the immunological abnormalities due to rheumatic disease affect most circulating T cells,

which evolve from an early stage in the rheumatic disease course.²⁸ T cell dynamics in patients with AIRD (i.e., lack of T cell receptor rearrangement excision circle-positive cells and abnormalities in T cell homeostasis) suggests that an AIRD patients' ability to react to novel antigens, such as during SARS-CoV-2 infection, is compromised.²⁸ 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 diseases²⁹ and chronic inflammatory diseases³⁰, suggesting that patients with AIRDs may be at a higher risk of poor COVID-19 outcomes, which is consistent with our finding that those with AIRDs have a higher COVID-19 severity and COVID-19-related mortality. Hence, we conjectured that SARS-CoV-2 could potentially aggravate AIRDs, which could, in turn, exacerbate viral infection and result in devastating COVID-19 sequelae. This indicates a complex biopathological mechanism wherein underlying AIRDs could adversely influence the pathogenesis of COVID-19.

Strengths and limitations

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

This study has some limitations. First, the diagnosis of AIRDs was based on ICD-10 codes, which may be imprecise; however, numerous previous studies have also used these definitions¹⁶ and the results of our cohort study were supported by those of our several additional matched cohorts. Second, as our database included patients who underwent SARS-CoV-2 tests; therefore, the systemic factors of our subjects may vary from those of the general population. Although there exists potential for prevalence-induced bias, our study was performed with a large population-established cohort and with exposure-driven propensity score matching to ensure the reliability of our results. Third, we did not have accurate data on the individual viral loads and contact tracing result, we need to be careful about the interpretation of SARS-CoV-2 test positive results although we used the large-scale and national level dataset. Finally, COVID-19 outcomes have improved in accordance with physician experience and management strategies for COVID-19.³¹ Since we used the dataset that reflected the initial period of the pandemic in Korea, caution should be exercised when generalizing our results.

Conclusions

AIRDs contribute to an increased likelihood of SARS-CoV-2 infection, worse clinical outcomes of COVID-19 and COVID-19-related deaths in the Republic of Korea. Patients with IAs and CTDs have an increased risk of SARS-CoV-2 infection and worse clinical outcomes of COVID-19. In addition, AIRD treatment with a high dose of systemic corticosteroid adversely affected SARS-CoV-2 infectivity, severe COVID-19 outcomes, and COVID-19-related mortality; treatment with DMARDs was not associated with an increased risk of worse clinical outcomes of COVID-19. Similar patterns of association were found between different sensitivity analyses from 12 matched cohorts. Thus, our study provides an advanced understanding of the relationship between AIRD, including its treatment, and the pathogenesis of COVID-19. Clinicians and patients should discern that those with a history of AIRDs might be at an increased risk of SARS-CoV-2 infection and severe COVID-19 outcomes and its mortality early in the COVID-19 pandemic.

447 **Acknowledgement**

448 The authors would like to thank the dedicated healthcare professionals treating patients with
449 COVID-19 in the Republic of Korea as well as the Ministry of Health and Welfare and the
450 Health Insurance Review and Assessment Service of Korea for sharing invaluable national
451 health insurance claims data.

452

Reference

1. Bae SH, Shin H, Koo HY, Lee SW, Yang JM, Yon DK. Asymptomatic Transmission of SARS-CoV-2 on Evacuation Flight. *Emerging infectious diseases* 2020; **26**(11): 2705-8.
2. Lee SW, Yuh WT, Yang JM, et al. Nationwide Results of COVID-19 Contact Tracing in South Korea: Individual Participant Data From an Epidemiological Survey. *JMIR medical informatics* 2020; **8**(8): e20992.
3. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; **8**(5): 475-81.
4. Gremese E, Brondani G, Apollonio L, Ferraccioli G. Correspondence on 'Prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases: a systematic review and meta-analysis'. *Annals of the rheumatic diseases* 2020.
5. Pablos JL, Galindo M, Carmona L, et al. Clinical outcomes of hospitalised patients with COVID-19 and chronic inflammatory and autoimmune rheumatic diseases: a multicentric matched cohort study. *Annals of the rheumatic diseases* 2020.
6. D'Silva KM, Serling-Boyd N, Wallwork R, et al. Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: a comparative cohort study from a US 'hot spot'. *Annals of the rheumatic diseases* 2020; **79**(9): 1156-62.
7. Patel P, Hiam L, Sowemimo A, Devakumar D, McKee M. Ethnicity and covid-19. *BMJ* 2020; **369**: m2282.
8. Lee SW, Yang JM, Moon SY, et al. Association between mental illness and COVID-19 susceptibility and clinical outcomes in South Korea: a nationwide cohort study. *The lancet*

475 *Psychiatry* 2020.

476 9. Yang JM, Koh HY, Moon SY, et al. Allergic disorders and susceptibility to and severity
477 of COVID-19: A nationwide cohort study. *The Journal of allergy and clinical immunology*
478 2020; **146**(4): 790-8.

479 10. Lee SW, Ha EK, Yeniova A, et al. Severe clinical outcomes of COVID-19 associated
480 with proton pump inhibitors: a nationwide cohort study with propensity score matching. *Gut*
481 2020.

482 11. Ha J, Lee SW, Yon DK. Ten-Year trends and prevalence of asthma, allergic rhinitis,
483 and atopic dermatitis among the Korean population, 2008-2017. *Clinical and experimental*
484 *pediatrics* 2020; **63**(7): 278-83.

485 12. Woo A, Lee SW, Koh HY, Kim MA, Han MY, Yon DK. Incidence of cancer after
486 asthma development: 2 independent population-based cohort studies. *The Journal of allergy*
487 *and clinical immunology* 2020.

488 13. Koh HY, Kim TH, Sheen YH, et al. Serum heavy metal levels are associated with
489 asthma, allergic rhinitis, atopic dermatitis, allergic multimorbidity, and airflow obstruction. *The*
490 *journal of allergy and clinical immunology In practice* 2019; **7**(8): 2912-5.e2.

491 14. Lee SW, Yang JM, Moon SY, et al. Association between mental illness and COVID-
492 19 in South Korea: a post-hoc analysis. *The lancet Psychiatry* 2021.

493 15. Freites Nuñez DD, Leon L, Mucientes A, et al. Risk factors for hospital admissions
494 related to COVID-19 in patients with autoimmune inflammatory rheumatic diseases. *Annals of*
495 *the rheumatic diseases* 2020; **79**(11): 1393-9.

496 16. Kjøller K, Friis S, Møllemejkjaer L, et al. Connective tissue disease and other rheumatic
497 conditions following cosmetic breast implantation in Denmark. *Archives of internal medicine*

498 2001; **161**(7): 973-9.

499 17. Akiyama S, Hamdeh S, Micic D, Sakuraba A. Prevalence and clinical outcomes of
500 COVID-19 in patients with autoimmune diseases: a systematic review and meta-analysis.
501 *Annals of the rheumatic diseases* 2020.

502 18. Salvarani C, Bajocchi G, Mancuso P, et al. Susceptibility and severity of COVID-19
503 in patients treated with bDMARDs and tsDMARDs: a population-based study. *Annals of the*
504 *rheumatic diseases* 2020; **79**(7): 986-8.

505 19. Gu T, Mack JA, Salvatore M, et al. COVID-19 outcomes, risk factors and associations
506 by race: a comprehensive analysis using electronic health records data in Michigan Medicine.
507 *medRxiv : the preprint server for health sciences* 2020.

508 20. Jorge A, D'Silva KM, Cohen A, et al. Temporal trends in severe COVID-19 outcomes
509 in patients with rheumatic disease: a cohort study. *The Lancet Rheumatology* 2021; **3**(2): e131-
510 e7.

511 21. Sagnella GA, Rothwell MJ, Onipinla AK, Wicks PD, Cook DG, Cappuccio FP. A
512 population study of ethnic variations in the angiotensin-converting enzyme I/D polymorphism:
513 relationships with gender, hypertension and impaired glucose metabolism. *Journal of*
514 *hypertension* 1999; **17**(5): 657-64.

515 22. Gupta R, Misra A. COVID19 in South Asians/Asian Indians: Heterogeneity of data
516 and implications for pathophysiology and research. *Diabetes research and clinical practice*
517 2020; **165**: 108267.

518 23. Schultze A, Walker AJ, MacKenna B, et al. Risk of COVID-19-related death among
519 patients with chronic obstructive pulmonary disease or asthma prescribed inhaled
520 corticosteroids: an observational cohort study using the OpenSAFELY platform. *The Lancet*

521 *Respiratory Medicine* 2020; **8**(11): 1106-20.

522 24. Cacciapaglia F, Manfredi A, Erre G, et al. Correspondence on 'Characteristics
523 associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the
524 COVID-19 global rheumatology alliance physician-reported registry' by Gianfrancesco M et
525 al. The impact of cardiovascular comorbidity on COVID-19 infection in a large cohort of
526 rheumatoid arthritis patients. *Annals of the rheumatic diseases* 2020.

527 25. Peters MC, Sajuthi S, Deford P, et al. COVID-19-related Genes in Sputum Cells in
528 Asthma. Relationship to Demographic Features and Corticosteroids. *American journal of*
529 *respiratory and critical care medicine* 2020; **202**(1): 83-90.

530 26. Finney LJ, Glanville N, Farne H, et al. Inhaled corticosteroids downregulate the
531 SARS-CoV-2 receptor ACE2 in COPD through suppression of type I interferon. *The Journal*
532 *of allergy and clinical immunology* 2021; **147**(2): 510-9.e5.

533 27. Nocturne G, Mariette X. Advances in understanding the pathogenesis of primary
534 Sjögren's syndrome. *Nature reviews Rheumatology* 2013; **9**(9): 544-56.

535 28. Koetz K, Bryl E, Spickschen K, O'Fallon WM, Goronzy JJ, Weyand CM. T cell
536 homeostasis in patients with rheumatoid arthritis. *Proceedings of the National Academy of*
537 *Sciences of the United States of America* 2000; **97**(16): 9203-8.

538 29. Burgueño JF, Reich A, Hazime H, et al. Expression of SARS-CoV-2 Entry Molecules
539 ACE2 and TMPRSS2 in the Gut of Patients With IBD. *Inflammatory bowel diseases* 2020;
540 **26**(6): 797-808.

541 30. Yao Y, Wang H, Liu Z. Expression of ACE2 in airways: Implication for COVID-19
542 risk and disease management in patients with chronic inflammatory respiratory diseases.
543 *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical*

544 *Immunology* 2020.

545 31. Gianfrancesco MA, Robinson PC. Changing COVID-19 outcomes in patients with
546 rheumatic disease-are we really getting better at this? *The Lancet Rheumatology* 2021; **3**(2):
547 e88-e90.

548

549

550

Figure 1

551

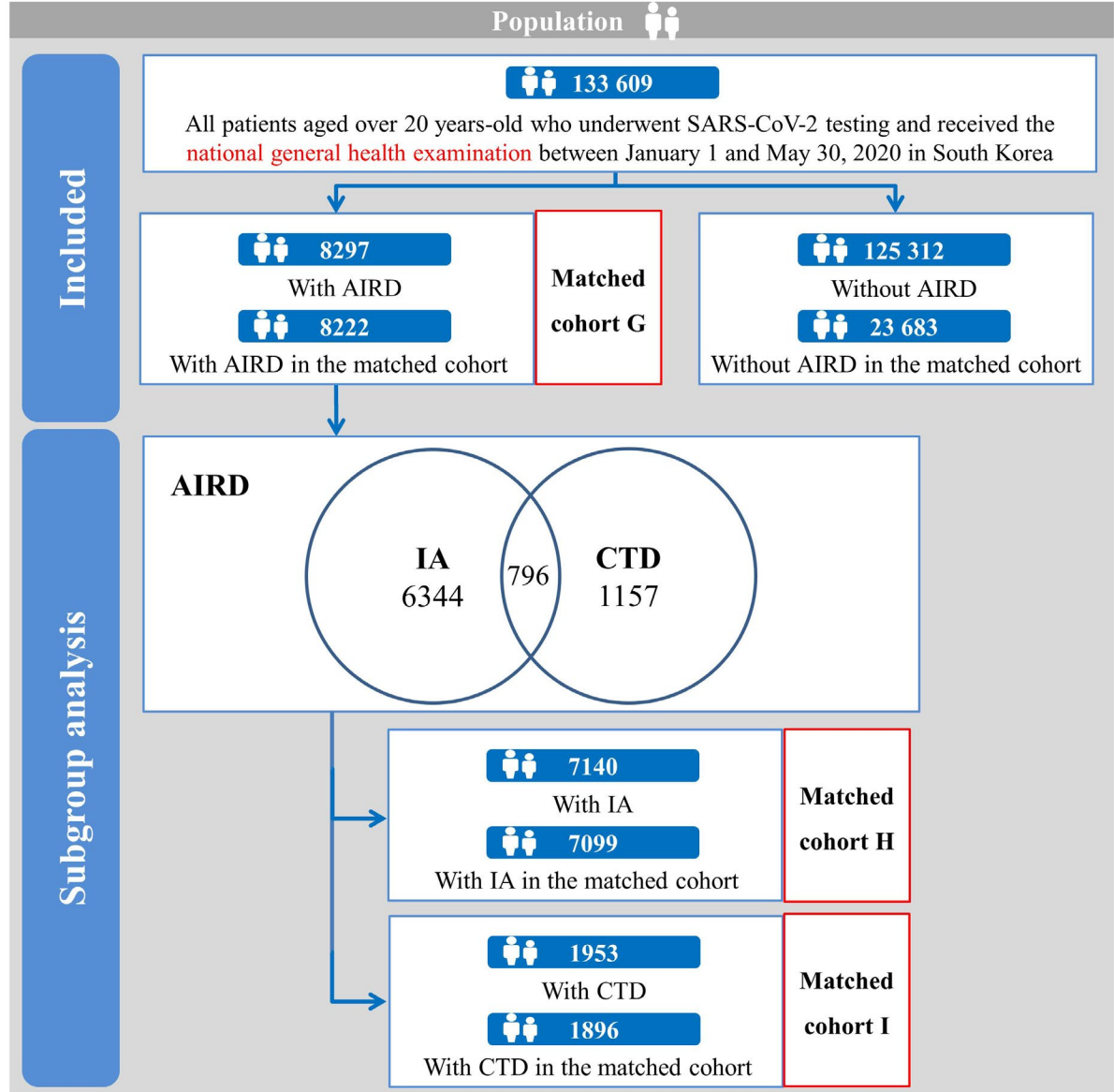
Disposition of patients in the Korean nationwide cohort linked to the general health examination records

552

553

AIRD, autoimmune inflammatory rheumatic disease; CTD, connective tissue disease; IA, inflammatory arthritis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

554

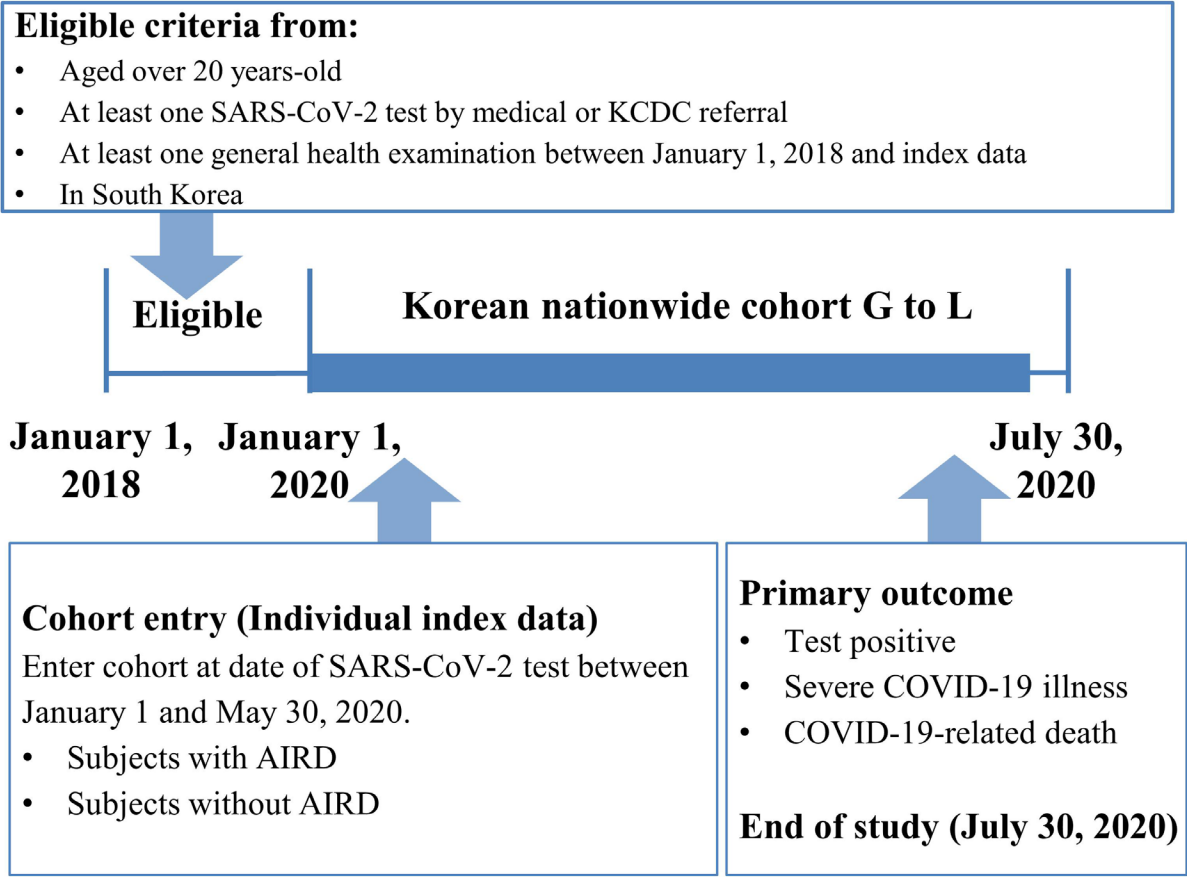


555

556

Figure 2

557 Flowchart depicting the study enrollment in the Korean nationwide cohort linked to the general
558 health examination records
559 AIRD, autoimmune inflammatory rheumatic disease; CTD, connective tissue disease; IA,
560 inflammatory arthritis; KCDC, Korea Centers for Disease Control; SARS-CoV-2, severe acute
561 respiratory syndrome coronavirus 2.



