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COVID-19 Outcomes in Patients with Systemic Autoimmune Rheumatic Diseases (SARDs) Compared to the General Population: A US Multi-Center Comparative Cohort Study

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Abstract

Objective: Patients living with systemic autoimmune rheumatic diseases (SARDs) continue to be concerned about risks of severe COVID-19 outcomes.

Methods: Using a large multi-center electronic health record network, we conducted a comparative cohort study of patients with SARDs diagnosed with COVID-19 (identified by diagnostic code or positive molecular test) versus non-SARD comparators with COVID-19, matched by age, sex, race/ethnicity, and body mass index (primary model) and comorbidities and health care utilization (extended model). Thirty-day outcomes were assessed, including hospitalization, intensive care unit (ICU) admission, mechanical ventilation, acute renal failure requiring renal replacement therapy (ARF), ischemic stroke, venous thromboembolism (VTE), and death.

Results: We initially identified 2,379 SARD patients with COVID-19 (mean age 58 years, 79% female) and 142,750 comparators (mean age 47 years, 54% female). In the primary matched model (2,379 SARD patients and 2,379 matched non-SARD comparators with COVID-19), SARD patients had significantly higher risks of hospitalization (RR 1.14, 95% CI: 1.03 to 1.26), ICU admission (RR 1.32, 95% CI: 1.03 to 1.68), ARF (RR 1.81, 95% CI: 1.07 to 3.07), and VTE (RR 1.74, 95% CI: 1.23 to 2.45) versus comparators but did not have significantly higher risks of mechanical ventilation or death. In the extended model, all risks were largely attenuated except risk of VTE (RR 1.60, 95% CI: 1.14 to 2.25).

Conclusions: SARD patients with COVID-19 may be at higher risk of hospitalization, ICU admission, ARF, and VTE versus matched comparators. These risks may be largely mediated by comorbidities, except for risk of VTE.

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Keywords

COVID-19; rheumatic diseases; epidemiology

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic is an unprecedented global health crisis. Patients living with systemic autoimmune rheumatic diseases (SARDs) may be at higher risk of severe outcomes from COVID-19 due to underlying immunodeficiency and/or immunosuppression; however, studies to date have been conflicting. Early case reports and series suggested that patients with rheumatic diseases generally had mild COVID-19 infections.[1] However, comparative cohort studies from early pandemic epicenters in Wuhan, China, and Boston, Massachusetts, reported up to threefold higher odds of mechanical ventilation in rheumatic disease patients versus comparators.[2,3] With schools, workplaces, and governments loosening physical distancing restrictions, patients with rheumatic diseases and providers remain concerned about potentially heightened risk of severe outcomes from COVID-19. We examined COVID-19 outcomes in SARD patients versus matched comparators in a multi-center research network in the US.

METHODS

Data Source

We conducted a comparative cohort study using the US-based data from the Dataworks network of TriNetX, a large federated health research network of electronic health record (EHR) data with real-time updates (including demographics, diagnoses, procedures, medications, laboratory values, and vital status), which has been used previously to study COVID-19 outcomes.[4–6] The data set included 41 healthcare organizations, including a mixture of academic medical centers and community hospitals across the US, with approximately 51 million individual patients in total. The TriNetX platform uses aggregate counts and statistical summaries of deidentified information so that no Protected Health Information (PHI) or Personal Data is disclosed. There was no patient or public involvement in this study.

Study Cohort

We identified patients with SARDs including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren's syndrome, systemic sclerosis (SSc), dermatomyositis/polymyositis, other connective tissue diseases (including mixed or undifferentiated connective tissue diseases), systemic vasculitis (including granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, microscopic polyangiitis, polyarteritis nodosa, giant cell arteritis, and Behçet's disease), psoriatic arthritis, and ankylosing spondylitis by two International Classification of Diseases 10th Revision (ICD-10) codes >2 months apart but within ≤ 2 years (Supplemental Table 1).[7] We identified patients with COVID-19 using specific ICD-10 diagnosis codes recommended by the World Health Organization and US Centers for Disease Control and Prevention (codes U07.1, J12.81, B97.29, B97.21)[8] and/or positive results on polymerase chain reaction (PCR) testing for

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Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) between January 20, 2020 and August 15, 2020. A comparator cohort with COVID-19 but without SARD was also identified.

