Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Temporal trends in severe COVID-19 outcomes in patients with rheumatic disease: a cohort study

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Summary

Background As the COVID-19 pandemic continues worldwide, severe COVID-19 outcomes remain a major concern for patients with rheumatic and musculoskeletal diseases. We aimed to investigate temporal trends in COVID-19 outcomes in patients with rheumatic and musculoskeletal diseases over the course of the pandemic.

Methods Using a large, multicentre, electronic health record network (TriNetX), we did a comparative cohort study of patients with rheumatic and musculoskeletal diseases who were diagnosed with COVID-19 (by International Classification of Diseases, Tenth Revision code or positive PCR test) during the first 90 days of the pandemic (early cohort) compared with the second 90 days of the pandemic (late cohort), matched (1:1) for demographics, comorbidities, laboratory results, glucocorticoid use, and previous hospitalisations using an exposure score method. Outcomes were assessed within 30 days of COVID-19 diagnosis, including hospitalisation, intensive care unit admission, invasive mechanical ventilation, renal failure, and death. We did a subgroup analysis among patients with rheumatic and musculoskeletal diseases who were hospitalised with COVID-19.

Findings We identified 8540 patients with rheumatic and musculoskeletal diseases who were diagnosed with COVID-19 during the 6-month study period, including 2811 in the early cohort and 5729 in the late cohort. In the exposure score matched analysis, the risk of hospitalisation was lower in the late cohort than in the early cohort (874 [32·4%] of 2701 patients *vs* 1227 [45·4%] of 2701 patients; relative risk [RR] 0·71, 95% CI 0·67–0·76). The risks of intensive care unit admission (214 [7·9%] *vs* 385 [14·3%]; RR 0·56, 95% CI 0·47–0·65), mechanical ventilation (96 [3·6%] *vs* 247 [9·1%]; 0·39, 0·31–0·49), acute kidney injury (372 [13·8%] *vs* 560 [20·7%]; 0·66, 0·59–0·75), renal replacement therapy (17 [0·6%] *vs* 32 [1·2%]; 0·53, 0·30–0·96), and death (122 [4·5%] *vs* 252 [9·3%]; 0·48, 0·39–0·60) were lower in the late cohort compared with the early cohort. Among the hospitalised subgroup, the risk of the composite outcome of intensive care unit admission, mechanical ventilation, and death was lower in the late cohort than in the early cohort (334 [30·7%] of 1089 patients *vs* 450 [41·3%] of 1089 patients; RR 0·74, 95% CI 0·67–0·83).

Interpretation The risks of severe COVID-19 outcomes have improved over time in patients with rheumatic and musculoskeletal disease but remain substantial. These findings might reflect ascertainment of milder cases in the later cohort and improvements in treatment and supportive care.

Funding None.

Lancet Rheumatol 2021; 3: e131–37

Published Online December 23, 2020 https://doi.org/10.1016/S2665-9913(20)30422-7

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Introduction

The COVID-19 pandemic has spread globally, with over 6 million confirmed cases and over 300 000 deaths in the USA since January, 2020.[1] Patients with rheumatic and musculoskeletal diseases have considerable concerns regarding the risks of severe outcomes after COVID-19, although the risk of such outcomes in these patients compared with the general population remains unclear. Some studies found higher odds of respiratory failure requiring mechanical ventilation in patients with rheumatic and musculoskeletal diseases than in the general population,[2,3] and two times higher odds of hospitalisation in patients with rheumatic and musculoskeletal diseases on prednisone doses above 10 mg daily than those not on prednisone,[4] whereas other studies have not shown higher incidence or severity of COVID-19 in patients with rheumatic and musculoskeletal diseases than in the general population.[5,6]

Although these early reports provide insight into the impact of the pandemic on patients with rheumatic and musculoskeletal diseases during the initial crisis phase, over the subsequent 6 months, there have been improvements in testing capacity, supportive care (eg, prone positioning), and treatments (eg, remdesivir and dexamethasone) for COVID-19, leading to a reduction in the case-fatality rate in the general population and speculation that other COVID-19 outcomes might have also improved over time.[1,7–9] However, temporal trends in COVID-19 outcomes have not been quantified in patients with rheumatic and musculoskeletal diseases. It is important to understand these temporal changes given that historical comparator groups are increasingly used to gauge the efficacy of potential treatments for COVID-19 and to inform patients with rheumatic and musculoskeletal diseases and their health-care providers of the current risks.[10,11] We aimed to investigate differences in mortality

