EPIDEMIOLOGICAL SCIENCE

Clinical outcomes of hospitalised patients with COVID-19 and chronic inflammatory and autoimmune rheumatic diseases: a multicentric matched cohort study

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ABSTRACT

Objectives The impact of inflammatory rheumatic diseases on COVID-19 severity is poorly known. Here, we compare the outcomes of a cohort of patients with rheumatic diseases with a matched control cohort to identify potential risk factors for severe illness.

Methods In this comparative cohort study, we identified hospital PCR+COVID-19 rheumatic patients with chronic inflammatory arthritis (IA) or connective tissue diseases (CTDs). Non-rheumatic controls were randomly sampled 1:1 and matched by age, sex and PCR date. The main outcome was severe COVID-19, defined as death, invasive ventilation, intensive care unit admission or serious complications. We assessed the association between the outcome and the potential prognostic variables, adjusted by COVID-19 treatment, using logistic regression.

Results The cohorts were composed of 456 rheumatic and non-rheumatic patients, in equal numbers. Mean age was 63 (IQR 53–78) years and male sex 41% in both cohorts. Rheumatic diseases were IA (60%) and CTD (40%). Most patients (74%) had been hospitalised, and the risk of severe COVID-19 was 31.6% in the rheumatic and 28.1% in the non-rheumatic cohort. Ageing, male sex and previous comorbidity (obesity, diabetes, hypertension, cardiovascular or lung disease) increased the risk in the rheumatic cohort by bivariate analysis. In logistic regression analysis, independent factors associated with severe COVID-19 were increased age (OR 4.83; 95% CI 2.78 to 8.36), male sex (1.93; CI 1.21 to 3.07) and having a CTD (OR 1.82; CI 1.00 to 3.30).

Conclusion In hospitalised patients with chronic inflammatory rheumatic diseases, having a CTD but not IA nor previous immunosuppressive therapies was associated with severe COVID-19.

Key messages

What is already known about this subject?

- There is limited evidence on the outcomes of COVID-19 in patients with rheumatic diseases and the impact of age, comorbidity, therapy or other factors associated to severity specifically in these patients.

What does this study add?

- We found that severe COVID-19 occurred in 31.6% of the rheumatic and 28.1% of non-rheumatic cohorts.
- Having a connective tissue disease but not its therapy was significantly associated with severe COVID-19.
- Other known risk factors as ageing or male sex also apply to patients with rheumatic diseases.

How might this impact on clinical practice or future developments?

- These findings have important implications to guide COVID-19 recommendations to specific groups of patients with rheumatic diseases and to provide evidence-based advice on the importance of maintaining therapies.

INTRODUCTION

The clinical spectrum of SARS-CoV-2 infection is quite broad, ranging from asymptomatic to life-threatening or fatal disease. Different factors have been associated with poor prognosis, including older age, gender and pre-existing comorbidities such as diabetes, hypertension and lung and cardiovascular disease.[1–3] Immune-mediated diseases and immunosuppressive therapies increase the susceptibility to viral and bacterial infections, and therefore, understanding how COVID-19 impacts on these patients is an urgent need.[4–6]

Since severe COVID-19 is associated with a hyperinflammatory process, it is of particular interest to investigate how pre-existing inflammatory diseases or the previous use of immunosuppressive agents influence COVID-19 expression.[7] We have previously reported an increased prevalence of hospital attended COVID-19 in patients with connective tissue diseases (CTDs) and in patients treated with targeted synthetic or biologic disease-modifying antirheumatic drug (ts/bDMARD) therapy compared with a reference population, reflecting

either increased risk of infection or increased severity.[8] In the largest COVID-19 series, neither CTD nor immunosuppressive therapies were represented, but incompleteness of information on these specific factors is possible.[1–3] In a recent report of a small cohort of hospitalised patients with rheumatic diseases, a higher need for mechanical ventilation compared with non-rheumatic controls was found, whereas in another similar series no differences with controls were found.[9 10] A global registry of patients with rheumatic diseases found glucocorticoids (GCs) but not other therapies associated with a higher risk for hospitalisation.[11] In patients with inflammatory bowel disease, GC but not anti-tumour necrosis factor-α (anti-TNF-α) drugs independently increase the risk of severe disease.[12] Other immunosuppressed patients, as solid organ transplanted, have more severe COVID-19; however, the role of age or comorbidities and the lack of controls do not permit to draw definitive conclusions.[13 14]

An additional concern among rheumatologists is that in most chronic inflammatory rheumatic diseases, clinical and subclinical metabolic and cardiovascular comorbidity is increased, which may also put these patients at higher risk of poor outcomes.[15 16] It is therefore necessary for contingency prevention plans to identify vulnerable patients and specific features at high risk requiring special vigilance or management.

We undertook a multicentric comparative cohort study to investigate the relationship between underlying rheumatic disease and COVID-19 outcomes and to identify specific risk factors associated with poor outcomes.

PATIENTS AND METHODS

We performed a retrospective observational matched cohort study from the databases of five reference centres pertaining to a public research network for the investigation of inflammation and rheumatic diseases (RIER, https://red-rier.org/). Each of the included centres has accessibility to updated medical record ID lists of adult patients under follow-up in rheumatology departments and was a reference centre for microbiology, where all SARS-CoV-2 PCR diagnostic tests in the covered population were performed. Patients' medical record IDs were matched against central SARS-CoV-2+PCR hospital registers up to 17 April, just after the incidence peak of SARS-CoV-2 infection had been reached in Spain (https://cnecovid.isciii.es/COVID-19). Electronic medical records were reviewed to confirm COVID-19 diagnosis and to obtain clinical data. Since at that time, availability of CoV-2 PCR testing was limited due to shortages, these registries only include patients attending referral hospitals and exclude the less severe community cases that did not require hospitalisation nor referral to hospitals' emergency departments.