562
563

Table 1

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

Characteristics	Entire cohort	AIRD	AIRD	
			IA	CTD
Total, n (%)	133,609	8297	7140	1953
Age, years, n (%)				
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, n (%)				

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, n (%)				
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 (20.6)	310 (15.9)
Other area	48,157 (36.0)	3032 (36.5)	2600 (36.4)	715 (36.6)
Resident of a skilled nursing facility, n (%)	6616 (5.0)	606 (7.3)	517 (7.2)	117 (6.0)
History of diabetes mellitus, n (%)	29,699 (22.23)	3441 (41.5)	3004 (42.1)	752 (38.5)
History of cardiovascular disease, n (%)	25,637 (19.2)	3134 (37.8)	2681 (37.6)	744 (38.1)
History of cerebrovascular disease, n (%)	15,905 (11.9)	1881 (22.7)	1640 (23.0)	393 (20.1)
History of COPD, n (%)	16,706 (12.5)	2006 (24.2)	1714 (24.0)	482 (24.7)
History of hypertension, n (%)	29,443 (22.0)	3146 (37.9)	2735 (38.3)	700 (35.8)

History of chronic kidney disease, n (%)	45,781 (34.3)	4654 (56.1)	4047 (56.7)	1015 (52.0)
Current use of aspirin, n (%)	11,891 (8.9)	1210 (14.6)	1045 (14.6)	282 (14.4)
Current use of metformin, n (%)	13,807 (10.3)	1260 (15.2)	1115 (15.6)	235 (12.0)
Current use of statin, n (%)	31,208 (23.4)	3230 (38.9)	2837 (39.7)	659 (33.7)
Household income, n (%)				
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 (29.8)	2106 (29.5)	594 (30.4)
Smoking, n (%)				
Never smoker	87,771 (65.7)	5955 (71.8)	5130 (71.9)	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)
Alcoholic drinks, days per week, n (%)				
<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 , n (%)				
<25	86,641 (64.9)	5298 (63.9)	4508 (63.1)	1374 (70.4)
25–30	39,081 (29.3)	2493 (30.1)	2189 (30.7)	491 (25.1)

≥30	7887 (5.9)	506 (6.1)	443 (6.2)	88 (4.5)
Sufficient aerobic activity, n (%)	62,418 (46.7)	4105 (49.5)	3527 (49.4)	984 (50.4)
Current use of systemic steroid, n (%)	16,268 (12.2)	2446 (29.5)	1977 (27.7)	859 (44.0)
Current use of DMARDs, n (%)				
Methotrexate–leflunomide–azathioprine, n (%)	8149 (6.1)	3519 (42.4)	3048 (42.7)	1313 (67.2)
Sulfasalazine, n (%)	487 (0.3)	439 (5.3)	432 (6.1)	80 (4.1)
Antimalarials, n (%)	7781 (5.8)	1692 (20.4)	1491 (20.9)	727 (37.2)
Anti-TNF-alpha agent, n (%)	852 (0.6)	489 (5.9)	452 (6.3)	124 (6.3)
Other biologics, n (%)	1413 (1.1)	348 (4.2)	327 (4.6)	72 (3.7)

566 AIRD, autoimmune inflammatory rheumatic disease; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; DMARD,

567 disease-modifying antirheumatic drug; IA, inflammatory arthritis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard

568 deviation; TNF; tumor necrosis factor.

569

570

Table 2

571 3:1 propensity score-matched covariates and aOR (95% CI) of positive SARS-CoV-2 test, severe COVID-19 outcomes, or COVID-19-related
572 death in patients with AIRD, IA, or CTD.

Characteristics	Matched cohort A			Matched cohort B			Matched cohort C		
	None	AIRD	SMD	None	IA	SMD	None	CTD	SMD
Total, n (%)	23,683	8222		20,834	7099		5541	1896	
Age, years, n (%)			0.008			0.002			0.018
20-39	2131 (9.0)	765 (9.3)		1766 (8.5)	617 (8.7)		662 (12.0)	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 (52.3)	976 (51.5)	
Sex, n (%)			0.037			0.022			0.003

Male	9206 (38.9)	3048 (37.1)		7908 (37.96)	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, n (%)			0.002			0.005			0.037
Seoul Capital Area	10,284(43.4)	3597 (43.8)		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, n (%)	1700 (7.2)	606 (7.4)	0.008	1526 (7.3)	517 (7.3)	0.002	345 (6.2)	116 (6.1)	0.004
History of diabetes mellitus, n (%)	9656 (40.8)	3426 (41.7)	0.020	8563 (41.1)	2993 (42.2)	0.023	2043 (36.9)	735 (38.8)	0.039
History of cardiovascular disease, n (%)	8393 (35.4)	3095 (37.6)	0.050	7391 (35.5)	2659 (37.5)	0.045	1932 (34.9)	710 (37.5)	0.054
History of cerebrovascular disease, n (%)	5092 (21.5)	1874 (22.8)	0.035	4573 (22.0)	163 1(23.0)	0.028	1069 (19.3)	388 (20.5)	0.029
History of COPD, n (%)	5028 (21.2)	1940 (23.6)	0.062	4351 (20.9)	1674 (23.6)	0.071	1246 (22.5)	458 (24.2)	0.039
History of hypertension, n (%)	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

History of chronic kidney disease, n (%)	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, n (%)	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, n (%)	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 statin, n (%)	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, n (%)			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, n (%)			0.007			0.002			0.054
Never smoker	16,938 (71.5)	5885 (71.6)		14971 (71.9)	5096 (71.8)		4248 (76.7)	1416 (74.7)	

Ex-smoker	3748 (15.8)	1336 (16.3)	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)
Alcoholic drinks, days per week, n (%)			<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 (76.0)
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 , n (%)			0.012		0.022	0.028
<25	15,175 (64.1)	5242 (63.8)	13,281 (63.8)	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, n (%)	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
COVID-19, n (%)	891 (3.8)	365 (4.4)		796 (3.8)	327 (4.6)		188 (3.4)	84 (4.4)	
Minimally aOR* (95% CI)	1.0 (ref)	1.18 (1.05-1.35)		1.0 (ref)	1.19 (1.03-1.38)		1.0 (ref)	1.32 (1.02-1.72)	
Fully aOR [§] (95% CI)	1.0 (ref)	1.19 (1.03-1.40)		1.0 (ref)	1.20 (1.03-1.40)		1.0 (ref)	1.33 (1.02-1.74)	
Severe COVID-19 [‡] , n (%)	285 (1.2)	127 (1.5)		234 (1.1)	103 (1.5)		51 (0.9)	30 (1.6)	
Minimally aOR* (95% CI)	1.0 (ref)	1.28 (1.04-1.60)		1.0 (ref)	1.28 (1.02-1.62)		1.0 (ref)	1.73 (1.09-2.73)	
Fully aOR [§] (95% CI)	1.0 (ref)	1.26 (1.02-1.59)		1.0 (ref)	1.27 (1.01-1.63)		1.0 (ref)	1.71 (1.06-2.71)	
COVID-19-related death, n (%)	40 (0.2)	24 (0.3)		32 (0.2)	20 (0.3)		11 (0.2)	7 (0.4)	
Minimally aOR* (95% CI)	1.0 (ref)	1.74 (1.04-2.88)		1.0 (ref)	1.84 (1.06-3.22)		1.0 (ref)	1.85 (0.72-4.82)	

Fully aOR [§] (95% CI)	1.0 (ref)	1.69 (1.01-2.84)	1.0 (ref)	1.81 (1.02-3.18)	1.0 (ref)	1.87 (0.71-4.85)
---------------------------------	-----------	-------------------------	-----------	-------------------------	-----------	------------------

573 An SMD <0.1 indicates no major imbalance. All SMD values were <0.08 in the propensity score-matched cohort.

574 Data in bold indicate significant differences ($P < 0.05$).

575

576 aOR, adjusted odds ratio; AIRD, autoimmune inflammatory rheumatic disease; CI, confidence interval; COPD, chronic obstructive pulmonary
 577 disease; CTD, connective tissue disease; DMARD, disease-modifying antirheumatic drug; IA, inflammatory arthritis; SARS-CoV-2, severe
 578 acute respiratory syndrome coronavirus 2; SD, standard deviation; SMD, standardized mean difference.

579

580 *Minimally adjusted: adjustment for age (20-39, 40-59, and ≥ 60 years) and sex.

581 [§]Fully adjusted: adjustment for age; sex; region of residence (Seoul Capital Area, Daegu/Gyeongbuk area, and other area); resident of a
 582 skilled nursing facility; history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, and chronic kidney
 583 disease; household income (low, middle, and high); smoking (never, ex-, and current); alcoholic drinks (<1, 1-2, 3-4, ≥ 5 days per week);
 584 body mass index (< 25, 25-30, and ≥ 30 kg/m²); sufficient aerobic activity; and current use of aspirin, metformin, and statin

585 ‡ Requirement of oxygen therapy, admission to the intensive care unit, invasive ventilation, or death.

586

587

Table 3

589 Propensity-score-matched subgroup analysis of aOR (95% CI) of positive SARS-CoV-2 test, severe COVID-19 outcomes, or COVID-19-related
 590 death in patients with AIRD stratified by DMARD and systemic steroid (matched cohort A).

Events	Factors	N (%)	Adjusted OR (95% CI)
COVID-19	Treated without DMARD	140/3021 (4.6)	1.0 (ref) [*]
	Treated with DMARD	225/5201 (4.3)	0.90 (0.70-1.17)
COVID-19	Treated without systemic steroid	244/5803 (4.2)	1.0 (ref) [‡]
	Treated with systemic steroid (any dose)	121/2419 (5.0)	1.18 (0.92-1.51)
	Treated with systemic steroid (≥ 10 mg/day)	49/802 (6.1)	1.47 (1.05-2.03)
Severe COVID-19 [§]	Treated without DMARD	45/3021 (1.5)	1.0 (ref) [*]
	Treated with DMARD	82/5201 (1.6)	1.01 (0.69-1.50)
Severe COVID-19 [§]	Treated without systemic steroid	82/5803 (1.4)	1.0 (ref) [‡]
	Treated with systemic steroid (any dose)	45/2419 (1.9)	1.34 (0.92-1.95)

	Treated with systemic steroid (≥ 10 mg/day)	20/802 (2.5)	1.76 (1.06-2.96)
COVID-19-related death	Treated without DMARD	8/3021 (0.3)	1.0 (ref)*
	Treated with DMARD	16/5201 (0.3)	1.19 (0.52-2.74)
COVID-19-related death	Treated without systemic steroid	13/5803 (0.2)	1.0 (ref) [‡]
	Treated with systemic steroid (any dose)	11/3419 (0.5)	2.02 (0.89-4.56)
	Treated with systemic steroid (≥ 10 mg/day)	6/802 (0.8)	3.34 (1.23-8.90)

591 Data in bold indicate significant differences ($P < 0.05$).

592

593 aOR, adjusted odds ratio; AIRD, autoimmune inflammatory rheumatic disease; CI, confidence interval; COPD, chronic obstructive pulmonary

594 disease; DMARD, disease-modifying antirheumatic drug; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

595

596 *Risk factors were adjusted for age (20-39, 40-59, and ≥ 60 years); sex; region of residence (Seoul Capital Area, Daegu/Gyeongbuk area, and

597 other area); resident of a skilled nursing facility; history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD,

598 hypertension, and chronic kidney disease; household income (low, middle, and high); smoking (never, ex-, and current); alcoholic drinks (<1 ,

599 1-2, 3-4, ≥ 5 days per week); body mass index (< 25 , 25-30, and ≥ 30 kg/m²); sufficient aerobic activity; and current use of aspirin,
600 metformin, statin, and systemic steroid.

601 [‡] Risk factors were adjusted for age (20-39, 40-59, and ≥ 60 years); sex; region of residence (Seoul Capital Area, Daegu/Gyeongbuk area, and
602 other area); resident of a skilled nursing facility; history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD,
603 hypertension, and chronic kidney disease; household income (low, middle, and high); smoking (never, ex-, and current); alcoholic drinks (< 1 ,
604 1-2, 3-4, ≥ 5 days per week); body mass index (< 25 , 25-30, and ≥ 30 kg/m²); sufficient aerobic activity; and current use of aspirin,
605 metformin, and statin and DMARD.

606 [§] Requirement of oxygen therapy, admission to the intensive care unit, invasive ventilation, or death.

607

Table S1	Sensitivity analyses and justification.	3
Table S2	Baseline covariates of patients who underwent the SARS-CoV-2 test in the nationwide cohort.	6
Table S3	3:1 propensity score-matched covariates and aOR (95% CI) of positive SARS-CoV-2 test, severe COVID-19 outcomes, or COVID-19-related death in patients with AIRD, IA, or CTD.	9
Table S4	Propensity-score-matched subgroup analysis of aOR (95% CI) of positive SARS-CoV-2 test, severe COVID-19 outcomes, or COVID-19-related death in patients with AIRD stratified by DMARD and systemic steroid (matched cohort D).	13
Table S5	3:1 propensity score-matched covariates selected by DAGs and aOR (95% CI) of positive SARS-CoV-2 test, severe COVID-19 outcomes, or COVID-19-related death in patients with AIRD, IA, or CTD in the Korean nationwide cohort linked with the general health examination records.	16
Table S6	3:1 propensity score-matched covariates selected by DAGs and aOR (95% CI) of positive SARS-CoV-2 test, severe COVID-19 outcomes, or COVID-19-related death in patients with AIRD, IA, or CTD in the Korean nationwide cohort.	22
Figure S1	Disposition of patients in the Korean nationwide cohort without linking the general health examination records	25
Figure S2	Flowchart showing the study enrollment in the Korean nationwide cohort without linking the general health examination records	26
Figure S3	The density and distribution of propensity scores before and after matching in matched cohort A	27
Figure S4	The density and distribution of propensity scores before and after	28

	matching in matched cohort B	
Figure S5	The density and distribution of propensity scores before and after matching in matched cohort C	29
Figure S6	The density and distribution of propensity scores before and after matching in matched cohort D	30

Contents of supplementary appendix

Figure S7	The density and distribution of propensity scores before and after matching in matched cohort E	31
Figure S8	The density and distribution of propensity scores before and after matching in matched cohort F	32
Figure S9	The density and distribution of propensity scores before and after matching in matched cohort G	33
Figure S10	The density and distribution of propensity scores before and after matching in matched cohort H	34
Figure S11	The density and distribution of propensity scores before and after matching in matched cohort I	35
Figure S12	The density and distribution of propensity scores before and after matching in matched cohort J	36
Figure S13	The density and distribution of propensity scores before and after matching in matched cohort K	37
Figure S14	The density and distribution of propensity scores before and after matching in matched cohort L	38
Figure S15	Directed acyclic graph demonstrating the implicitly assumed causal association between AIRD (“exposure”) and risk of COVID-19 (“outcome”) in the Korean nationwide cohort linked to the general health examination records before matching.	39
Figure S16	Directed acyclic graph showing the implicitly assumed causal association between AIRD (“exposure”) and risk of COVID-19 (“outcome”) in the Korean nationwide cohort without linking the general health examination records before matching.	40
Figure S17	Propensity score-matched association of AIRD with SARS-CoV-2	41
Figure S18	Propensity score-matched association of IA with SARS-CoV-2	42

Figure S19	Propensity score-matched association of CTD with SARS-CoV-2	43
-------------------	---	-----------

Table S1. Sensitivity analyses and justification.