Research in context

Evidence before this study

We searched PubMed on Oct 26, 2020, for studies published in any language using the search terms ("coronavirus" OR "COVID-19") AND ("rheumatic disease" OR "autoimmune disease"), which yielded 124 results. We identified four cohort or case-control studies examining whether patients with rheumatic disease had more severe COVID-19 outcomes than did the general population, with two studies reporting that patients with rheumatic disease had a higher risk of mechanical ventilation compared with the general population, and two studies reporting no such risk. However, none of the studies identified by our search reported whether severe COVID-19 outcomes have improved over time in patients with rheumatic disease during the ongoing pandemic. Additionally, we reviewed online dashboards, including the WHO COVID-19 Dashboard, the Johns Hopkins Coronavirus Resource Center, and Our World in Data for trends in COVID-19 outcomes, including the case-fatality rate. These sources revealed a decline in the case-fatality rate for patients diagnosed with COVID-19 at the US population level between April 30 and Oct 26, 2020.

Added value of this study

To our knowledge, we provide the first report of improving COVID-19 outcomes,including hospitalisation, mechanical ventilation, renal failure, and death, in patients with rheumatic and musculoskeletal diseases in a multicentre US electronic health record database during the ongoing pandemic.

Implications of all the available evidence

We observed lower risks of respiratory failure, renal failure, and death after COVID-19 diagnosis in patients with rheumatic and musculoskeletal diseases in later months compared with earlier months of the ongoing pandemic in the USA. Given these improvements in severe COVID-19 outcomes over time, historical comparators should be used cautiously in observational studies of new therapies for COVID-19.

and other critical outcomes after COVID-19 diagnosis between an early cohort and late cohort of patients with rheumatic and musculoskeletal diseases within the first 180 days of the pandemic in the USA.

See Online for appendix

Methods

Data source

In this population-based comparative cohort study, we used US-based data from the Dataworks network TriNetX, a large federated health research network with real-time updates of electronic health record data including demographics, diagnoses, procedures, medications, laboratory values, and vital statuses. This network includes 36 healthcare organisations, including academic medical centres, community hospitals, specialists, and general practitioners across the USA, with data for around 51 million patients, and has been previously used for COVID-19 outcome studies.[12,13] The TriNetX platform uses aggregated counts and statistical summaries of deidentified information so that no protected health information or personal data are made available to users of the platform. There was no patient or general public involvement in this study.

This study received ethical approval from the Partners Healthcare Institutional Review Board (Boston, MA, USA).

Study cohort

We identified patients with rheumatic and musculoskeletal diseases who were diagnosed with COVID-19 using specific International Classification of Diseases, Tenth Revision (ICD-10) diagnosis codes recommended by WHO and the US Centers for Disease Control and Prevention (codes U07·1, J12·81, B97·29, B97·21)[14] or had positive results on PCR tests for severe acute respiratory syndrome coronavirus 2. The index date of COVID-19 diagnosis was determined by the earliest date of positive PCR testing or relevant ICD-10 code. Rheumatic and musculoskeletal diseases were defined by one or more ICD-10 codes (appendix p 1) and included rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, systemic sclerosis, dermatomyositis, polymyositis, Sjögren's syndrome, other systemic connective tissue diseases, systemic vasculitis (including antineutrophil cytoplasmic antibody-associated vasculitis, Behçet's disease, polyarteritis nodosa, and giant cell arteritis), polymyalgia rheumatica, and gout.

We divided patients based on the index date of COVID-19 diagnosis into an early cohort (in the first 90 days between Jan 20 and April 19, 2020) and a late cohort (in the subsequent 90 days between April 20 and July 19, 2020).