Covariates

We assessed baseline covariates within one year prior to the index date (date of COVID-19 diagnosis) including demographics (age, sex, race/ethnicity), comorbidities (hypertension, ischemic heart disease, chronic kidney disease, asthma, chronic obstructive pulmonary disease [COPD], and diabetes mellitus), body mass index (BMI), and prior hospitalization. Comorbidities were defined by at least one occurrence of an ICD-10 code during the covariate assessment period. Disease-modifying anti-rheumatic drug (DMARD) use was defined by 2 prescriptions greater than 30 days apart but within 1 year of the index date.

Outcome Definition

Outcomes were assessed within 30 days of COVID-19 diagnosis by relevant ICD-10 and/or procedure codes for hospitalization, intensive care unit (ICU) admission, mechanical ventilation, acute renal failure (ARF) requiring the initiation of renal replacement therapy (RRT), ischemic stroke, venous thromboembolism (VTE) including pulmonary embolism and deep venous thrombosis, death, and a composite outcome of ICU admission, mechanical ventilation, or death (Supplemental Table 2).[9,10]

Statistical Analyses

Using the TriNetX online platform for real-time analyses, we performed exposure score (ES) matching between COVID-19 patients with SARD and those without SARD, analogous to propensity score matching, using logistic regression and a greedy nearest-neighbor matching algorithm with a caliper of 0.1 pooled standard deviations.[11] Our primary model used the following covariates in the exposure score: age, sex, race/ethnicity, and BMI. Comorbidities were not included in our primary model, as they would likely have occurred due to SARD (thus causal intermediates for poor COVID-19 outcomes), but not as a cause of SARD (to qualify as a confounder). For example, RA, SLE, or small vessel vasculitis can directly or indirectly (through treatments such as glucocorticoids) contribute to developing cardiovascular-renal-metabolic sequelae, whereas these conditions are not risk factors for the development of SARDs. Nevertheless, our extended model additionally included comorbidities and health care utilization (which also would likely be a consequence of having SARD, as opposed to a cause of SARD). We assessed covariate balance between the ES-matched cohorts using standardized differences, with a value below 0.1 indicating minimal differences between groups. We compared the incidences and relative risks (RR) of these outcomes among the unmatched and ES-matched cohorts. Within the SARD cohort, we examined the risk of the composite outcome (ICU admission, mechanical ventilation, or death) in patients on certain immunosuppressive medications versus those not on those medications, including conventional synthetic DMARDs, biologic/targeted synthetic DMARDs, and glucocorticoids (Supplemental Table 3). For all measures, we calculated 95% confidence intervals (95% CI). All p-values were two-sided, and a significance level was set at 0.05.

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RESULTS

Study Population

We identified 2,379 SARD patients with COVID-19 and 142,750 non-SARD patients with COVID-19 (Table 1). The SARD cohort had a mean age of 58 years and 1,873 (79%) were female, while the non-SARD unmatched comparator pool had a lower mean age of 47 years and lower proportion of females (77,438 [54%]). The SARD cohort had a greater proportion with comorbidities and prior hospitalization than the unmatched comparator pool. Mean BMI (30.7 kg/m^2 versus 30.5 kg/m^2) and creatinine (1.1 mg/dL versus 1.2 mg/dL) were similar in the unmatched SARD and non-SARD cohorts (Table 1).

In the primary ES-matched model, there were 2,379 SARD patients and 2,379 matched comparators. Age, sex, race/ethnicity, BMI, and creatinine were similar between the primary ES-matched groups (all standardized differences <0.1), although comorbidities and prior hospitalization were more prevalent in the SARD cohort versus non-SARD comparators (Table 1). In the extended ES-matched model, age, sex, race/ethnicity, BMI, creatinine, comorbidities, and prior hospitalization were similar between the SARD cohort and non-SARD comparators (all standardized differences <0.1) (Table 1).