Sensitivity analysis (1 to 10)	Cohort	Justification
1. Risk of positive SARS-CoV-2 test, severe COVID-19 outcomes, or COVID-19-related death in patients with AIRD, IA, or CTD	Matched cohort A, B, C	<ul style="list-style-type: none">- Main results- Social-economic status, body mass index, physical activity, cigarette smoking, and consuming alcoholic drinks can affect the COVID-19 and AIRD. We consider these covariates by linking the national general health examination results.- Matching covariates were selected for age; sex; region of residence; resident of a skilled nursing facility; a history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, and chronic kidney disease; household income ; smoking; alcoholic drinks; body mass index; sufficient aerobic activity; and current use of aspirin, metformin, and statin
2. Subgroup analysis of the risk of positive SARS-CoV-2 test, severe COVID-19 outcomes, or COVID-19-related	Matched cohort A	<ul style="list-style-type: none">- To investigate the association of COVID-19-related outcomes by current use of DMARD and systemic steroid.

death in patients with AIRD stratified by DMARD and systemic steroid		
3. Risk of positive SARS-CoV-2 test, severe COVID-19 outcomes, or COVID-19-related death in patients with AIRD, IA, or CTD	Matched cohort D, E, F	<ul style="list-style-type: none"> - We constructed an original dataset without linking the general health examination records to obtain a large sample number. - Matching covariates were selected for age; sex; region of residence; resident of a skilled nursing facility; a history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, and chronic kidney disease; and current use of aspirin, metformin, and statin
4. Subgroup analysis of the risk of positive SARS-CoV-2 test, severe COVID-19 outcomes, or COVID-19-related death in patients with AIRD stratified by DMARD and systemic steroid	Matched cohort D	<ul style="list-style-type: none"> - To investigate the association of COVID-19-related outcomes by current use of DMARD and systemic steroid.

5. Risk of positive SARS-CoV-2 test, severe COVID-19 outcomes, or COVID-19-related death in patients with AIRD	Full-unmatched cohort	- Propensity score matching can introduce unintended bias into the estimation. We repeated the main analysis by analysis from unmatched subjects.
7. Risk of positive SARS-CoV-2 test, severe COVID-19 outcomes, or COVID-19-related death in patients with AIRD, IA, or CTD	Matched cohort G, H, I	<p>- To avoid overmatching issues, we selected the matching covariates in matched A, B, C by using the DAG approach. DAGs can be used to select covariates for support causal interpretation.</p> <p>- Matching covariates were selected for age; sex; region of residence; resident of a skilled nursing facility.</p>
8. Risk of positive SARS-CoV-2 test, severe COVID-19 outcomes, or COVID-19-related death in patients with AIRD, IA, or CTD	Matched cohort J, K, L	<p>- To avoid overmatching issues, we selected the matching covariates in matched D, E, F by using the DAG approach. DAGs can be used to select covariates for support causal interpretation.</p> <p>- Matching covariates were selected for age; sex; region of residence; resident of a skilled nursing facility; household income ; smoking; alcoholic drinks; body mass index.</p>

AIRD, autoimmune inflammatory rheumatic disease; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; DMARD,

disease-modifying antirheumatic drug; IA, inflammatory arthritis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table S2. Baseline covariates of patients who underwent the SARS-CoV-2 test in the nationwide cohort.

Characteristics	Entire cohort	AIRD	AIRD	
			IA	CTD
Total, n (%)	212,678	11,766	10,038	2875
Age, years, n (%)				
20-39	78,372 (36.9)	1590 (13.5)	1247 (12.4)	581 (20.2)
40-59	63,057 (29.7)	3303 (28.1)	2772 (27.6)	950 (33.0)
≥ 60	71,249 (33.5)	6873 (58.4)	6019 (60.0)	1344 (46.8)
Sex, n (%)				
Male	100,038 (47.0)	4284 (36.4)	3647 (36.3)	905 (31.5)
Female	112,640 (53.0)	7482 (63.6)	6391 (63.7)	1970 (68.5)

Region of residence, n (%)				
Seoul Capital Area	97,733 (46.0)	5410 (46.0)	4527 (45.1)	1433 (49.8)
Daegu/Gyeongbuk area	39,063 (18.4)	2150 (18.3)	1925 (19.2)	431(15.0)
Other area	75,882 (35.7)	4206 (35.8)	3586 (35.7)	1011 (35.2)
Resident of a skilled nursing facility, n (%)	13,015 (6.1)	1045 (8.9)	898 (9.0)	190 (6.6)
History of diabetes mellitus, n (%)	44,845 (21.1)	4890 (41.6)	4257 (42.4)	1072 (37.3)
History of cardiovascular disease, n (%)	40,526 (19.1)	4640 (39.4)	3956 (39.4)	1126 (39.2)
History of cerebrovascular disease, n (%)	25,991 (12.2)	2784 (23.7)	2420 (24.1)	586 (20.4)
History of COPD, n (%)	25,081 (11.8)	2841 (24.2)	2435 (24.3)	667 (23.2)
History of hypertension, n (%)	68,817 (32.4)	6706 (57.0)	5801 (57.8)	1502 (52.2)
History of chronic kidney disease, n (%)	18,561 (8.7)	2306 (19.6)	1900 (18.9)	651 (22.6)
Current use of aspirin, n (%)	17,551 (8.3)	1722 (14.6)	1490 (14.8)	398 (13.8)
Current use of metformin, n (%)	19,687 (9.3)	1734 (14.7)	1538 (15.3)	316 (11.0)

Current use of statin, n (%)	42,695 (20.1)	4294 (36.5)	3759 (37.5)	891 (31.0)
Current use of systemic steroid, n (%)	26,048 (12.2)	2808 (23.9)	2992 (29.8)	1404 (48.8)
Current use of DMARDs, n (%)	7713			
Methotrexate–leflunomide–azathioprine, n (%)	12,503 (5.9)	5243 (44.6)	4592 (45.7)	1921 (66.8)
Sulfasalazine, n (%)	716 (0.3)	652 (5.5)	636 (6.3)	153 (5.3)
Antimalarials, n (%)	11749 (5.5)	2620 (22.2)	2257 (22.5)	1196 (41.6)
Anti-TNF-alpha agent, n (%)	1448 (0.7)	752 (6.4)	685 (6.8)	203 (7.1)
Other biologics, n (%)	2160 (1.0)	529 (4.5)	490 (4.9)	121 (4.2)

AIRD, autoimmune inflammatory rheumatic disease; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; DMARD, disease-modifying antirheumatic drug; IA, inflammatory arthritis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; TNF; tumor necrosis factor.

Table S3. 3:1 propensity score-matched covariates and aOR (95% CI) of positive SARS-CoV-2 test, severe COVID-19 outcomes, or COVID-19-related death in patients with AIRD, IA, or CTD.

Characteristics	Matched cohort D			Matched cohort E			Matched cohort F		
	None	AIRD	SMD	None	IA	SMD	None	CTD	SMD
Total, n (%)	34,343	11,698		29,578	9991		8352	2832	
Age, years, n (%)			0.022			0.014			0.023
20-39	4352 (12.7)	1559 (13.3)		3541 (12.0)	1237 (12.4)		1552 (18.6)	547 (19.3)	
40-59	9475 (27.6)	3276 (28.0)		8062 (27.3)	2750 (27.5)		2744 (32.9)	942 (33.3)	
≥ 60	20,516 (59.7)	6863 (58.7)		17,975 (60.8)	6004 (60.1)		4056 (48.6)	1343 (47.4)	
Sex, n (%)			0.019			0.013			0.007
Male	12,894 (37.5)	4284 (36.6)		10,976 (37.1)	3646 (36.5)		2691 (32.2)	903 (31.9)	
Female	21,449 (62.5)	7414 (63.4)		18,602 (62.9)	6345 (63.5)		5661 (67.8)	1929 (68.1)	

Region of residence, n (%)			0.004			0.002			0.018
Seoul Capital Area	15,808 (46.0)	5377 (46.0)		13,389(45.3)	4505 (45.1)		4242 (50.8)	1417 (50.0)	
Daegu/Gyeongbuk area	6348 (18.5)	2132 (18.2)		5593 (18.9)	1910 (19.1)		1241 (14.9)	417 (14.7)	
Other area	12,187 (35.5)	4189 (35.8)		10,596 (35.8)	3576 (35.8)		2869 (34.4)	998 (35.2)	
Resident of a skilled nursing facility, n (%)	2992(8.7)	1044 (8.9)	0.008	2623 (8.9)	897 (9.0)	0.004	546 (6.5)	190 (6.7)	0.007
History of diabetes mellitus, n (%)	14,130 (41.1)	4868 (41.6)	0.010	12,395 (41.9)	4230 (42.3)	0.010	3097 (37.1)	1058 (37.4)	0.006
History of cardiovascular disease, n (%)	13,323 (38.8)	4599 (39.3)	0.012	11,460 (38.8)	3929 (39.3)	0.013	3199 (38.3)	1096 (38.7)	0.009
History of cerebrovascular disease, n (%)	8089 (23.6)	2771 (23.7)	0.004	6994 (23.7)	2408 (24.1)	0.012	1634 (19.6)	566 (20.0)	0.012
History of COPD, n (%)	7838 (22.8)	2796 (23.9)	0.029	6793 (23.0)	2398 (24.0)	0.028	1871 (22.4)	651 (23.0)	0.016
History of hypertension, n (%)	19,649 (57.2)	6676 (57.1)	0.003	17,188 (58.1)	5782 (57.9)	0.005	4314 (51.7)	1469 (51.9)	0.005
History of chronic kidney disease, n (%)	6377 (18.6)	2266 (19.4)	0.024	5255 (17.8)	1876 (18.8)	0.030	1769 (21.2)	624 (22.0)	0.024
Current use of aspirin, n (%)	4892 (14.2)	1707 (14.6)	0.011	4288 (14.5)	1480 (14.8)	0.010	1048 (12.6)	380 (13.4)	0.028

Current use of metformin, n (%)	5049 (14.7)	1731 (14.8)	0.003	4481 (15.2)	1538 (15.4)	0.008	920 (11.0)	315 (11.1)	0.004
Current use of statin, n (%)	12,459 (36.3)	4264 (36.5)	0.004	10,967(37.1)	3733 (37.4)	0.006	2577 (30.9)	868 (30.7)	0.005
COVID-19, n (%)	1345 (3.9)	527 (4.5)		1156 (3.9)	457 (4.6)		298 (3.6)	127 (4.5)	
Minimally aOR* (95% CI)	1.0 (ref)	1.16 (1.02-1.31)		1.0 (ref)	1.18 (1.06-1.32)		1.0 (ref)	1.26 (1.03-1.57)	
Fully aOR [§] (95% CI)	1.0 (ref)	1.21 (1.06-1.39)		1.0 (ref)	1.22 (1.09-1.38)		1.0 (ref)	1.28 (1.03-1.61)	
Severe COVID-19 [‡] , n (%)	391 (1.1)	165 (1.4)		349 (1.2)	144 (1.4)		85 (1.0)	44 (1.6)	
Minimally aOR* (95% CI)	1.0 (ref)	1.21 (1.02-1.45)		1.0 (ref)	1.22 (1.01-1.49)		1.0 (ref)	1.54 (1.07-2.21)	
Fully aOR [§] (95% CI)	1.0 (ref)	1.24 (1.04-1.49)		1.0 (ref)	1.23 (1.02-1.50)		1.0 (ref)	1.55 (1.08-2.22)	
COVID-19-related death, n (%)	55 (0.2)	30 (0.3)		45 (0.2)	27 (0.3)		13 (0.2)	9 (0.3)	
Minimally aOR* (95% CI)	1.0 (ref)	1.62 (1.03-2.51)		1.0 (ref)	1.79 (1.10-2.88)		1.0 (ref)	2.05 (0.89-4.80)	
Fully aOR [§] (95% CI)	1.0 (ref)	1.62 (1.03-2.53)		1.0 (ref)	1.80 (1.10-2.89)		1.0 (ref)	2.06 (0.89-4.83)	

An SMD <0.1 indicates no major imbalance. All SMD values were <0.03 in the propensity score-matched cohorts.

Data in bold indicate significant differences ($P < 0.05$).

aOR, adjusted odds ratio; AIRD, autoimmune inflammatory rheumatic disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; DMARD, disease-modifying antirheumatic drug; IA, inflammatory arthritis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; SMD, standardized mean difference.

*Minimally adjusted: adjustment for age (20-39, 40-59, and ≥ 60 years) and sex.

§Fully adjusted: adjustment for age; sex; region of residence (Seoul Capital Area, Daegu/Gyeongbuk area, and other area); resident of a skilled nursing facility; history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, and chronic kidney disease; and current use of aspirin, metformin, and statin

‡ Requirement of oxygen therapy, admission to the intensive care unit, invasive ventilation, or death.

Table S4. Propensity-score-matched subgroup analysis of aOR (95% CI) of positive SARS-CoV-2 test, severe COVID-19 outcomes, or COVID-19-related death in patients with AIRD stratified by DMARD and systemic steroid (matched cohort D).

Events	Factors	N (%)	Adjusted OR (95% CI)
COVID-19	Treated without DMARD	210/4444 (4.7)	1.0 (ref) [*]
	Treated with DMARD	317/7254 (4.4)	0.91 (0.72-1.17)
COVID-19	Treated without systemic steroid	382/8901 (4.3)	1.0 (ref) [‡]
	Treated with systemic steroid (any dose)	145/2797 (5.2)	1.21 (0.93-1.57)
	Treated with systemic steroid (≥ 10 mg/day)	58/920 (6.3)	1.50 (1.05-2.15)
Severe COVID-19 [§]	Treated without DMARD	60/4444 (1.4)	1.0 (ref) [*]
	Treated with DMARD	105/7254 (1.5)	1.10 (0.77-1.57) ^{*\}
Severe COVID-19 [§]	Treated without systemic steroid	116/8901 (1.3)	1.0 (ref) [‡]
	Treated with systemic steroid (any dose)	49/2797 (1.8)	1.34 (0.90-1.91)
	Treated with systemic steroid (≥ 10 mg/day)	23/920 (2.5)	1.95 (1.13-3.35)
COVID-19-related death	Treated without DMARD	10/4444 (2.3)	1.0 (ref) [*]

COVID-19-related death	Treated with DMARD	20/7254 (2.8)	1.24 (0.59-2.65)
	Treated without systemic steroid	18/8901 (0.2)	1.0 (ref) [‡]
	Treated with systemic steroid (any dose)	12/2797 (0.4)	2.14 (0.99-4.50)
	Treated with systemic steroid (≥ 10 mg/day)	6/920 (0.7)	3.26 (1.20-8.28)

Data in bold indicate significant differences ($P < 0.05$).

aOR, adjusted odds ratio; AIRD, autoimmune inflammatory rheumatic disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DMARD, disease-modifying antirheumatic drug; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

*Risk factors were adjusted for age (20-39, 40-59, and ≥ 60 years); sex; region of residence (Seoul Capital Area, Daegu/Gyeongbuk area, and other area); resident of a skilled nursing facility; history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, and chronic kidney disease; and current use of aspirin, metformin, statin, and systemic steroid.

[‡] Risk factors were adjusted for age (20-39, 40-59, and ≥ 60 years); sex; region of residence (Seoul Capital Area, Daegu/Gyeongbuk area, and other area); resident of a skilled nursing facility; history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, and chronic kidney disease; and current use of aspirin, metformin, and statin and DMARD.

§ Requirement of oxygen therapy, admission to the intensive care unit, invasive ventilation, or death.

Table S5. 3:1 propensity score-matched covariates selected by DAGs and aOR (95% CI) of positive SARS-CoV-2 test, severe COVID-19 outcomes, or COVID-19-related death in patients with AIRD, IA, or CTD in the Korean nationwide cohort linked with the general health examination records.