Covariates

We assessed baseline covariates associated with severe COVID-19 outcomes within one year before the index date, including demographics, comorbidities (eg, hypertension, ischaemic heart disease, chronic kidney disease, diabetes, asthma or chronic obstructive pulmonary disease, liver disease, and malignancy), rheumatic and musculoskeletal diseases, glucocorticoid use, oral disease modifying antirheumatic drug (DMARD) use (eg, hydroxychloroquine, methotrexate, azathioprine, mycophenolate, leflunomide, ciclosporin, and tofacitinib), biological DMARD use (eg, adalimumab, etanercept, tocilizumab, rituximab, and abatacept), serum creatinine, body-mass index (BMI), and previous hospitalisations.

Outcomes

We assessed prespecified primary outcomes between the index date and 30 days after COVID-19 diagnosis by relevant ICD-10 and Current Procedural Terminology codes including hospitalisation, intensive care unit

admission, invasive mechanical ventilation, acute kidney injury, acute renal failure requiring initiation of renal replacement therapy, death, and a composite outcome of intensive care unit admission, mechanical ventilation, and death.[15–17]

Statistical analysis

Using an online platform for real-time analyses, we undertook exposure score matching (1:1) between the early and late cohorts, incorporating the previously mentioned covariates into the exposure score (analogous to propensity scores) using logistic regression and a greedy nearest neighbour matching algorithm with a caliper of 0·1 pooled SDs.[18] We assessed covariate balance between the exposure score matched cohorts using standardised differences, with a value less than 0·1 indicating minimal differences between groups. We compared the incidences and relative risks (RRs) of these outcomes among the unmatched and exposure score matched cohorts at 30 days after the index date, and we generated cumulative incidence curves of the composite outcome over that timeframe. We did a subgroup analysis restricted to patients with rheumatic and musculoskeletal diseases who were hospitalised within 7 days of diagnosis with COVID-19. Among the hospitalised subgroup, we additionally assessed the use of medications in the 30 days after the index date, including remdesivir, dexamethasone, tocilizumab, and hydroxychloroquine. We did a sensitivity analysis with a washout period between the early and late cohorts and compared patients diagnosed with COVID-19 in the first 60-day period with those diagnosed in the final 60-day period, excluding patients diagnosed in the middle 60-day period. We additionally did a sensitivity analysis restricted to patients with two or more ICD codes for a rheumatic or musculoskeletal disease. For all measures, we calculated 95% CIs. All p-values were two-sided, and the significance level was set at 0·05. Statistical analysis was done through TriNetX Analytics function.

Role of the funding source

There was no funding source for this study. All authors had full access to the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 8540 patients with rheumatic and musculoskeletal diseases who were diagnosed with COVID-19 during the 6-month study period (figure 1), including 2811 in the early cohort and 5729 in the late cohort. 1216 (43·3%) of 2811 patients in the early cohort and 2263 (39·5%) of 5729 patients in the late cohort were diagnosed by confirmed positive PCR testing. The rheumatic and musculoskeletal disease diagnoses (not mutually exclusive) were gout (3295 [38·6%] of 8540 patients), spondyloarthritis (2583 [30·2%] patients), and rheumatoid arthritis (2451 [28·7%] patients), followed by other connective tissue diseases (1469 [17·2%] patients), systemic lupus erythematosus

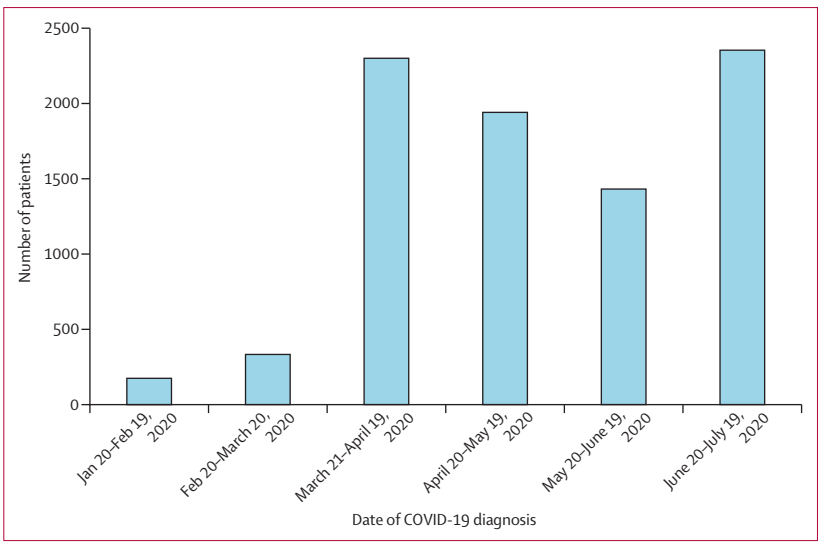

Figure 1: **Timing of COVID-19 diagnosis in patients with rheumatic and musculoskeletal diseases**