In the SARD cohort, the most common rheumatic diseases were rheumatoid arthritis (1,181 [50%]), systemic lupus erythematosus (528 [22%]), Sjögren's syndrome (317 [13%]), mixed or undifferentiated connective tissue disease (188 [8%]), systemic vasculitis (175 [7%]), and psoriatic arthritis (200 [8%], Table 2). Regarding immunomodulatory therapy, 1,304 (55%) were on glucocorticoids, 374 (16%) were on biologic/targeted synthetic DMARDs, and 981 (41%) were on conventional synthetic DMARDs such as hydroxychloroquine (534 [22%]) and methotrexate (302 [13%]).

COVID-19 Outcomes

Prior to ES matching, risks of hospitalization, ICU admission, mechanical ventilation, ARF, ischemic stroke, VTE, death, and the composite outcome (ICU admission, mechanical ventilation, or death) were significantly higher in the SARD cohort versus comparators (Table 3). In the primary ES-matched analysis, SARD patients had significantly higher risk of hospitalization (RR 1.14, 95% CI: 1.03 to 1.26), intensive care unit admission (RR 1.32, 95% CI: 1.03 to 1.68), ARF requiring RRT (RR 1.81, 95% CI: 1.07 to 3.07), and VTE (RR 1.74, 95% CI: 1.23 to 2.45) versus matched comparators. There was a trend towards higher risk of ischemic stroke (RR 1.50, 95% CI: 0.93 to 2.41) in the SARD cohort versus comparators, although this was not statistically significant. There were no significantly higher risks of mechanical ventilation (RR 1.05, 95% CI: 0.77 to 1.44), death (RR 1.08, 95% CI 0.81 to 1.44), or a composite outcome of ICU admission, mechanical ventilation, or death (RR 1.19, 95% CI: 0.98 to 1.44) in the SARD cohort versus comparators.

In the extended ES-matched analysis, the previously observed higher risks of hospitalization, ICU admission, and ARF requiring RRT were attenuated and no longer significantly higher in the SARD cohort versus the comparator cohort. However, SARD patients continued to have significantly higher risk of VTE versus non-SARD patients in the extended ES-matched analysis (RR 1.60, 95% CI: 1.14 to 2.25).

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Lastly, within the SARDs cohort, the relative risks of the composite outcome in the primary ES-matched model were 1.19 (95% CI: 0.87 to 1.62) and 1.31 (95% CI: 0.80 to 2.14) for conventional synthetic DMARDs and biologic/targeted synthetic DMARDs, respectively, whereas corresponding extended ES-matched RRs were 1.00 (95% CI: 0.70 to 1.42) and 1.17 (95% CI: 0.73 to 1.89). For patients on glucocorticoids versus non-users, there were significantly higher risks of the composite outcome in the primary ES-matched (RR 1.74, 95% CI: 1.28 to 2.38) and extended ES-matched (RR 1.50, 95% CI: 1.07 to 2.10) analyses.

DISCUSSION

In a large multi-center EHR database in the US, SARD patients with COVID-19 had higher risks of hospitalization, ICU admission, ARF requiring RRT, and VTE versus comparators without COVID-19 matched on age, sex, race/ethnicity, and BMI in the 30 days following COVID-19 diagnosis. However, the risks of mechanical ventilation and death were not higher, which may provide some reassurance during the ongoing COVID-19 pandemic. Additionally, in an extended model after matching for the above covariates as well as comorbidities and health care utilization, the risks of hospitalization, ICU admission, and ARF requiring RRT were attenuated, suggesting that comorbidities are likely key mediators of the excess risk of these outcomes in SARD patients, similar to risk factors for poor COVID-19 outcomes in the general population. However, the risk of VTE was not substantially attenuated in the extended ES-matched model, suggesting having a SARD has a direct causal mechanism for a higher risk of VTE in COVID-19 infection than comparators, beyond the mediating effects of comorbidities.