Characteristics	Matched cohort G			Matched cohort H			Matched cohort I		
	None	AIRD	SMD	None	IA	SMD	None	CTD	SMD
Total, n (%)	24,782	8286		21,342	7132		5854	1952	
Matched covariates selected by DAGs									
Age, years, n (%)			0.001			<0.001			0.003
20-39	2341 (9.45)	782 (9.4)		1865 (8.8)	622 (8.7)		771(13.2)	255 (13.1)	
40-59	7775 (31.4)	2592 (31.3)		6607 (31.0)	2206 (30.9)		2155 (36.8)	719 (36.8)	
≥ 60	14,666 (59.2)	4912 (59.3)		12,870 (60.3)	4304 (60.4)		2928 (50.0)	978 (50.1)	

Sex, n (%)			0.002			0.001		<0.001
Male	9130 (36.8)	3044 (36.7)		7848 (36.8)	2618 (36.7)		1875 (32.0)	625 (32.0)
Female	15,652 (63.2)	5242 (63.3)		13,494 (63.2)	4514 (63.3)		3979 (68.0)	1327 (68.0)
Region of residence, n (%)			0.001			<0.001		0.002
Seoul Capital Area	10,888 (43.9)	3640 (43.9)		9204 (43.1)	3071 (43.1)		2790 (47.7)	927 (47.5)
Daegu/Gyeongbuk area	4811 (19.4)	1617 (19.5)		4347 (20.4)	1462 (20.5)		918 (15.7)	310 (15.9)
Other area	9083 (36.7)	3029 (36.6)		7791 (36.5)	2599 (36.4)		2146 (36.7)	715 (36.6)
Resident of a skilled nursing facility, n (%)	1775 (7.2)	601 (7.3)	0.003	1498 (7.0)	515(7.2)	0.008	345 (5.9)	116 (5.9)
Household income, n (%)			0.002					<0.001
Low (0–39 percentile)	8854 (35.7)	2973 (35.9)		7644 (35.8)	2569 (36.0)		2054 (35.1)	685 (35.1)
Middle (40–79 percentile)	8547 (34.5)	2848 (34.4)		7383 (34.6)	2460 (34.5)		2017 (34.5)	673 (34.5)
High (80–100 percentile)	7381 (29.8)	2465 (29.8)		6315 (29.6)	2103 (29.5)		1783 (30.5)	594 (30.4)

Smoking, n (%)			0.002		0.003		0.003
Never smoker	17,840 (72.0)	5953 (71.8)		15,378 (72.1)	5129 (71.9)	4408 (75.3)	1468 (75.2)
Ex-smoker	3964 (16.0)	1336 (16.1)		3361 (15.8)	1128 (15.8)	895 (15.3)	298 (15.3)
Current smoker	2978 (12.0)	997 (12.0)		2603 (12.2)	875 (12.3)	551 (9.4)	186 (9.5)
Alcoholic drinks, days per week, n (%)			0.005		0.004		0.001
<1	18,989 (76.6)	6341 (76.5)		16,463 (77.1)	5502 (77.2)	4457 (76.1)	1485 (76.1)
1–2	4487 (18.1)	1494 (18.0)		3738 (17.5)	1239 (17.4)	1147 (19.6)	383 (19.6)
3–4	890 (3.6)	304 (3.7)		761 (3.6)	257 (3.6)	183 (3.1)	62 (3.2)
≥5	416 (1.7)	147 (1.8)		380 (1.8)	134 (1.9)	67 (1.1)	22 (1.1)
Body mass index, kg/m ² , n (%)			0.006		0.009		0.006
<25	15,886 (64.1)	5297 (63.9)		13,553 (63.5)	4507 (63.2)	4131 (70.6)	1373 (70.3)

25–30	7444 (30.0)	2490 (30.1)	6527 (30.6)	2186 (30.7)	1466 (25.0)	491 (25.2)
≥30	1452 (5.9)	499 (6.0)	1262 (5.9)	439 (6.2)	257 (4.4)	88 (4.5)
Unmatched covariates						
History of diabetes mellitus, n (%)	7401 (29.9)	3434 (41.4)	6528 (30.6)	3001 (42.1)	1526 (26.1)	751 (38.5)
History of cardiovascular disease, n (%)	6570 (26.5)	3130 (37.8)	5725 (26.8)	2677 (37.5)	1392(23.8)	743 (38.1)
History of cerebrovascular disease, n (%)	4318 (17.4)	1878 (22.7)	3830 (18.0)	1636 (22.9)	924 (15.8)	392 (20.1)
History of COPD, n (%)	3974 (16.0)	2000 (24.1)	3523 (16.5)	1710 (24.0)	839 (14.3)	481 (24.6)
History of hypertension, n (%)	11,671 (47.1)	4649 (56.1)	10,117 (47.4)	4041 (56.7)	2390 (40.8)	1014 (52.0)
History of chronic kidney disease, n (%)	2736 (11.0)	1472 (17.8)	2343 (11.0)	1236 (17.3)	590 (10.1)	399 (20.4)
Current use of aspirin, n (%)	3185 (12.9)	1209 (14.6)	2738 (12.8)	1044 (14.6)	652 (11.1)	282 (14.5)
Current use of metformin, n (%)	3506 (14.2)	1256 (15.2)	3100 (14.5)	1114 (15.6)	692 (11.8)	234 (12.0)
Current use of statin, n (%)	8044 (32.5)	3223 (38.9)	7057 (33.1)	2833 (39.7)	1593 (27.2)	658 (33.7)

Sufficient aerobic activity, n (%)	11,934 (48.2)	4096 (49.4)	10,238 (48.0)	3521 (49.4)	2829 (48.3)	983 (50.4)
COVID-19, n (%)	1024 (3.7)	365 (4.4)	816 (3.8)	327 (4.6)	191 (3.3)	84 (4.3)
Fully aOR [§] (95% CI)	1.0 (ref)	1.21 (1.07-1.38)	1.0 (ref)	1.21 (1.06-1.39)	1.0 (ref)	1.35 (1.04-1.76)
Severe COVID-19 [‡] , n (%)	315 (1.1)	127 (1.5)	240 (1.1)	103 (1.4)	51 (0.9)	30 (1.5)
Fully aOR [§] (95% CI)	1.0 (ref)	1.38 (1.12-1.68)	1.0 (ref)	1.30 (1.03-1.65)	1.0 (ref)	1.78 (1.14-2.82)
COVID-19-related death, n (%)	46 (0.2)	24 (0.3)	32 (0.2)	20 (0.3)	11 (0.2)	7 (0.4)
Fully aOR [§] (95% CI)	1.0 (ref)	1.77 (1.06-2.90)	1.0 (ref)	1.89 (1.06-3.34)	1.0 (ref)	1.93 (0.72-4.96)

An SMD <0.1 indicates no major imbalance. All SMD values were <0.01 in the propensity score-matched cohort.

Data in bold indicate significant differences ($P < 0.05$).

aOR, adjusted odds ratio; AIRD, autoimmune inflammatory rheumatic disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; DAGs, directed acyclic graphs; DMARD, disease-modifying antirheumatic drug; IA, inflammatory arthritis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; SMD, standardized mean difference.

*Minimally adjusted: adjustment for age (20-39, 40-59, and ≥ 60 years) and sex.

§Fully adjusted: adjustment for age; sex; region of residence (Seoul Capital Area, Daegu/Gyeongbuk area, and other area); resident of a skilled nursing facility; history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, and chronic kidney disease; household income (low, middle, and high); smoking (never, ex-, and current); alcoholic drinks (<1 , 1-2, 3-4, ≥ 5 days per week); body mass index (< 25 , 25-30, and ≥ 30 kg/m²); sufficient aerobic activity; and current use of aspirin, metformin, and statin

‡ Requirement of oxygen therapy, admission to the intensive care unit, invasive ventilation, or death.

Table S6. 3:1 propensity score-matched covariates selected by DAGs and aOR (95% CI) of positive SARS-CoV-2 test, severe COVID-19 outcomes, or COVID-19-related death in patients with AIRD, IA, or CTD in the Korean nationwide cohort.

Characteristics	Matched cohort J			Matched cohort K			Matched cohort L		
	None	AIRD	SMD	None	IA	SMD	None	CTD	SMD
Total, n (%)	35,298	11,766		30,114	10,038		8625	2875	
Matched covariates selected by DAGs									
Age, years, n (%)			<0.001			<0.001			<0.001
20-39	4770 (13.5)	1590(13.5)		3741 (12.4)	1247 (12.4)		1743 (20.2)	581 (20.2)	
40-59	9909 (28.1)	3303(28.1)		8316 (27.6)	2772 (27.6)		2850 (33.0)	950 (33.0)	
≥ 60	20,619 (58.4)	6873(58.41)		18,057 (60.0)	6019(60.0)		4032 (46.8)	1344 (46.8)	
Sex, n (%)			<0.001			<0.001			<0.001
Male	12,852 (36.4)	4284 (36.4)		10,941 (36.3)	3647 (36.3)		2715 (31.5)	905 (31.5)	

Female	22,446 (63.6)	7482 (63.6)		19,173 (63.7)	6391 (63.7)		5910 (68.5)	1970 (68.5)	
Region of residence, n (%)			<0.001			<0.001			<0.001
Seoul Capital Area	16,230 (46.0)	5410 (46.0)		13,581 (45.1)	4527 (45.1)		4299 (49.8)	1433 (49.8)	
Daegu/Gyeongbuk area	6450 (18.3)	2150 (18.3)		5775 (19.2)	1925 (19.2)		1293 (15.0)	431 (15.0)	
Other area	12,618 (35.8)	4206 (35.8)		10,758 (35.7)	3586 (35.7)		3033 (35.2)	1011 (35.2)	
Resident of a skilled nursing facility, n (%)	3135 (8.9)	1045 (8.9)	<0.001	2694 (9.0)	898 (9.0)	<0.001	570 (6.6)	190 (6.6)	<0.001
Unmatched covariates									
History of diabetes mellitus, n (%)	10,407 (29.5)	4890 (41.6)		9082 (30.2)	4257 (42.4)		2433 (28.2)	1072 (37.3)	
History of cardiovascular disease, n (%)	9678 (27.4)	4640 (39.4)		8494 (28.2)	3956 (39.4)		2186 (25.3)	1126 (39.2)	
History of cerebrovascular disease, n (%)	6546 (18.5)	2784 (23.7)		5785 (19.2)	2420 (24.1)		1508 (17.5)	586 (20.4)	
History of COPD, n (%)	5527 (15.7)	2841 (24.2)		4877 (16.2)	2435 (24.3)		1394 (16.2)	667 (23.2)	
History of hypertension, n (%)	16,575 (47.0)	6706 (57.0)		14,494 (48.1)	5801 (57.8)		3595 (41.7)	1502 (52.2)	

History of chronic kidney disease, n (%)	4186 (11.9)	2306 (19.6)	3635 (12.1)	1900 (18.9)	1003 (11.6)	651 (22.6)
Current use of aspirin, n (%)	4432 (12.6)	1722 (14.6)	3917 (13.0)	1490 (14.8)	957 (11.1)	398 (13.8)
Current use of metformin, n (%)	4612 (13.1)	1734 (14.7)	4016 (13.3)	1538 (15.3)	1058 (12.3)	316(11.0)
Current use of statin, n (%)	10,380 (29.4)	4294 (36.5)	9092 (30.2)	3759 (37.5)	2266 (26.3)	891 (31.0)
COVID-19, n (%)	1288 (3.7)	530 (4.5)	1136 (3.8)	457 (4.6)	290 (3.4)	127 (4.4)
Fully aOR* (95% CI)	1.0 (ref)	1.20 (1.02-1.38)	1.0 (ref)	1.19 (1.02-1.42)	1.0 (ref)	1.31 (1.05-1.62)
Severe COVID-19 [§] , n (%)	388 (1.1)	168 (1.4)	327 (1.1)	144 (1.4)	79 (0.9)	40 (1.4)
Fully aOR* (95% CI)	1.0 (ref)	1.26 (1.03-1.54)	1.0 (ref)	1.35 (1.14-1.62)	1.0 (ref)	1.56 (1.08-2.28)
COVID-19-related death, n (%)	51 (0.1)	31 (0.3)	42 (0.1)	27 (0.3)	12 (0.1)	9 (0.3)
Fully aOR* (95% CI)	1.0 (ref)	1.73 (1.05-2.78)	1.0 (ref)	1.90 (1.20-2.99)	1.0 (ref)	2.23 (0.91-5.35)

An SMD <0.1 indicates no major imbalance. All SMD values were <0.001 in the propensity score-matched cohort.

Data in bold indicate significant differences ($P < 0.05$).

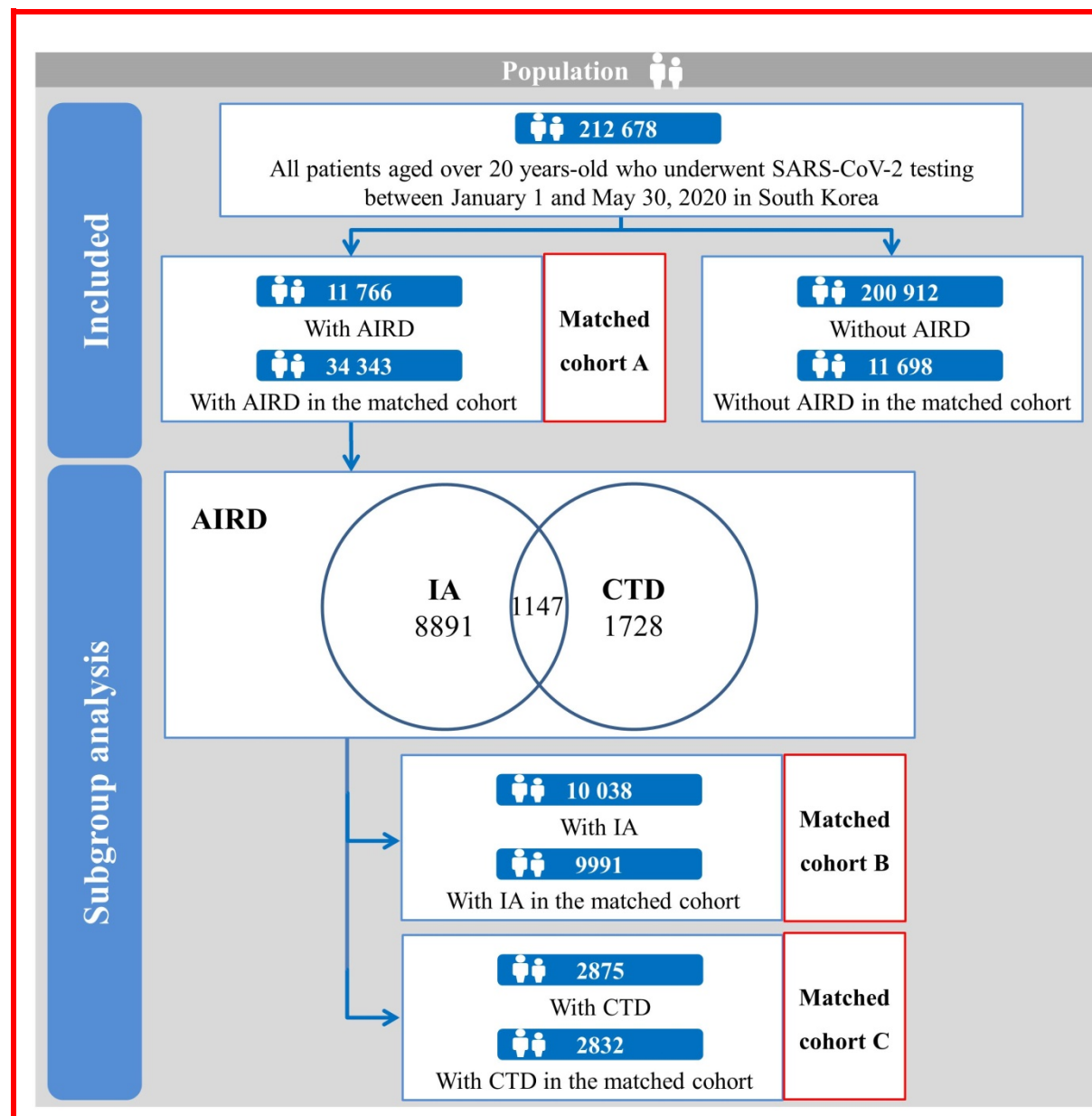
aOR, adjusted odds ratio; AIRD, autoimmune inflammatory rheumatic disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; DAGs, directed acyclic graphs; DMARD, disease-modifying antirheumatic drug; IA, inflammatory arthritis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; SMD, standardized mean difference.

*Fully adjusted: adjustment for age (20-39, 40-59, and ≥ 60 years); sex; region of residence (Seoul Capital Area, Daegu/Gyeongbuk area, and other area); resident of a skilled nursing facility; history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, and chronic kidney disease; and current use of aspirin, metformin, and statin

§ Requirement of oxygen therapy, admission to the intensive care unit, invasive ventilation, or death.

Figure S1. Disposition of patients in the Korean nationwide cohort without linking the general health examination records

AIRD, autoimmune inflammatory rheumatic disease; CTD, connective tissue disease; IA, inflammatory arthritis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.