(811 [9·5%] patients), and systemic vasculitis (318 [3·7%] patients). The composition was similar between the early and late cohorts (appendix p 1). The mean patient ages were 62 years (SD 16) in the early cohort and 60 years (17) in the late cohort. Patient baseline characteristics are reported in table 1. After exposure score matching, the 2701 patients in each cohort had similar demographics, comorbidities, rheumatic and musculoskeletal disease diagnoses, creatinine, BMI, glucocorticoid use, oral DMARD use, biological DMARD use, and previous hospitalisations (all standardised differences <0·1).

Before matching, the risks of hospitalisation, intensive care unit admission, mechanical ventilation, acute kidney injury, initiation of renal replacement therapy, and death were lower in the late cohort than in the early cohort (table 2). In the exposure score matched analysis, the risk of hospitalisation was lower in the late cohort than the early cohort (874 [32·4%] of 2701 patients *vs* 1227 [45·4%] of 2701 patients; RR 0·71, 95% CI 0·67–0·76). The risks of intensive care unit admission (214 [7·9%] patients *vs* 385 [14·3%] patients; RR 0·56, 95% CI 0·47–0·65), mechanical ventilation (96 [3·6%] patients *vs* 247 [9·1%] patients; 0·39, 0·31–0·49), and death (122 [4·5%] patients *vs* 252 [9·3%] patients; 0·48, 0·39–0·60) were lower in the late cohort than in the early cohort, as was the composite outcome of these three severe COVID-19 outcomes (309 [11·4%] patients *vs* 605 [22·4%] patients; 0·51, 0·45–0·58; figure 2A). The risks of acute kidney injury (372 [13·8%] patients *vs* 560 [20·7%] patients; RR 0·66, 95% CI 0·59–0·75) and acute renal failure requiring the initiation of renal replacement therapy (17 [0·6%] patients *vs* 32 [1·2%] patients; 0·53, 0·30–0·96) were also lower in the late cohort than the early cohort (table 2).

1252 patients with rheumatic and musculoskeletal diseases in the early cohort and 1561 with rheumatic and