Our study supports and extends from prior work regarding COVID-19 outcomes in SARD patients. Reports from center-specific studies in early pandemic epicenters in Wuhan, China, and Boston, Massachusetts, between January and April 2020 reported up to threefold higher odds of mechanical ventilation in SARD patients versus comparators, although there was no significantly higher risk of death.[2,3] We used a multi-center US EHR network including patients diagnosed with COVID-19 up to August 15, 2020 (six months into the US pandemic) to examine COVID-19 outcomes and found no significantly higher risk of mechanical ventilation or death in SARD patients versus matched comparators. Compared to prior studies, our study had a larger sample size of SARD patients from broader geographic representation in the US, which may explain the differing results. It is also possible that higher testing capacity (potentially leading to increased detection of milder COVID-19 cases) and/or improvements in COVID-19 management may have ameliorated the previously observed higher risk of mechanical ventilation in SARD patients early in the pandemic.[12] We did observe a higher risk of hospitalization, ICU admission, ARF requiring RRT, and VTE in SARD patients versus comparators, emphasizing the need for continued vigilance to physical distancing recommendations to prevent COVID-19 transmission during the ongoing pandemic, especially in patients with SARDs and significant comorbidities.

We observed a significantly higher risk of VTE in SARD patients versus matched comparators in our primary and extended models. COVID-19 has been associated with severe endothelial injury resulting in widespread thrombosis and microangiopathy.[13] Patients living with SARDs at baseline may be at higher risk of VTE due to a chronic

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inflammatory state and/or antiphospholipid syndrome. For example, a comparative cohort study using US claims data showed a 40% higher risk of VTE in patients with RA versus comparators.[14] Due to the low event rate, we were unable to determine the risk of VTE in specific diseases, and further studies are warranted to determine disease-specific risk and optimal thromboprophylaxis strategies for SARD patients with COVID-19.

Lastly, we examined the risk of the composite outcome (intensive care unit admission, mechanical ventilation, or death) in users versus non-users of various immunosuppressive medications within the SARD cohort. Similar to prior studies, conventional synthetic DMARDs and biologic/targeted synthetic DMARDs were not associated with higher risks of severe COVID-19 outcomes, while glucocorticoid use was associated with severe COVID-19 outcomes.[15–18] Future studies are needed with larger sample sizes to examine the effects of individual medications.

This is the first national multi-center cohort study examining COVID-19 outcomes in SARD patients. The data source is representative of academic and community healthcare settings across the US, and the results are therefore likely generalizable. Additionally, the availability of real-time data from a large-scale network enabled the timely analysis of COVID-19 outcomes. However, the limitations of our study deserve comment, including the typical limitations of observational EHR data such as the potential for residual confounding and inaccuracies in ICD-10 coding. Outcomes may have been incompletely captured if occurring outside of the included healthcare organizations, but this would not be expected to differentially impact the SARD and comparator cohorts. Additionally, due to privacy regulations, we cannot identify the relative contributions of COVID-19 cases from individual healthcare organizations or geographic regions, and we have no available measures of the social determinants of health. Lastly, given that the study population selection conditioned upon a diagnosis of COVID-19, there is the possibility of collider bias, which may bias the results towards a null effect.[19]

In a large comparative cohort study using a multi-center EHR research network in the US, we found that SARD patients with COVID-19 had higher risk of hospitalization, ICU admission, ARF requiring RRT, and VTE than comparators, but did not have higher risk of mechanical ventilation or death. Except for VTE, the other risks were largely attenuated in an extended model matching for comorbidities, suggesting that these risks are mediated by comorbidities. SARD patients with COVID-19 should be closely monitored for thrombotic complications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Baseline Characteristics of Systemic Autoimmune Rheumatic Disease (SARD) Patients and Non-SARD Comparators with COVID-19