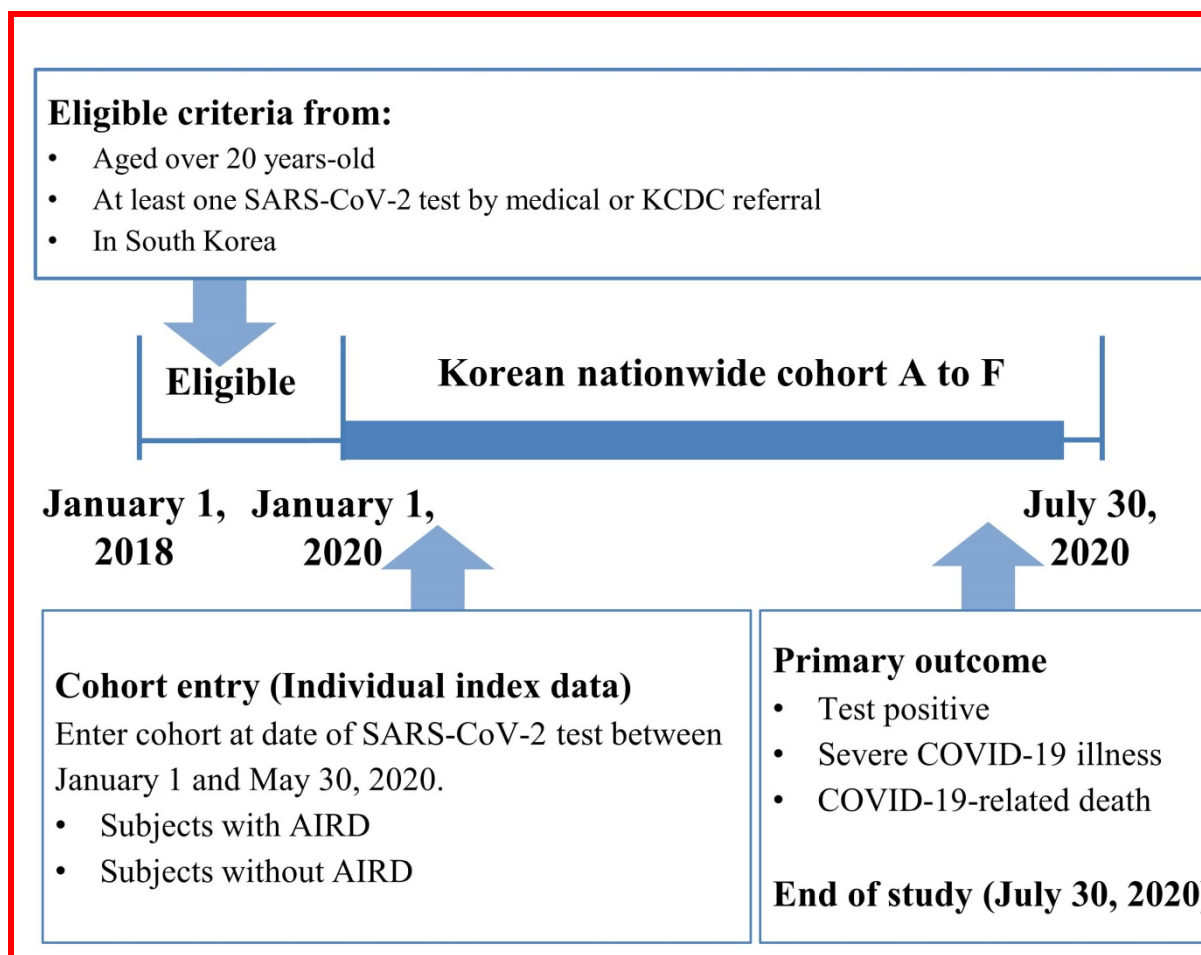
8

9 **Figure S2.** Flowchart showing the study enrollment in the Korean nationwide cohort without
10 linking the general health examination records

11 AIRD, autoimmune inflammatory rheumatic disease; CTD, connective tissue disease; IA,
12 inflammatory arthritis; KCDC, Korea Centers for Disease Control; SARS-CoV-2, severe acute
13 respiratory syndrome coronavirus 2.

14

15



16

17

18

19

20 **Figure S3.** The density and distribution of propensity scores before and after matching in matched
21 cohort A

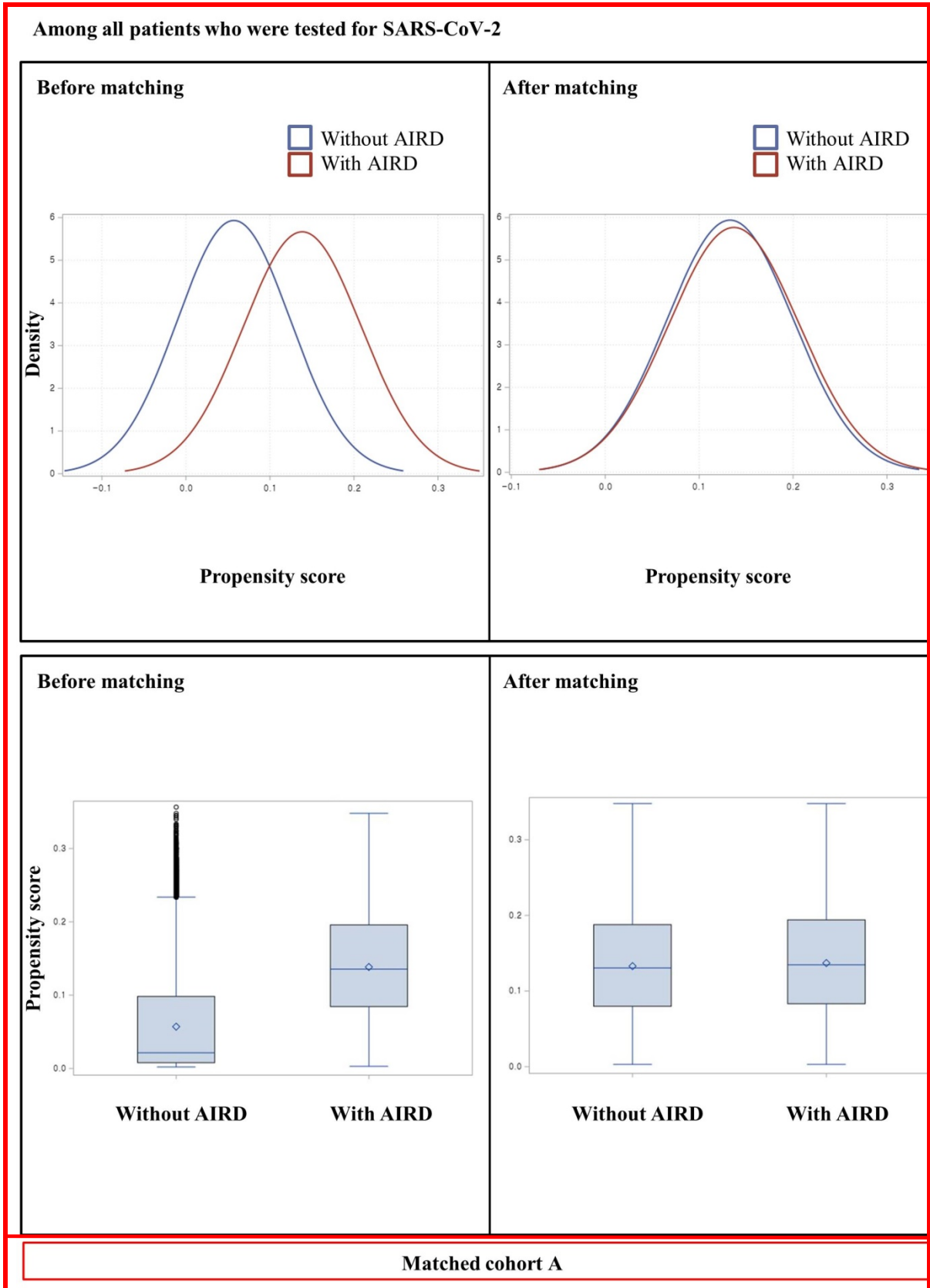


Figure S4. The density and distribution of propensity scores before and after matching in matched cohort B

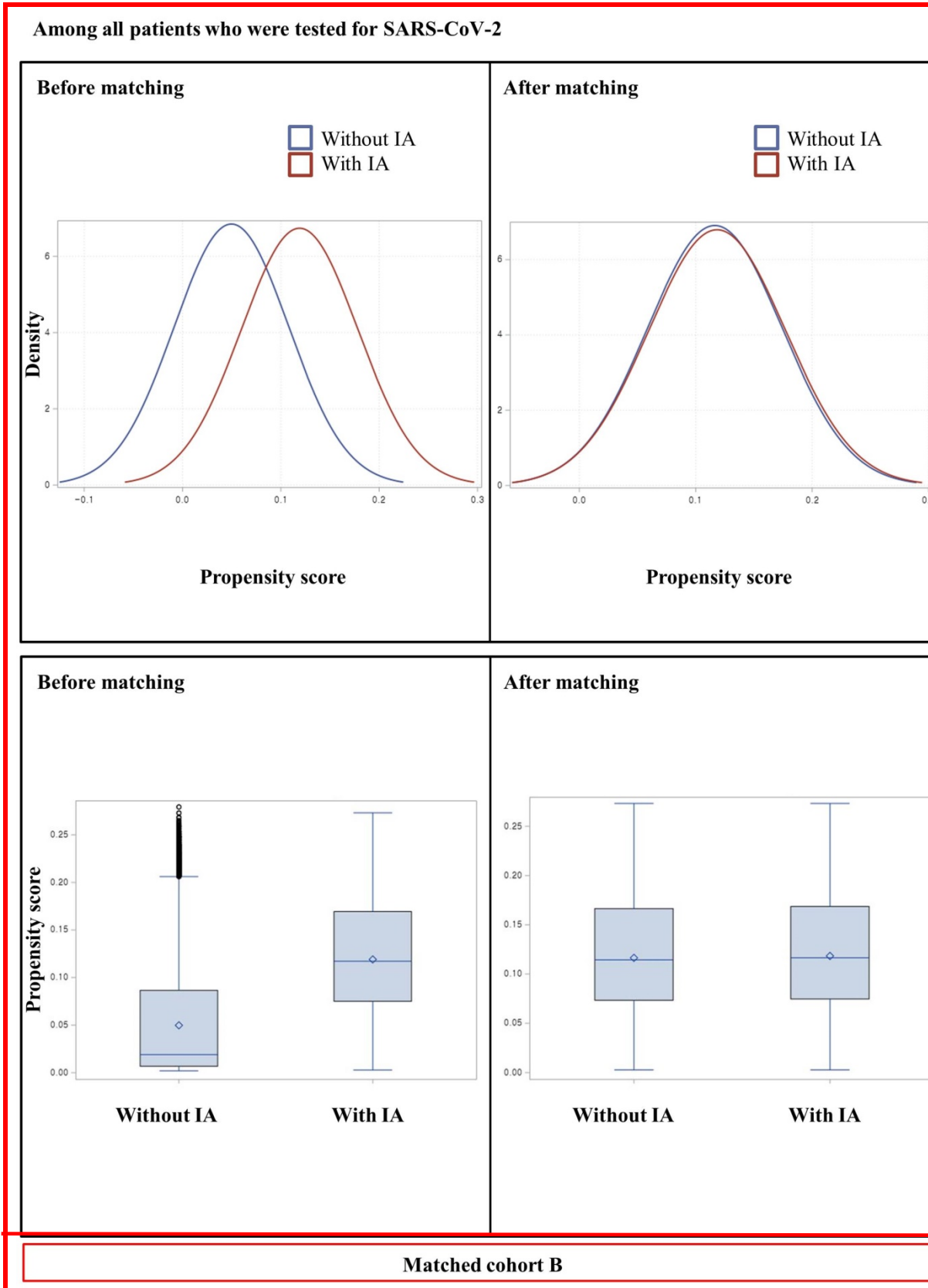
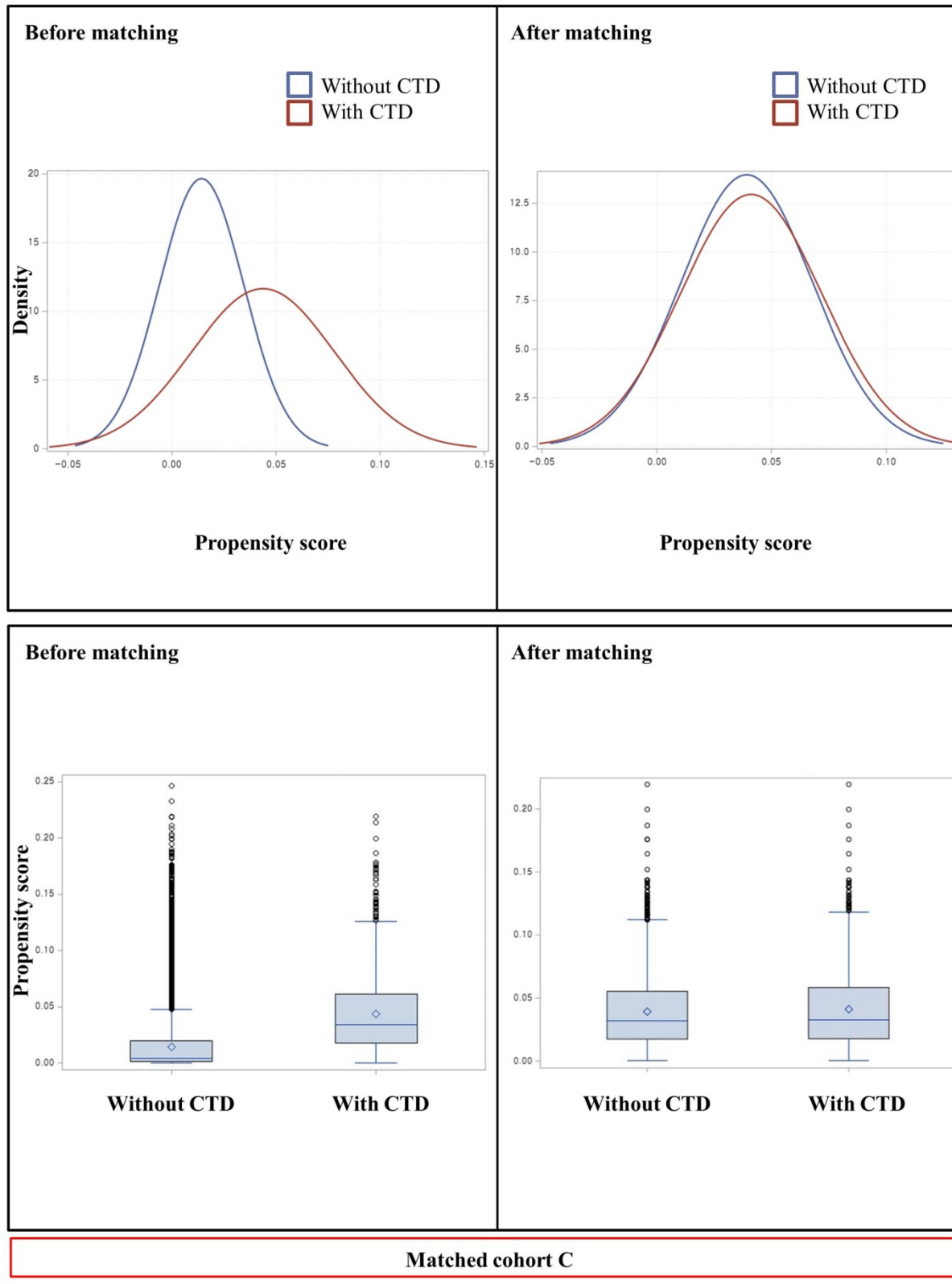
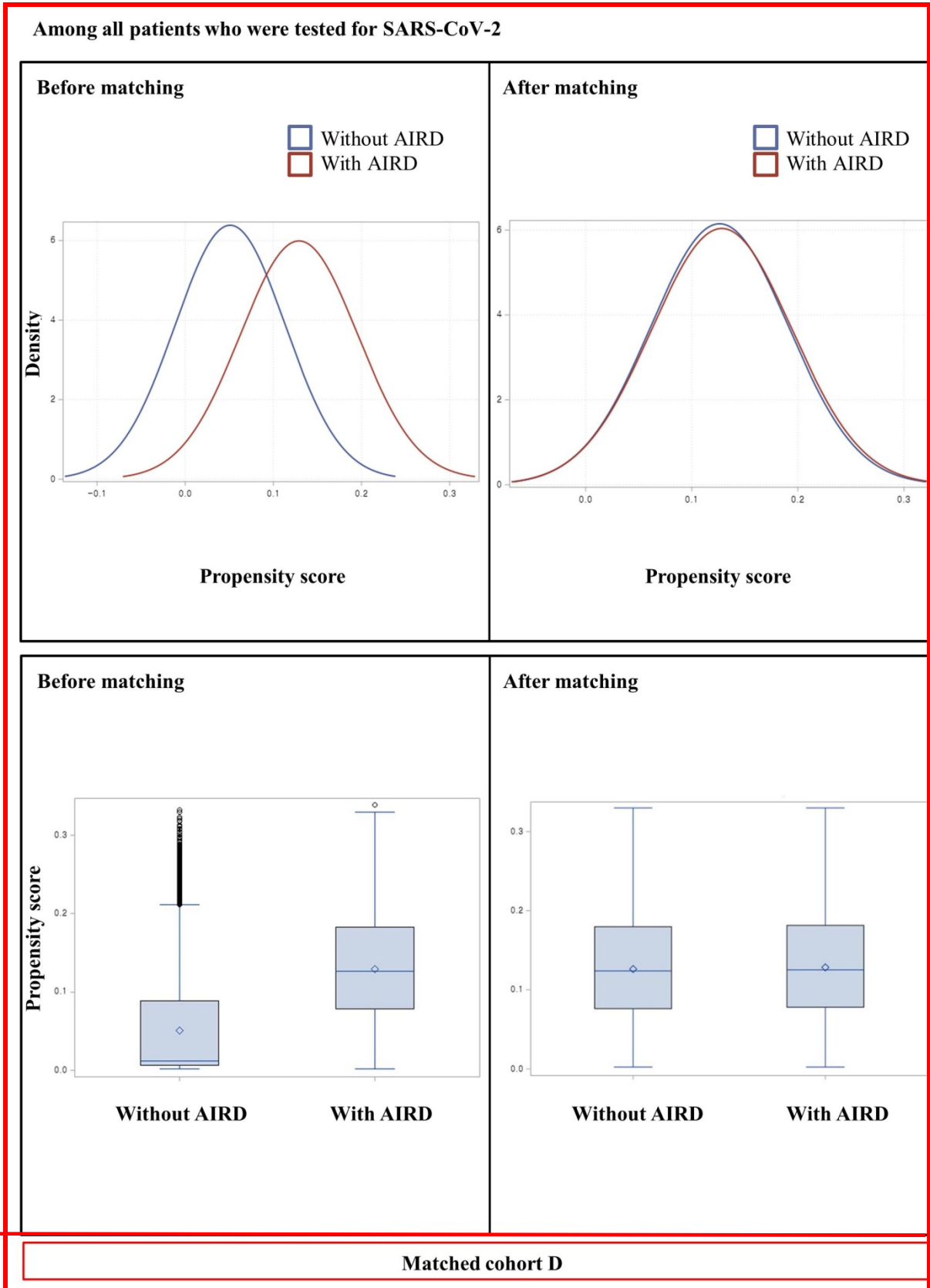