	Unmatched cohorts			Exposure score matched cohorts		
	Early cohort (n=2811)	Late cohort (n=5729)	Standardised difference	Early cohort (n=2701)	Late cohort (n=2701)	Standardised difference
Age, years	62 (16)	60 (17)	0·13	62 (16)	62 (16)	0·001
Sex						
Female	1497 (53·3%)	3341 (58·3%)	0·10	1458 (54·0%)	1486 (55·0%)	0·02
Male	1314 (46·7%)	2388 (41·7%)	0·08	1243 (46·0%)	1215 (45·0%)	0·01
Race						
White	1305 (46·4%)	3148 (54·9%)	0·17	1296 (48·0%)	1314 (48·6%)	0·01
African American	890 (31·7%)	1579 (27·6%)	0·09	834 (30·9%)	823 (30·5%)	0·009
Other	616 (21·9%)	1002 (17·4%)	0·10	571 (21·1%)	564 (20·9%)	0·02
Hispanic ethnicity	256 (9·1%)	689 (12·0%)	0·10	255 (9·4%)	260 (9·6%)	0·006
Comorbidities						
Hypertension	1691 (60·2%)	3109 (54·3%)	0·12	1598 (59·2%)	1543 (57·1%)	0·04
Ischaemic heart disease	630 (22·4%)	987 (17·2%)	0·13	573 (21·2%)	568 (21·0%)	0·005
Chronic kidney disease	674 (24·0%)	1053 (18·4%)	0·14	615 (22·8%)	613 (22·7%)	0·002
Diabetes	928 (33·0%)	1608 (28·1%)	0·11	864 (32·0%)	839 (31·1%)	0·02
Asthma or chronic obstructive pulmonary disease	744 (26·5%)	1208 (21·1%)	0·13	681 (25·2%)	681 (25·2%)	<0·0001
Liver disease	262 (9·3%)	445 (7·8%)	0·06	242 (9·0%)	247 (9·1%)	0·006
Malignancy	716 (25·5%)	1122 (19·6%)	0·14	652 (24·1%)	651 (24·1%)	0·0009
Rheumatic disease						
Spondyloarthritis	541 (19·2%)	1017 (17·8%)	0·04	512 (19·0%)	492 (18·2%)	0·02
Rheumatoid arthritis	392 (13·9%)	766 (13·4%)	0·02	376 (13·9%)	357 (13·2%)	0·02
Systemic lupus erythematosus	136 (4·8%)	280 (4·9%)	0·002	130 (4·8%)	119 (4·4%)	0·02
Other connective tissue disease	219 (7·8%)	443 (7·7%)	0·02	210 (7·8%)	183 (6·8%)	0·03
Systemic vasculitis	44 (1·6%)	70 (1·2%)	0·03	41 (1·5%)	36 (1·3%)	0·02
Gout	491 (17·5%)	881 (15·4%)	0·06	468 (17·3%)	427 (15·8%)	0·04
Glucocorticoid use	1457 (51·8%)	2719 (47·5%)	0·09	1371 (50·8%)	1374 (50·9%)	0·002
Oral DMARD use						
Hydroxychloroquine	252 (9·0%)	355 (6·2%)	0·10	204 (7·6%)	212 (7·8%)	0·01
Methotrexate	101 (3·6%)	217 (3·8%)	0·01	97 (3·6%)	88 (3·3%)	0·02
Azathioprine	25 (0·9%)	74 (1·3%)	0·04	25 (0·9%)	29 (1·1%)	0·01
Mycophenolate	142 (5·1%)	209 (3·6%)	0·07	133 (4·9%)	111 (4·1%)	0·04
Leflunomide	36 (1·3%)	71 (1·2%)	0·001	34 (1·3%)	27 (1·0%)	0·02
Cyclosporine	45 (1·6%)	77 (1·3%)	0·07	42 (1·6%)	39 (1·4%)	0·009
Tofacitinib	11 (0·4%)	36 (0·6%)	0·001	11 (0·4%)	12 (0·4%)	0·006
Biological DMARD use						
Adalimumab	31 (1·1%)	71 (1·2%)	0·01	31 (1·1%)	21 (0·8%)	0·04
Etanercept	16 (0·6%)	54 (0·9%)	0·04	16 (0·6%)	15 (0·6%)	0·005
Tocilizumab*	<11	23 (0·4%)	NA	<11	<11	NA
Rituximab	43 (1·5%)	33 (0·6%)	0·09	39 (1·4%)	19 (0·7%)	0·07
Abatacept	13 (0·5%)	28 (0·5%)	0·004	12 (0·4%)	13 (0·5%)	0·005
Body-mass index	31·5 (8·0)	31·6 (8·6)	0·01	31·6 (7·9)	31·4 (8·8)	0·03
Creatinine	1·5 (1·9)	1·3 (1·5)	0·10	1·4 (1·4)	1·4 (1·6)	0·0006
Previous hospitalisation	685 (24·4%)	864 (15·1%)	0·24	585 (21·7%)	606 (22·4%)	0·02

Data are mean (SD) or mean (%). Baseline characteristics were assessed in year prior to the index date. DMARD=disease-modifying antirheumatic drug. NA=not available.
*Per our data-use agreement, we cannot provide exact numbers when there are less than 11 patients in a cell.

Table 1: **Baseline characteristics of early and late cohorts**

musculoskeletal diseases in the late cohort were hospitalised with COVID-19 (table 3; appendix p 2). The mean patient ages were 65 years (SD 16) in the early cohort and 64 years (17) in the late cohort. 596 (47·6%) of 1252 patients were female in the early cohort and 811 (52·0%) of 1561 patients were female in the late cohort. 835 (67·7%) patients in the hospitalised early cohort had hypertension and 953 (61·1%) patients in the hospitalised late cohort