	Unmatched Cohorts			Exposure Score-Matched Cohorts†			Extended Exposure Score-Matched Cohorts‡		
Characteristics*	**SARD Patients**	**Non-SARD Comparators**	**Std. Diff.**	**SARD Patients**	**Non-SARD Comparators**	**Std. Diff.**	**SARD Patients**	**Non-SARD Comparators**	**Std. Diff.**
N	2,379	142,750		2,379	2,379		2,374	2,374	
Age, years, mean (SD)	58 (16)	47 (19)	0.61	58 (16)	57 (16)	0.01	58 (16)	58 (16)	0.02
Female, n (%)	1,873 (79)	77,438 (54)	0.54	1,873 (79)	1,873 (79)	<0.01	1,868 (79)	1,866 (79)	<0.01
Race/Ethnicity, n (%)									
White	1,295 (54)	72,946 (51)	0.07	1,295 (54)	1,295 (54)	<0.01	1,293 (54)	1,297 (55)	<0.01
Black	649 (27)	32,347 (23)	0.11	649 (27)	649 (27)	<0.01	648 (27)	662 (28)	0.01
Hispanic	312 (13)	26,388 (18)	0.15	312 (13)	312 (13)	<0.01	312 (13)	304 (13)	0.01
Comorbidities, n (%)									
Hypertension	1,206 (51)	24,171 (17)	0.76	1,206 (51)	758 (32)	0.39	1,201 (51)	1,209 (51)	0.01
Ischemic Heart Disease	360 (15)	5,378 (4)	0.40	360 (15)	165 (7)	0.26	355 (15)	348 (15)	0.01
Chronic Kidney Disease	376 (16)	5,549 (4)	0.41	376 (16)	183 (8)	0.25	372 (16)	361 (15)	0.01
Diabetes Mellitus	599 (25)	13,026 (9)	0.44	599 (25)	384 (16)	0.22	595 (25)	588 (25)	0.01
Asthma	372 (16)	5,800 (4)	0.40	372 (16)	200 (8)	0.22	367 (15)	360 (15)	0.01
COPD	87 (4)	969 (1)	0.21	87 (4)	34 (1)	0.14	85 (4)	74 (3)	0.03
BMI, kg/m^2, mean (SD)	30.7 (8.2)	30.5 (7.9)	0.02	30.7 (8.2)	30.6 (7.8)	<0.01	30.7 (8.2)	31.0 (8.2)	0.03
Creatinine, mg/dL, mean (SD)	1.1 (1.3)	1.2 (2.6)	0.01	1.1 (1.3)	1.1 (1.2)	0.03	1.1 (1.3)	1.3 (1.7)	0.10
Prior Hospitalization, n (%)	360 (15)	5,761 (4)	0.38	360 (15)	187 (8)	0.23	355 (15)	335 (14)	0.02

*Assessed in year prior to index date. SARD, systemic autoimmune rheumatic disease; COPD, chronic obstructive pulmonary disease; BMI, body mass index; Std. Diff., standardized difference.

†One-to-one exposure score-matching was performed using a method analogous to propensity score-matching. The exposure score included age, sex, race/ethnicity, and BMI.

‡Extended exposure score included age, sex, race/ethnicity, BMI, comorbidities, and prior hospitalization.

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Table 2.

Baseline Rheumatic Disease Characteristics of Systemic Autoimmune Rheumatic Disease (SARD) Patients with COVID-19

Characteristics*	SARD Patients (n = 2,379)
Rheumatic Disease, n (%)**	
Rheumatoid Arthritis	1,181 (50)
Systemic Lupus Erythematosus	528 (22)
Sjögren's Syndrome	317 (13)
Systemic Sclerosis	92 (4)
Dermatomyositis/PM	79 (3)
Other CTD†	188 (8)
Systemic Vasculitis	175 (7)
Psoriatic Arthritis	200 (8)
Ankylosing Spondylitis	76 (3)
Rheumatic Disease Medications, n (%)	
Glucocorticoids	1,304 (55)
Conventional DMARDs‡	981 (41)
Azathioprine	80 (3)
Cyclophosphamide	20 (1)
Cyclosporine	58 (2)
Hydroxychloroquine	534 (22)
Leflunomide	45 (2)
Methotrexate	302 (13)
Mycophenolate/mycophenolic acid	160 (7)
Sulfasalazine	55 (2)
Tacrolimus	92 (4)
Biologic/targeted synthetic DMARDs§	374 (16)
B-cell activating factor inhibitor	17 (1)
CD20 inhibitor	60 (3)
CTLA-4 immunoglobulin	38 (2)
IL-1 inhibitor	<10 (<1)

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Characteristics*	SARD Patients (n = 2,379)
IL-6 receptor inhibitor	38 (2)
IL-17 inhibitor	26 (1)
IL-23 inhibitor	23 (1)
JAK inhibitor	56 (2)
TNF inhibitor	200 (8)

*Assessed in year prior to index date. SARD, systemic autoimmune rheumatic disease; PM, polymyositis; CTD, connective tissue disease; TNF, tumor necrosis factor; DMARD, disease-modifying anti-rheumatic drug; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; IL, interleukin; JAK, janus kinase.