Figure S5. The density and distribution of propensity scores before and after matching in matched cohort C

Among all patients who were tested for SARS-CoV-2



27 **Figure S6.** The density and distribution of propensity scores before and after matching in matched
28 cohort D



29 **Figure S7.** The density and distribution of propensity scores before and after matching in matched
 30 cohort E

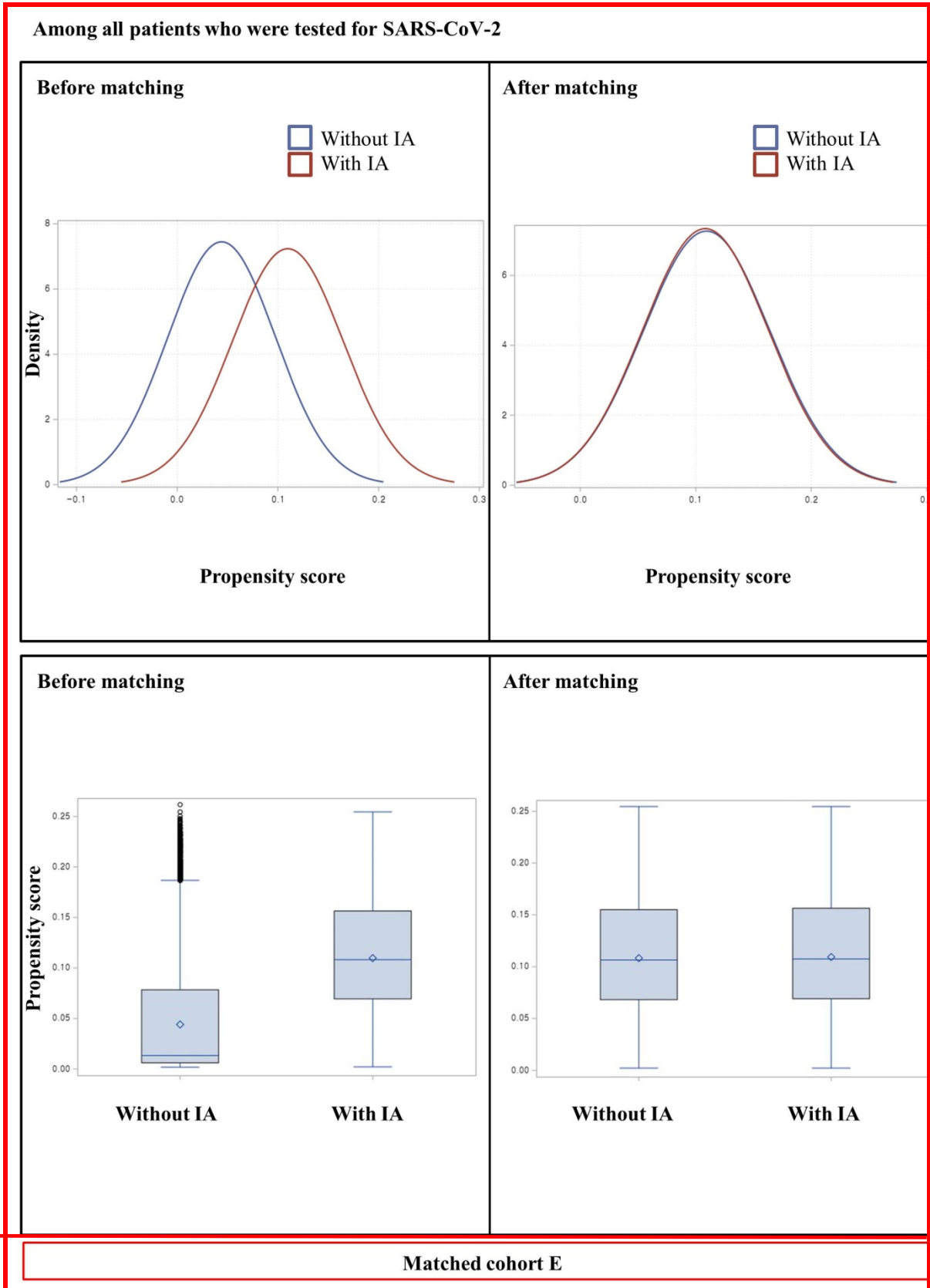


Figure S8. The density and distribution of propensity scores before and after matching in matched cohort F

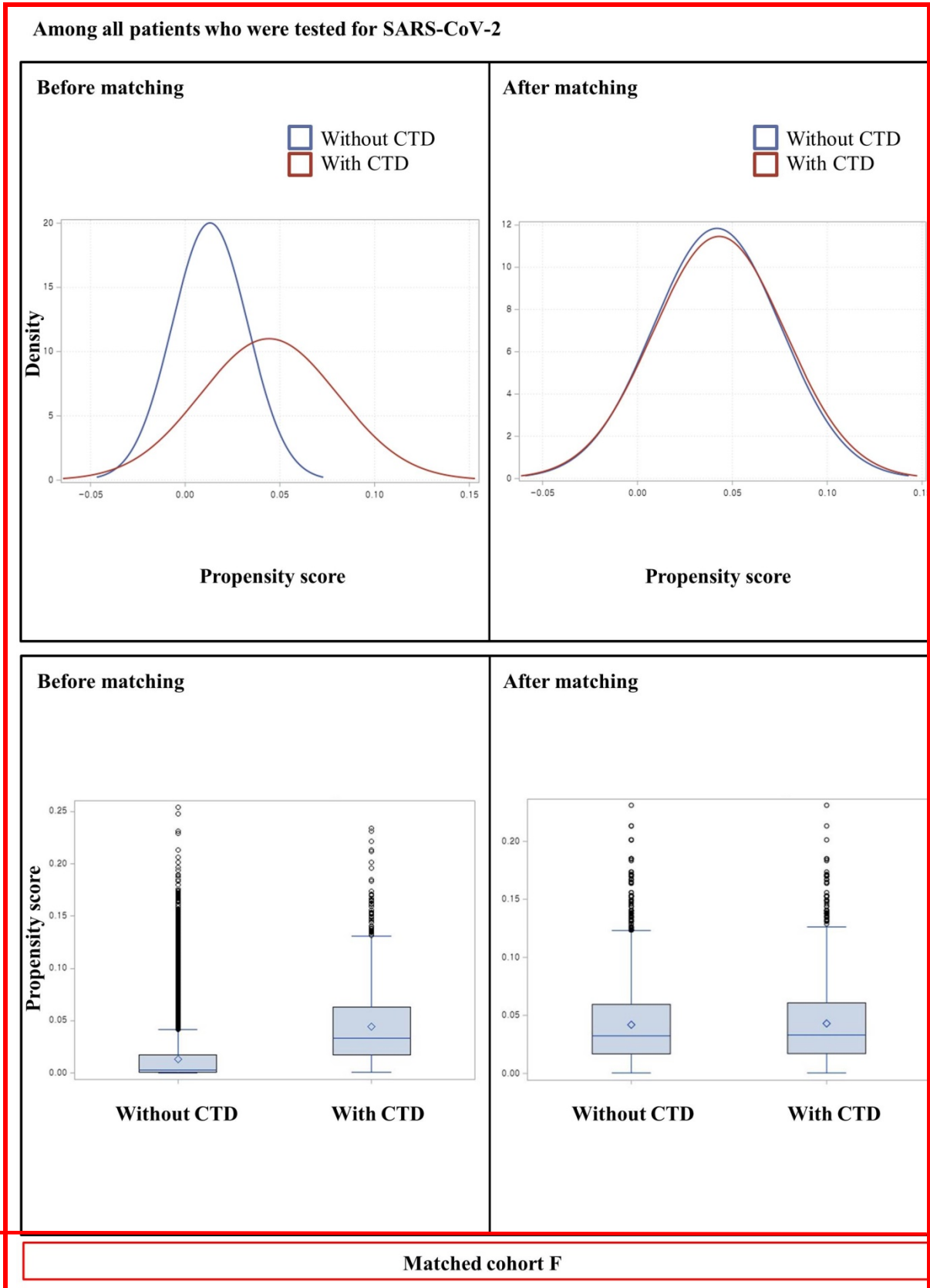


Figure S9. The density and distribution of propensity scores before and after matching in matched cohort G

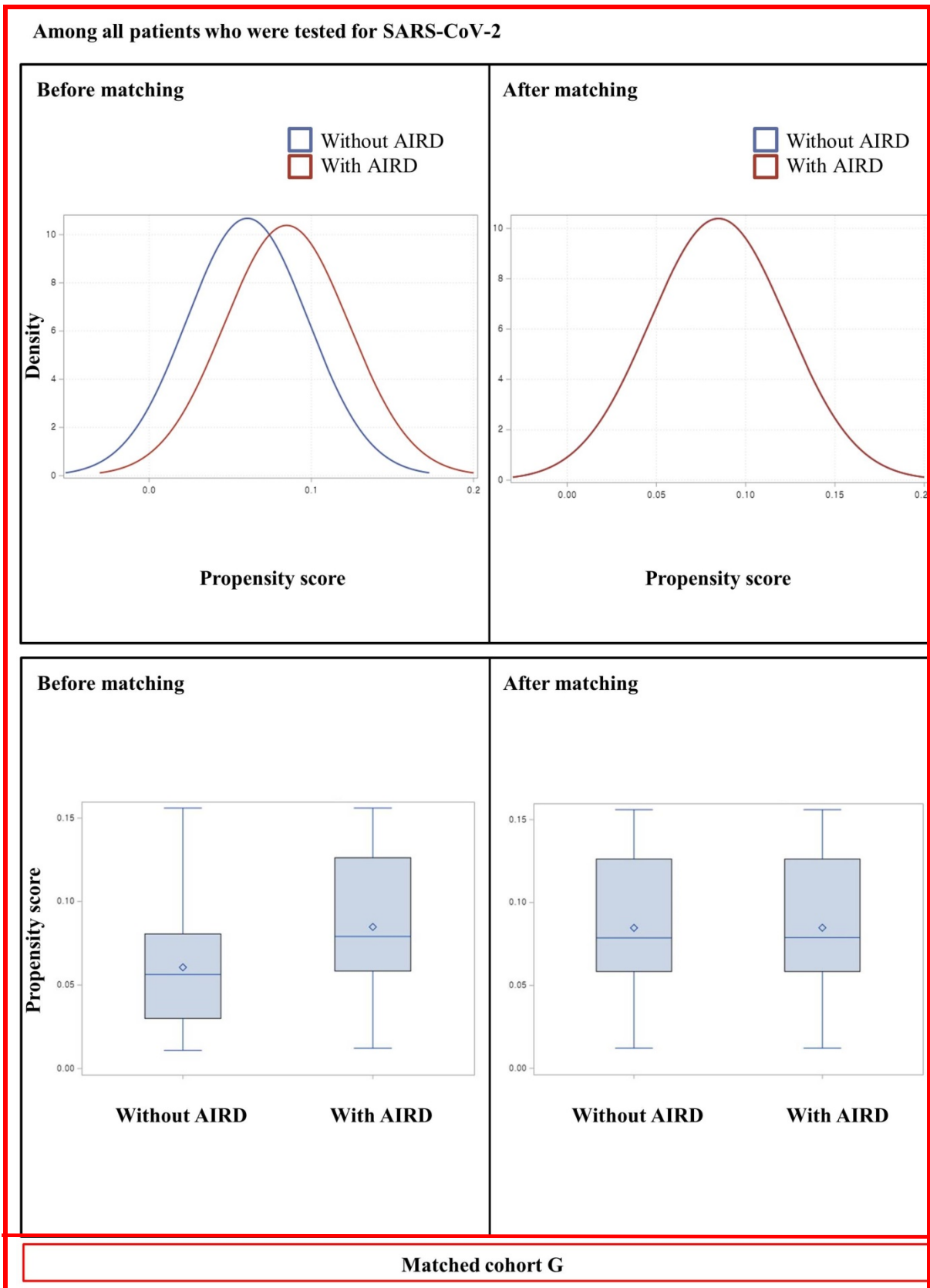
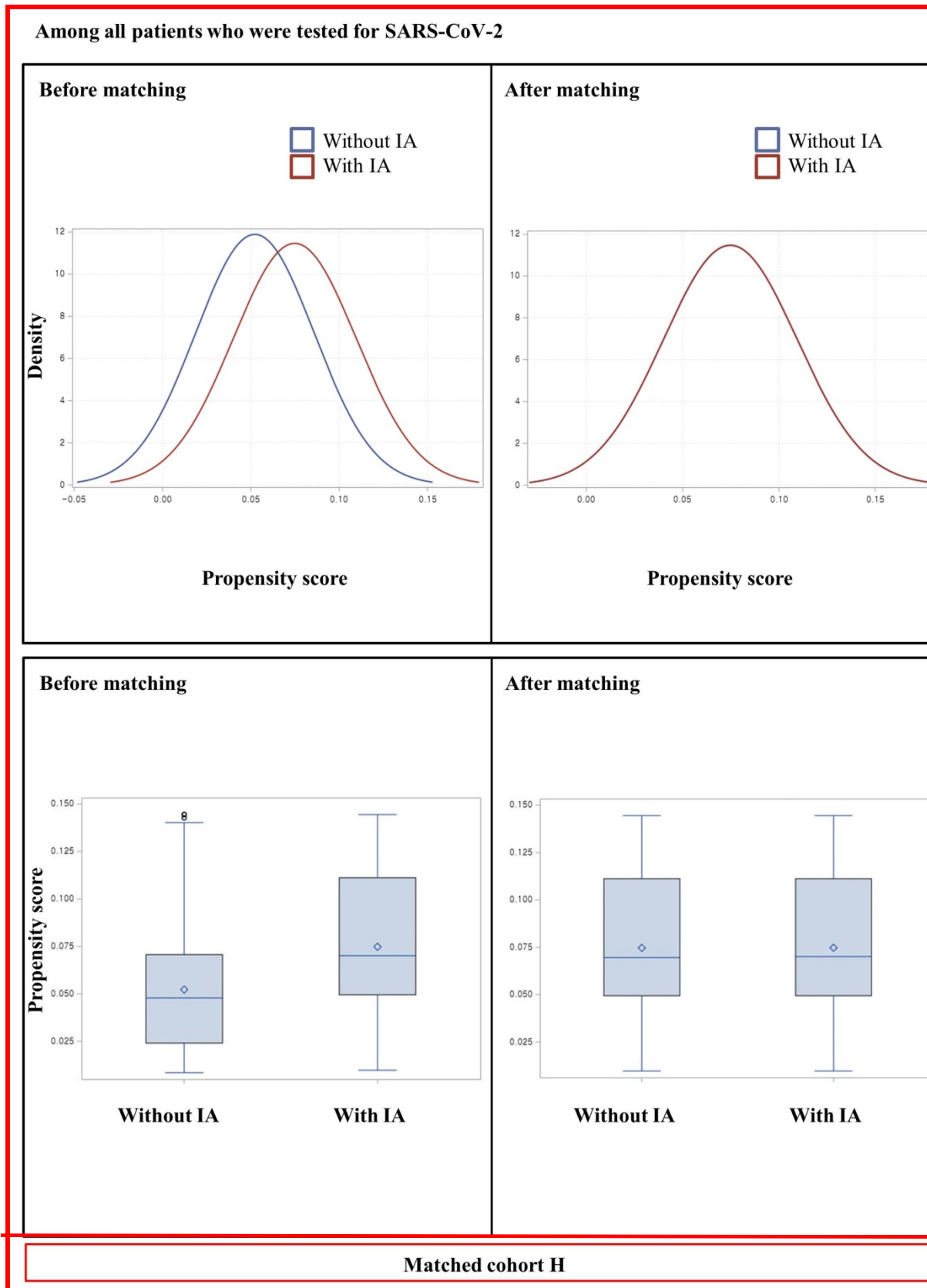
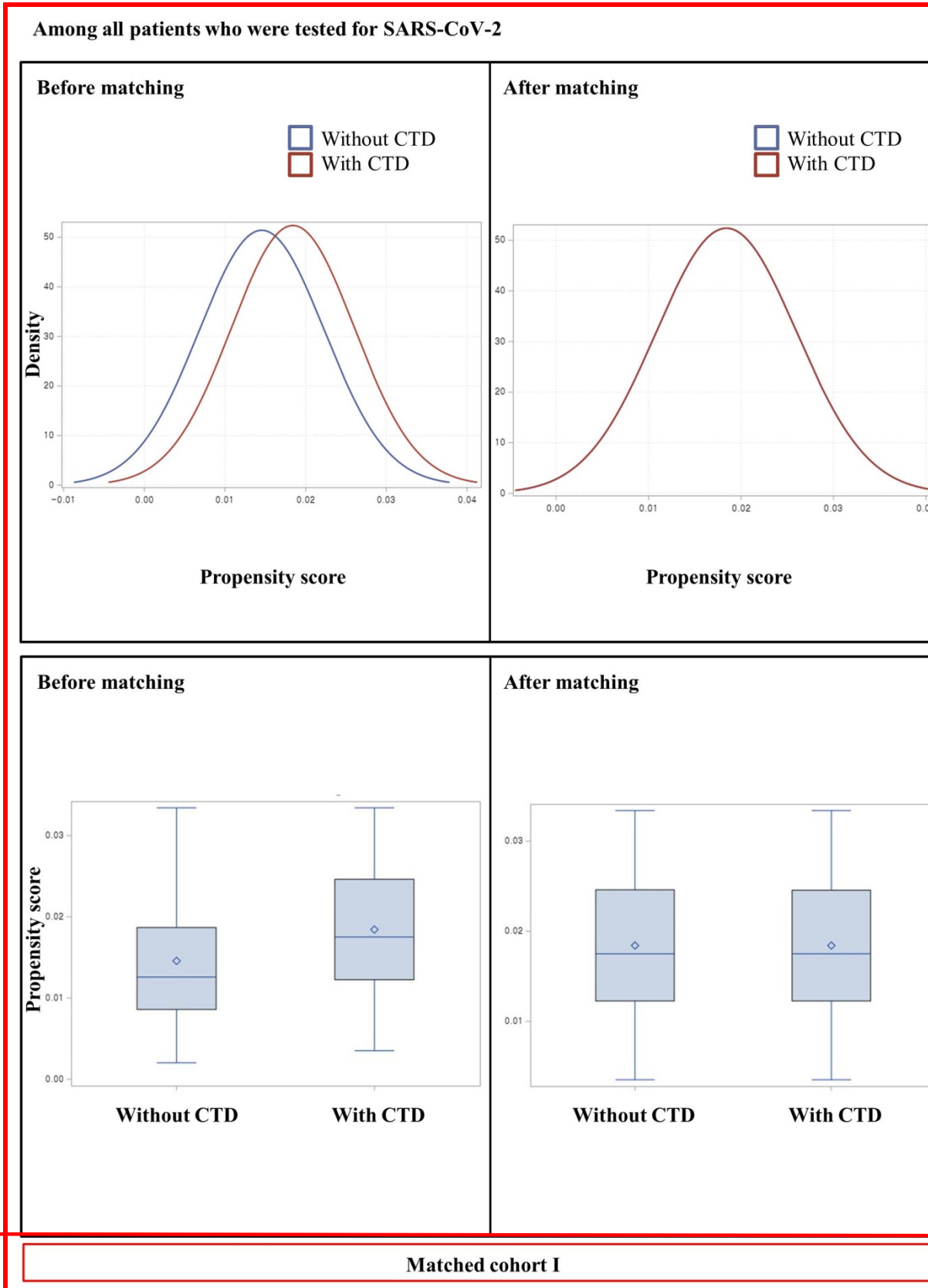