	Unmatched cohorts			Exposure score matched cohorts		
	Early cohort events (n=2811)	Late cohort events (n=5729)	RR (95% CI)	Early cohort events (n=2701)	Late cohort events (n=2701)	RR (95% CI)
Hospitalisation	1309 (46·6%)	1658 (28·9%)	0·62 (0·59–0·66)	1227 (45·4%)	874 (32·4%)	0·71 (0·67–0·76)
Intensive care unit admission	417 (14·8%)	370 (6·5%)	0·44 (0·38–0·50)	385 (14·3%)	214 (7·9%)	0·56 (0·47–0·65)
Mechanical ventilation	257 (9·1%)	171 (3·0%)	0·33 (0·27–0·39)	247 (9·1%)	96 (3·6%)	0·39 (0·31–0·49)
Acute kidney injury	601 (21·4%)	672 (11·7%)	0·55 (0·50–0·61)	560 (20·7%)	372 (13·8%)	0·66 (0·59–0·75)
Renal replacement therapy	34 (1·2%)	38 (0·7%)	0·54 (0·34–0·86)	32 (1·2%)	17 (0·6%)	0·53 (0·30–0·96)
Death	273 (9·7%)	209 (3·6%)	0·38 (0·32–0·45)	252 (9·3%)	122 (4·5%)	0·48 (0·39–0·60)
Composite outcome*	647 (23·0%)	544 (9·5%)	0·41 (0·37–0·46)	605 (22·4%)	309 (11·4%)	0·51 (0·45–0·58)

Data are n (%), unless otherwise indicated. RR=relative risk. *Death, intensive care unit admission, or mechanical ventilation. Exposure score includes all covariates in table 1.

Table 2: **30-day outcomes after COVID-19 diagnosis among patients with rheumatic and musculoskeletal diseases**

had hypertension. The exposure score matched cohorts included 1089 patients each in the early and late cohorts and were similar in terms of demographics, comorbidities, rheumatic and musculoskeletal disease diagnoses, creatinine, BMI, glucocorticoid use, oral DMARD use, and previous hospitalisations (appendix p 2). Tofacitinib and biological DMARDs including adalimumab, etanercept, tocilizumab, rituximab, and abatacept were each used by fewer than 11 patients in the exposure score matched early and late cohorts. We found no differences in the risks of acute kidney injury in the late cohort versus the early cohort or of acute renal failure requiring initiation of renal replacement therapy (table 3). We observed a lower risk of the composite outcome of intensive care unit admission, mechanical ventilation, and death in the late cohort than in the early cohort (334 [30·7%] of 1089 patients *vs* 450 [41·3%] of 1089 patients; RR 0·74, 95% CI 0·67–0·83; table 3; figure 2B).

Among the exposure score matched hospitalised subgroup, in the 30 days after COVID-19 diagnosis, remdesivir was used by 27 (2·5%) patients in the early cohort and 120 (11·0%) patients in the late cohort, and dexamethasone was used by 80 (7·3%) patients in the early cohort and 270 (24·8%) patients in the late cohort. Tocilizumab was used by 42 (3·9%) patients in the early cohort and 32 (2·9%) patients in the late cohort. Use of hydroxychloroquine declined from 473 (43·4%) patients in the early cohort to 112 (10·3%) patients in the late cohort.

In a sensitivity analysis comparing the first 60-day cohort with the last 60-day cohort, we found a lower risk of the composite outcome in the last 60-day period (RR 0·52, 95% CI 0·37–0·71; appendix pp 3–4). Results were similar in an analysis restricted to patients with two or more ICD codes for a rheumatic and musculoskeletal disease (appendix p 4).