**Some patients may have more than one rheumatic disease diagnosis.

†Other CTD includes mixed connective tissue disease and undifferentiated connective tissue disease.

‡Includes azathioprine, cyclophosphamide, cyclosporine, hydroxychloroquine, leflunomide, methotrexate, mycophenolate/mycophenolic acid, sulfasalazine, tacrolimus.

§Includes B-cell activating factor inhibitors (belimumab), CD20 inhibitors (rituximab, ocrelizumab, ofatumumab), CTLA-4 immunoglobulin (abatacept), IL-1 inhibitors (anakinra, canakinumab, rilonacept), IL-6 receptor inhibitors (tocilizumab, sarilumab), IL-17 inhibitors (secukinumab, ixekizumab, brodalumab), IL-23 inhibitors (ustekinumab, guselkumab, risankizumab, tildrakizumab), JAK inhibitors (upadacitinib, baricitinib, tofacitinib), TNF inhibitors (adalimumab, etanercept, infliximab, golimumab, certolizumab).

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Table 3.

Outcomes at 30 Days Following COVID-19 Among Patients with Systemic Autoimmune Rheumatic Diseases (SARDs) and Non-SARD Comparators

	Unmatched			Exposure Score-Matched*			Extended Exposure Score-Matched†		
	SARD Events, n (%)	Non-SARD Comparator Events, n (%)	Relative Risk (95% CI)	SARD Events, n (%)	Non-SARD Comparator Events, n (%)	Relative Risk (95% CI)	SARD Events, n (%)	Non-SARD Comparator Events, n (%)	Relative Risk (95% CI)
Hospitalization	620 (26)	21,501 (15)	**1.73 (1.62, 1.85)**	620 (26)	546 (23)	**1.14 (1.03, 1.26)**	616 (26)	579 (24)	1.06 (0.96, 1.17)
ICU Admission	142 (6)	4,615 (3)	**1.85 (1.57, 2.17)**	142 (6)	108 (5)	**1.32 (1.03, 1.68)**	141 (6)	134 (6)	1.05 (0.84, 1.32)
Mechanical Ventilation	78 (3)	2,938 (2)	**1.59 (1.28, 1.99)**	78 (3)	74 (3)	1.05 (0.77, 1.44)	77 (3)	85 (4)	0.91 (0.67, 1.23)
ARF requiring RRT	38 (2)	737 (1)	**3.09 (2.24, 4.28)**	38 (2)	21 (1)	**1.81 (1.07, 3.07)**	38 (2)	41 (2)	0.93 (0.60, 1.44)
Ischemic Stroke	42 (2)	833 (1)	**3.03 (2.23, 4.11)**	42 (2)	28 (1)	1.50 (0.93, 2.41)	42 (2)	39 (2)	1.08 (0.70, 1.66)
VTE	85 (4)	1,721 (1)	**2.96 (2.39, 3.67)**	85 (4)	49 (2)	**1.74 (1.23, 2.45)**	85 (4)	53 (2)	**1.60 (1.14, 2.25)**
Death	94 (4)	2,962 (2)	**1.90 (1.56, 2.33)**	94 (4)	87 (4)	1.08 (0.81, 1.44)	93 (4)	79 (3)	1.18 (0.88, 1.58)
Composite outcome‡	213 (9)	7,069 (5)	**1.81 (1.59, 2.06)**	213 (9)	179 (8)	1.19 (0.98, 1.44)	212 (9)	191 (8)	1.11 (0.92, 1.34)

SARD, systemic autoimmune rheumatic disease; ICU, intensive care unit; ARF, acute renal failure; RRT, renal replacement therapy; VTE, venous thromboembolism (including deep venous thrombosis and pulmonary embolism). Significant findings in bold.

*One-to-one exposure score-matching was performed using a method analogous to propensity score-matching. The exposure score included age, sex, race/ethnicity, and BMI.

†Extended exposure score included age, sex, race/ethnicity, body mass index, comorbidities, and prior hospitalization.

‡Composite outcome included intensive care unit admission, mechanical ventilation, or death.