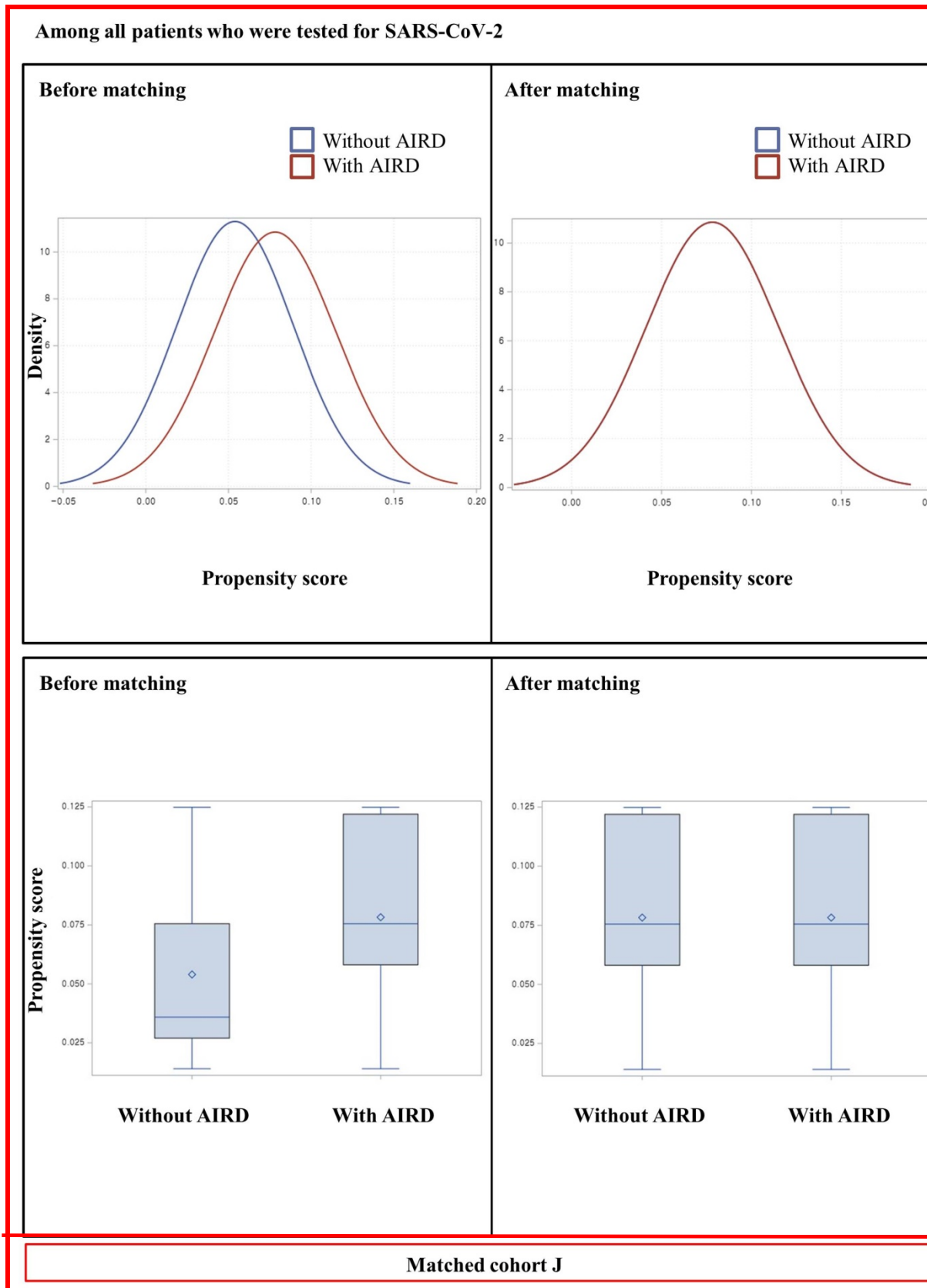
Figure S10. The density and distribution of propensity scores before and after matching in matched cohort H



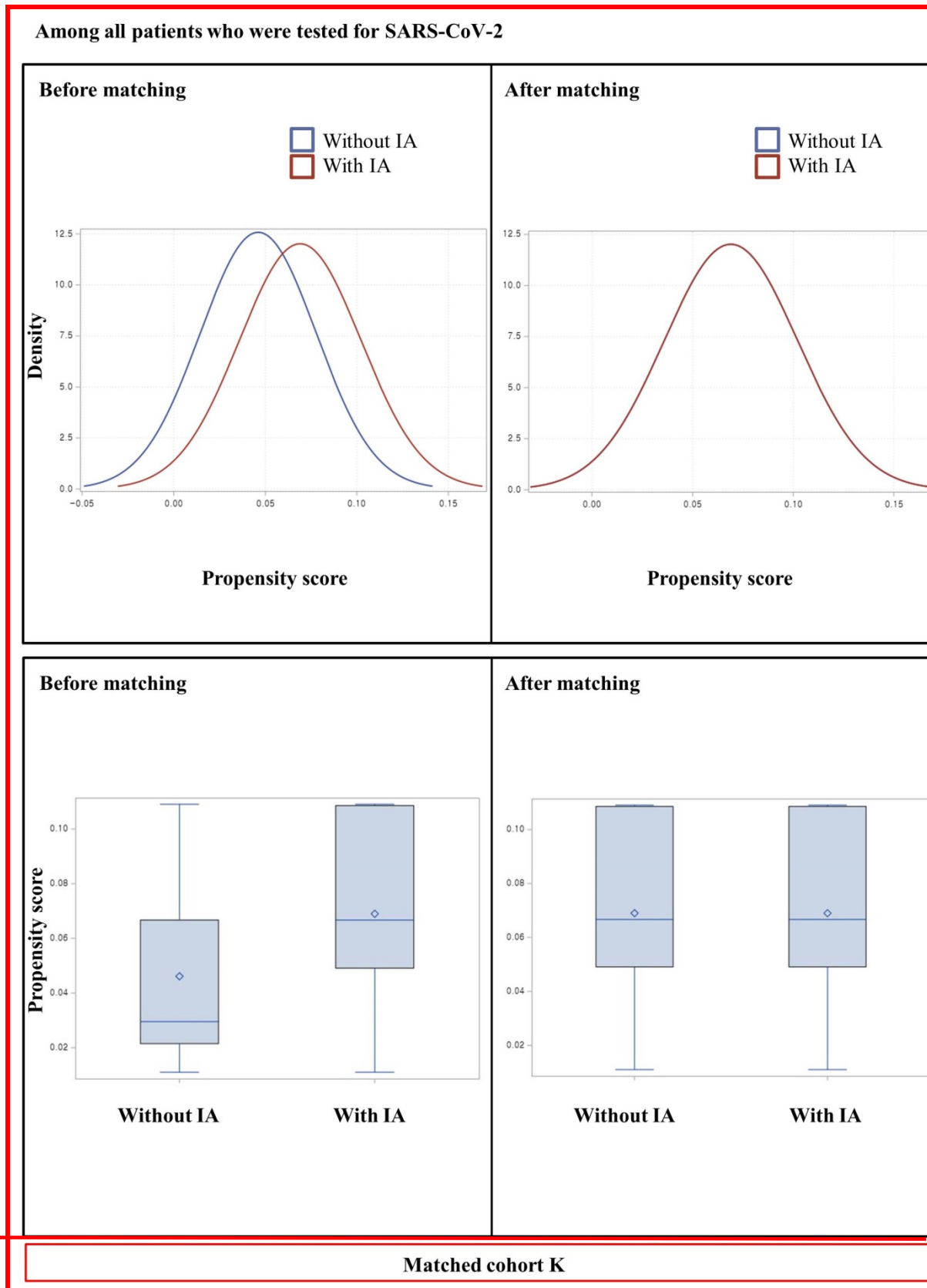
37 **Figure S11.** The density and distribution of propensity scores before and after matching in matched
 38 cohort I



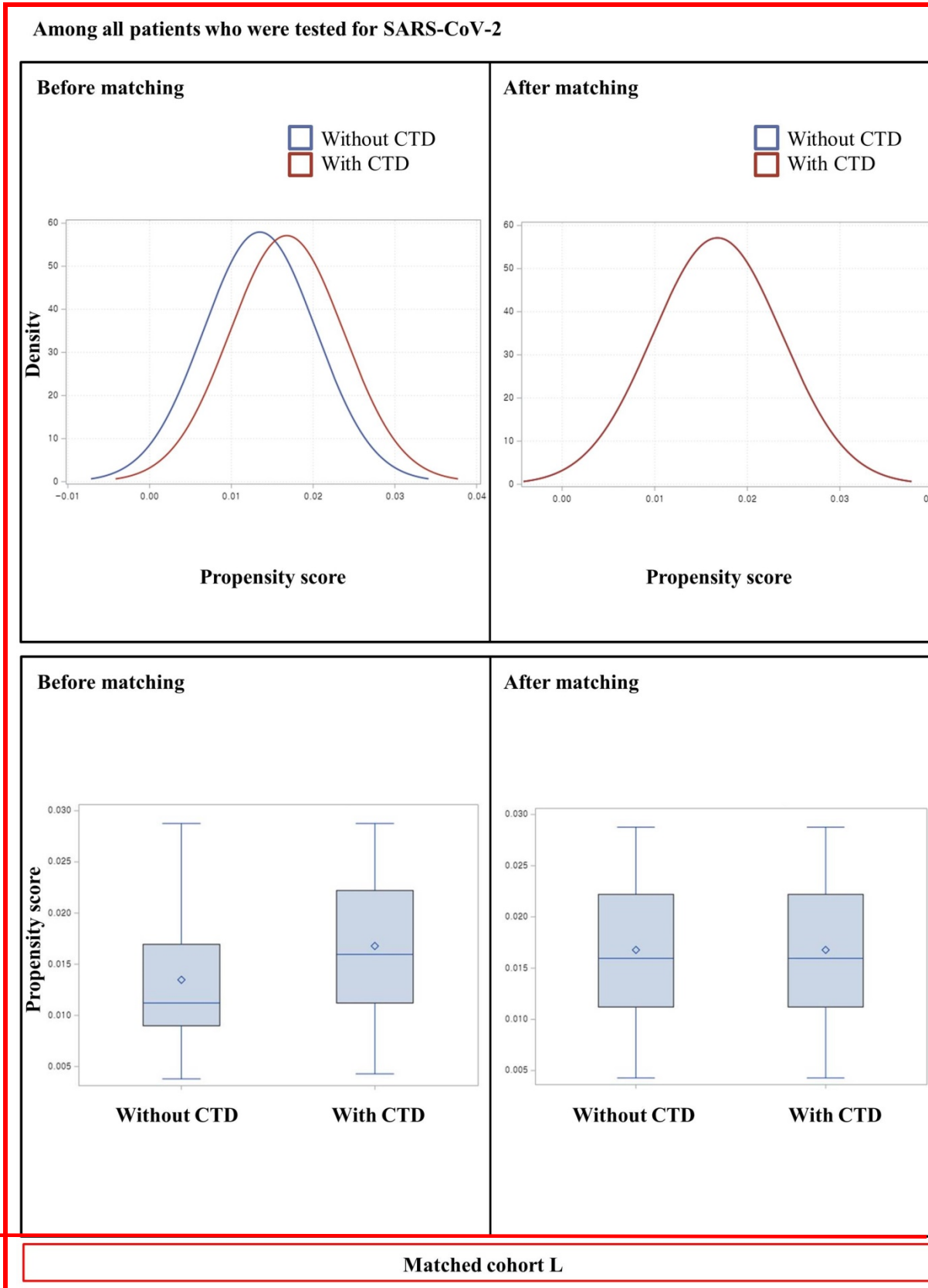
39 **Figure S12.** The density and distribution of propensity scores before and after matching in matched
 40 cohort J



41 **Figure S13.** The density and distribution of propensity scores before and after matching in matched
 42 cohort K



43 **Figure S14.** The density and distribution of propensity scores before and after matching in matched
 44 cohort L



45 **Figure S15.** Directed acyclic graph demonstrating the implicitly assumed causal association
 46 between AIRD (“exposure”) and risk of COVID-19 (“outcome”) in the Korean nationwide

cohort linked to the general health examination records before matching. Confounders, potential mediators, and exposure-outcome associations are indicated.