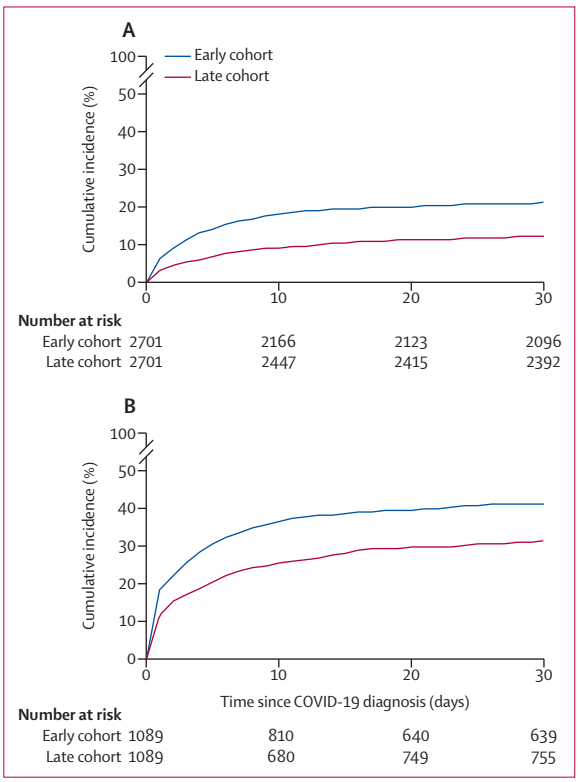

Figure 2: **Cumulative incidence of intensive care unit admission, mechanical ventilation, or death after COVID-19 diagnosis in patients with rheumatic and musculoskeletal diseases**
(A) Overall exposure score matched analysis in early and late cohorts. (B) Hospitalised subgroup exposure score matched analysis in early and late cohorts.

Discussion

In this large, population-based cohort study in the USA, we found improved outcomes for patients with rheumatic and musculoskeletal diseases after COVID-19 diagnosis in more recent months of the pandemic compared with earlier months, including lower risks of death, respiratory failure, and renal failure. This finding is probably multifactorial, due to increased testing capacity allowing for detection of milder cases, improved supportive care, and improved treatments.[1,7,8,19,20] When we restricted our analysis to patients who were hospitalised, and therefore had more similar illness severity, these differences were attenuated, suggesting that some of our observed improvements in the primary analysis could be driven by temporal

	Unmatched cohorts			Exposure score matched cohorts		
	Early cohort events (n=1252)	Late cohort events (n=1561)	RR (95% CI)	Early cohort events (n=1089)	Late cohort events (n=1089)	RR (95% CI)
Intensive care unit admission	387 (30·9%)	357 (22·9%)	0·74 (0·65–0·84)	337 (30·9%)	261 (24·0%)	0·77 (0·67–0·89)
Mechanical ventilation	213 (17·0%)	148 (9·5%)	0·56 (0·46–0·68)	179 (16·4%)	99 (9·1%)	0·51 (0·44–0·70)
Acute kidney injury	493 (39·4%)	538 (34·5%)	0·88 (0·79–0·96)	422 (38·8%)	389 (35·7%)	0·92 (0·83–1·03)
Renal replacement therapy	30 (2·4%)	37 (2·4%)	0·99 (0·62–1·60)	28 (2·6%)	20 (1·8%)	0·72 (0·41–1·27)
Death	199 (15·9%)	154 (9·9%)	0·62 (0·51–0·76)	149 (13·7%)	105 (9·6%)	0·70 (0·56–0·89)
Composite outcome*	532 (42·5%)	463 (29·7%)	0·70 (0·63–0·77)	450 (41·3%)	334 (30·7%)	0·74 (0·67–0·83)

RR=relative risk. *Death, intensive care unit admission, or mechanical ventilation.

Table 3: **30-day outcomes after COVID-19 diagnosis among hospitalised patients with rheumatic and musculoskeletal diseases**

changes in illness severity at the time of COVID-19 diagnosis.

Use of investigational agents for the treatment of COVID-19, including remdesivir[21] and dexamethasone,[22] has increased over time, but these medications were used by a minority of patients with rheumatic and musculoskeletal diseases and were therefore unlikely to have been a major factor contributing to the observed improvement in severe COVID-19 outcomes. We have insufficient data on the use of specific supportive measures such as prone positioning,[23,24] which might have contributed to our findings. Additional studies are needed to understand the effect of specific interventions on severe COVID-19 outcomes in patients with rheumatic and musculoskeletal diseases. We cannot exclude the possibility that other potential temporal changes in the care of patients with COVID-19 could have contributed to our observations. For example, if standards for when to hospitalise or proceed with invasive mechanical ventilation in patients with rheumatic and musculoskeletal diseases and COVID-19 changed over time, this could explain a reduction in those endpoints. However, this hypothesis does not explain our observed improvement in mortality between the early and late cohorts.

Despite the temporal improvements we observed in our study, there continues to be a considerable risk of morbidity and mortality from COVID-19 among patients with rheumatic and musculoskeletal diseases. The risk of death remains substantial, with 5·6% of patients dying within 30 days of a diagnosis of COVID-19 in our study. This death rate is similar to other population-based estimates[1,25] and indicates the ongoing severe nature and guarded prognosis of this illness. Furthermore, among patients with rheumatic and musculoskeletal diseases who were hospitalised with COVID-19 during recent months, more than a third had an acute kidney injury and nearly 30% had intensive care unit admission, invasive mechanical ventilation, or death.

Our findings also indicate that comparison of COVID-19 treatments with a historical reference group might overestimate the efficacy of proposed COVID-19 treatments. Observational studies of therapies for COVID-19 have used historical controls as a reference group—eg, a study of methylprednisolone followed by tocilizumab if needed versus historical care found lower mortality in the methylprednisolone plus tocilizumab group compared with the historical comparator group (hazard ratio 0·35; 95% CI 0·19–0·65).[10] Similarly, a study of colchicine treatment versus a historical comparator showed a lower risk of death with colchicine use compared with the historical standard of care (hazard ratio 0·15, 95% CI 0·06–0·37).[11] These results must be interpreted in the context of improving temporal trends.

Our study has several limitations. As with all observational studies using electronic health record databases, there might be misclassification, for example, inaccuracies in ICD code documentation. Secular trends in ICD-10 documentation (with the approval of U07.1 as an ICD-10 code specific for COVID-19 on April 1, 2020) and availability and performance characteristics of molecular testing for COVID-19 are a potential limitation of this study. Although we adjusted for many confounders, residual confounding might exist. Outcomes could have been incompletely captured for patients who received subsequent care outside the multicentre network. However, we would not expect these limitations to have different effects on the early and late cohorts. We do not have information on the geographical locations of patients because of privacy requirements, and different regions of the USA might have had variable access to COVID-19 testing and treatments. Additionally, although we included glucocorticoid use in the exposure score, we did not have information on glucocorticoid dose, and previous studies have found an increased risk of adverse COVID-19 outcomes associated with higher doses of glucocorticoids.[4,26] This study had multiple endpoints, and we did not correct for multiplicity in our estimation of type 1 error. However, the consistent findings across all endpoints in our primary analysis support the validity of our findings. Despite these limitations, our study has several strengths. The multicentre electronic health record database allows for broad geographical representation across academic and community settings in the USA, supporting the generalisability of the temporal trends observed in this study. Additionally, the real-time updated data from the

multicentre network allows for timely analysis of population-level trends.

In conclusion, we have shown lower risks of respiratory failure, renal failure, and death after COVID-19 diagnosis in patients with rheumatic and musculoskeletal diseases in more recent months compared with the earlier months of the ongoing pandemic in the USA. However, risks of severe COVID-19 outcomes remain substantial. Major improvements in prevention and treatment are urgently needed to reduce the overall burden of COVID-19 among patients with rheumatic and musculoskeletal diseases in the USA.

Contributors

AJ and KMD conceived the study, did the literature search, and did the data analysis. AJ and KMD accessed and verified the underlying data. AJ generated the figure. All authors drafted the Article and made critical revisions. All authors contributed to the study design and data interpretation and approved the final version of the Article.

Declaration of interests

AC is employed by TriNetX Research. ZSW receives consulting fees from Viela Bio and grant support from Bristol Myers Squibb and is on the steering committee of the COVID-19 Global Rheumatology Alliance. HKC receives research support from AstraZeneca and consultancy fees from Takeda, Selecta, GlaxoSmithKline, and Horizon. All other authors declare no competing interests.

Data sharing

Data for this study are not publicly available because of a data-use agreement. For requests to access to the study data, please contact the corresponding author.

Acknowledgments

AJ receives funding from the Rheumatology Research Foundation (Scientist Development Award) and the National Institutes of Health (NIH) Loan Repayment Program. NM is supported in part by a Fellowship Award from the Canadian Institutes of Health Research. KMD is supported in part by the Ruth L Kirschstein Institutional National Research Service Award (T32-AR-007258). ZSW receives funding from NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases (K23-AR-073334). YZ and HKC are supported in part by NIH P60-AR-047785.

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