AIRD, autoimmune inflammatory rheumatic disease; BMI, body mass index; CBVD, Cerebrovascular disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, Diabetes Mellitus

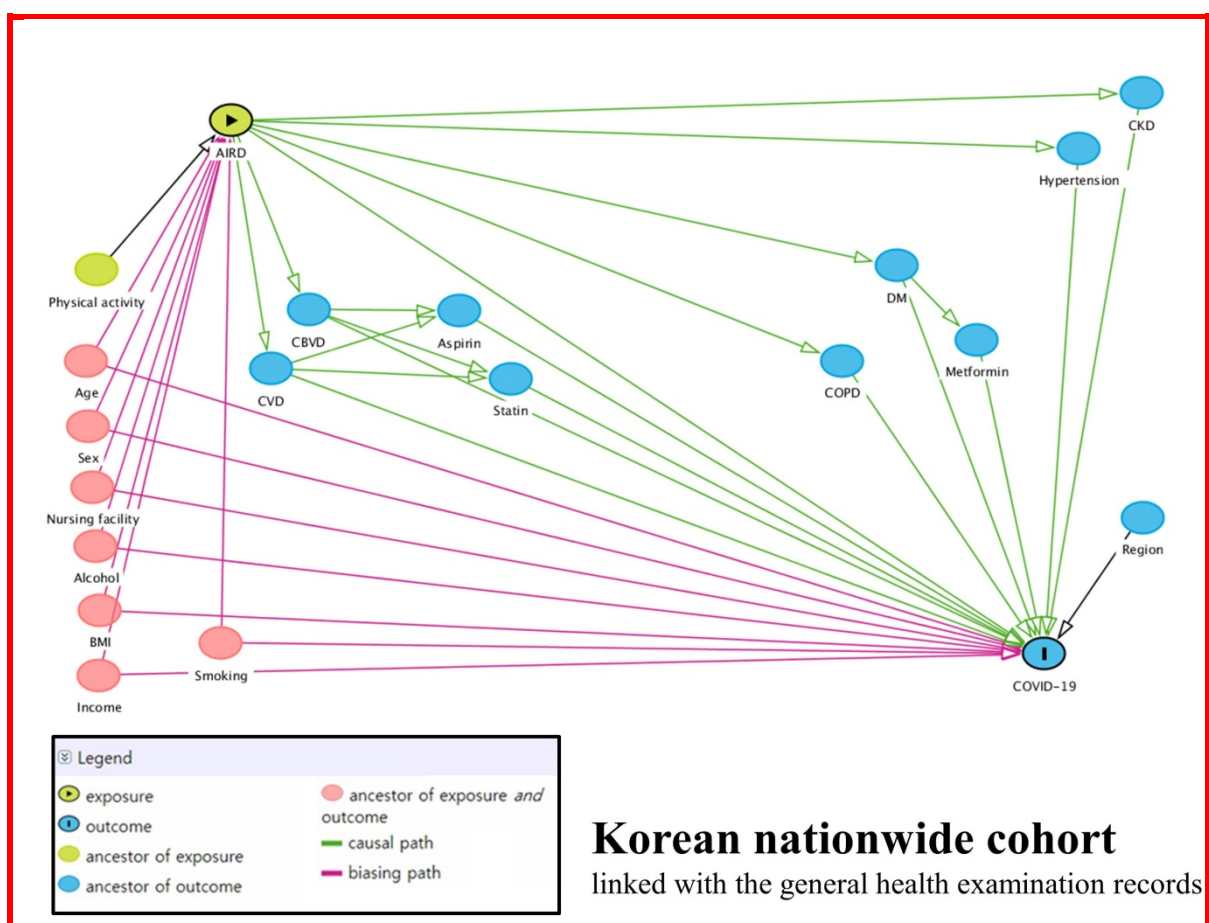


Figure S16. Directed acyclic graph showing the implicitly assumed causal association between AIRD (“exposure”) and risk of COVID-19 (“outcome”) in the Korean nationwide cohort without linking the general health examination records before matching. Confounders, potential mediators, and exposure-outcome associations are indicated.

AIRD, autoimmune inflammatory rheumatic disease; CBVD, Cerebrovascular disease; CKD, Chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, Diabetes Mellitus

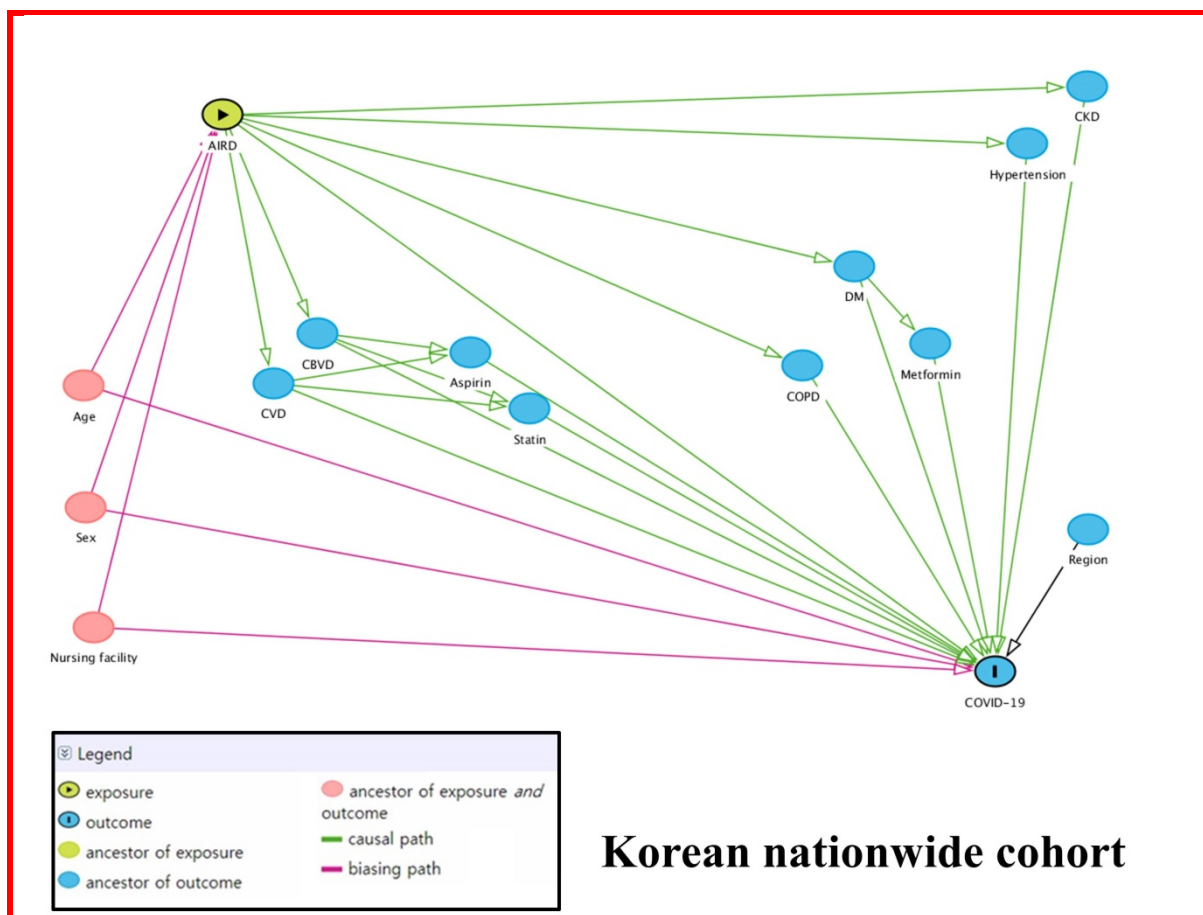
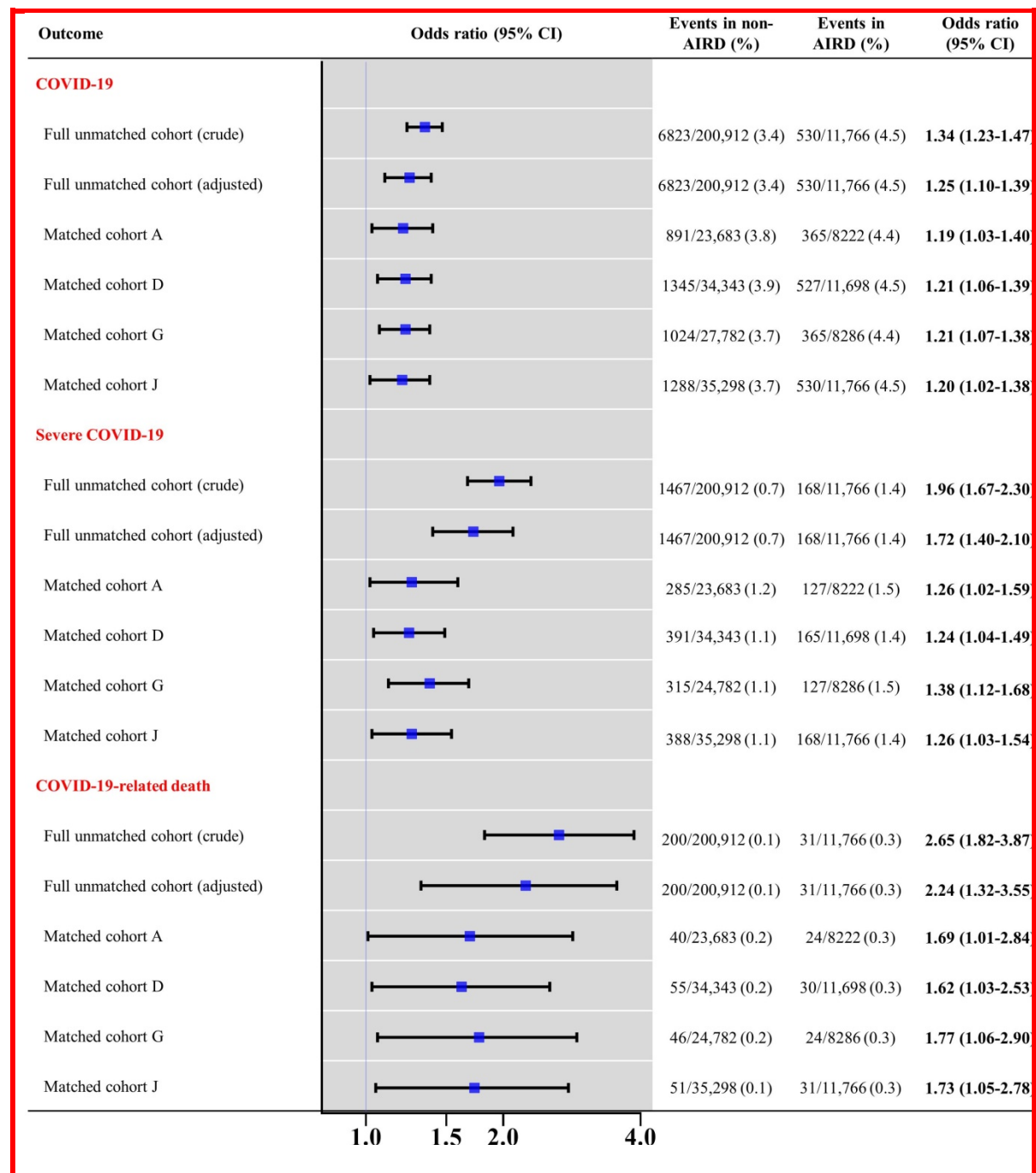


Figure S17. Propensity score-matched association of AIRD with SARS-CoV-2

AIRD, autoimmune inflammatory rheumatic disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.



70

71 **Figure S18.** Propensity score-matched association of IA with SARS-CoV-2

72 AIRD, autoimmune inflammatory rheumatic disease; IA, inflammatory arthritis; SARS-CoV-

73 2, severe acute respiratory syndrome coronavirus 2.

74

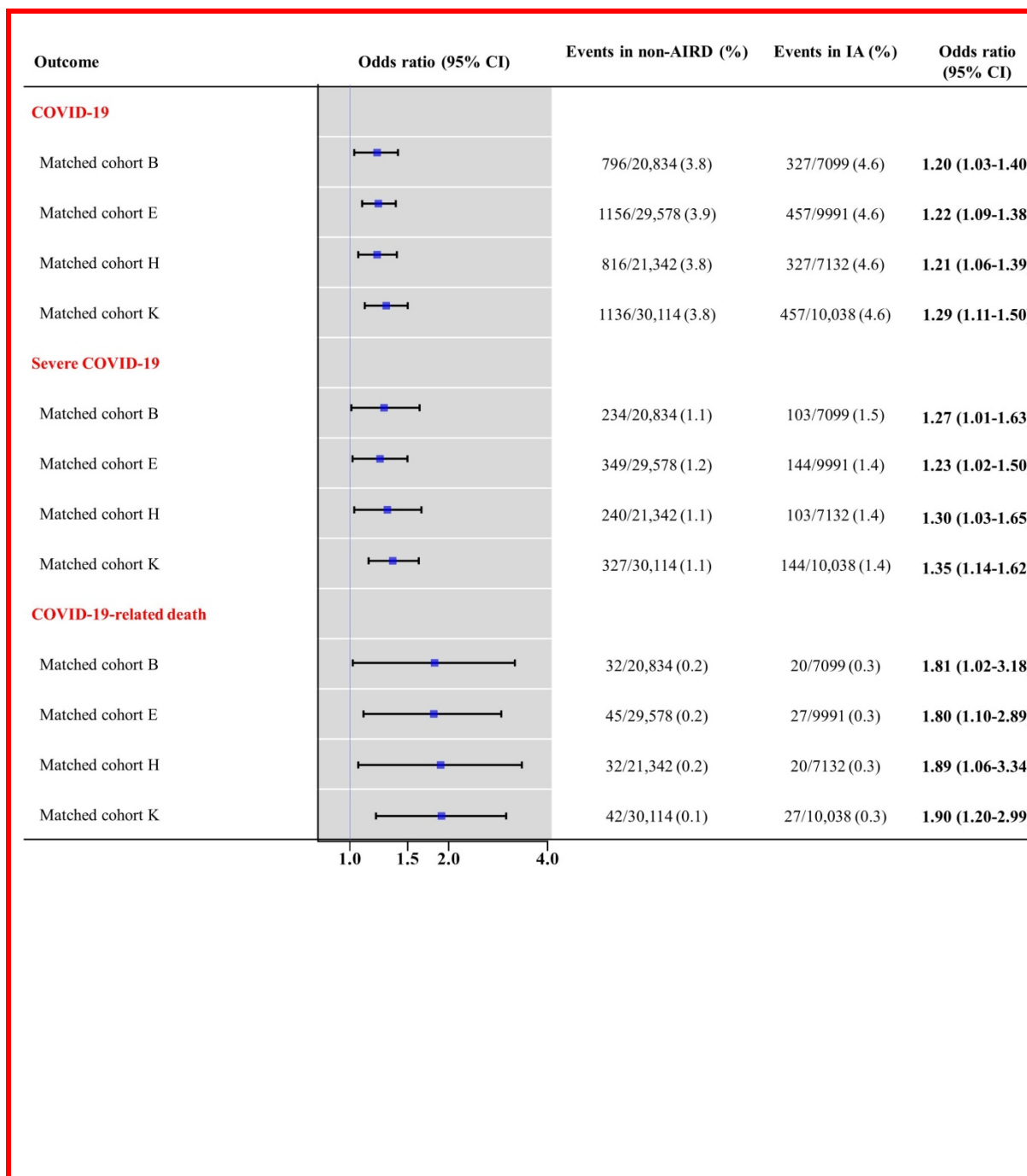


Figure S19. Propensity score-matched association of CTD with SARS-CoV-2

AIRD, autoimmune inflammatory rheumatic disease; CTD, connective tissue disease; SARS-

CoV-2, severe acute respiratory syndrome coronavirus 2.