The rheumatology cohort included all adult patients diagnosed with chronic inflammatory arthritis (IA), including rheumatoid arthritis, psoriatic arthritis (PsA) and spondyloarthritis (SpA); CTD, including systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), systemic sclerosis, polymyalgia rheumatica (PMR), vasculitides and so on (online supplementary table S1) with a PCR+COVID-19 diagnosis. The control cohort was assembled from the Microbiology databases of the participating centres matched on a 1:1 basis with the rheumatic cohort on the date of COVID-19 diagnosis ('index date'), sex and age, and blinded to outcome or other variables. In this control cohort, patients with CTD were excluded.

Variables and measurements

We collected the following data from the electronic health record to describe COVID-19 evolution: evidence of pneumonia by plain X-ray, respiratory insufficiency, oxygen necessities (collected as ordinal variable ranging from 0 'no external oxygen required', to 1 'oxygen by nasal cannula', 2 'reservoir', 3 'non-invasive ventilation' and 4 'tracheal intubation'), serious complications (including myocarditis or heart failure, encephalopathy, thrombosis, kidney failure and septic shock as defined in online supplementary information), duration of admission and death. Laboratory data were also collected at baseline and at peak levels for the following variables: C reactive protein (CRP), interleukin-6 (IL-6), lymphocyte counts, D-dimer, lactate dehydrogenase and ferritin.

The primary outcome was a composite outcome, 'severe COVID-19', including death, intensive care unit admission, intratracheal intubation or serious COVID-19 complications as previously enumerated. The definitions of these complications are described in online supplementary information.

Factors studied in relation to the outcome were those common to all patients with COVID-19, such as age (with a

Table 1 Description of the cohorts compared

Characteristics	n	Non-rheumatic n=228	Rheumatic n=228	P value
Age, median (IQR)	456	65 (53–77)	63 (54–78)	0.865
Age >60 years	456	132 (57.9)	127 (55.7)	0.636
Male sex	456	95 (41.7)	87 (38.2)	0.444
Comorbidity				
Obesity	451	38 (16.6)	71 (31.7)	<0.001
Diabetes	456	39 (17.1)	46 (20.2)	0.400
Hypertension	455	99 (43.4)	111 (48.9)	0.241
Cardiovascular disease	455	42 (18.4)	64 (28.2)	0.014
Lung disease	455	48 (21.1)	45 (19.8)	0.745

Values in cells represent n (%) unless otherwise indicated.

Table 2 Baseline therapies of patients with rheumatic diseases

Treatment	n (%)
Glucocorticoids	91 (40.1)
Dose*, m±SD when taken	9.9±11.5
>10 mg/day prednisone equivalent	15 (6.6)
csDMARD	129 (56.6)
Methotrexate	64 (28.1)
Antimalarial drugs	28 (12.4)
Leflunomide	20 (8.9)
Sulfasalazine	17 (7.5)
Other immunosuppressants	28 (12.3)
Mofetil mycophenolate	12 (5.3)
Azathioprine	7 (3.1)
Cyclophosphamide	2 (0.8)
Calcineurin inhibitors	7 (3.1)
ts/bDMARD	53 (23.2)
TNF-α antagonists	35 (15.4)
Rituximab	5 (2.2)
IL-17/IL-23 antagonists	4 (1.8)
Abatacept	3 (1.3)
Tocilizumab	2 (0.8)
Sarilumab	1 (0.4)
Tofacitinib	3 (1.3)

*In mg/day of prednisone equivalents.
csDMARD, conventional synthetic disease-modifying antirheumatic drug; IL, interleukin; TNF, tumour necrosis factor; ts/bDMARD, targeted synthetic or biological disease-modifying antirheumatic drug.

cut-off at 60 years), male sex, cardiovascular disease, obesity, diabetes, hypertension and lung disease. Specific factors for rheumatic diseases included diagnostic group, disease duration, treatments—such as GCs, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), other immunosuppressants (including azathioprine, cyclophosphamide, mofetil mycophenolate and calcineurin inhibitors), or ts/bDMARD, including Jakinibs (tofacitinib or baricitinib), or any biological agents (TNF-α, IL-1, IL-6 or IL-23/IL-17 antagonists, abatacept or rituximab). COVID-19 treatment was also collected and treated as potentially confounding covariate. The most commonly used treatments were hydroxychloroquine, antivirals (lopinavir/ritonavir and remdesivir), GC and anticytokines. We used summary statistics to describe the cohorts, and t tests, χ^2, Fisher's exact and log rank tests to refute hypothetical differences between them. For time to variables, we used 15 May as censor date.

We then estimated the risk of developing severe COVID-19 in each cohort, in terms of point estimates and 95% CIs, risk difference, risk ratio and attributable fractions for the rheumatic and total population. The relative risk of prognostic factors was estimated, and the hypothesis of an effect modification of having a CTD rheumatic disease tested with the Mantel-Haenszel method.

Subsequently, we run bivariable and multivariable logistic regression models to assess the association between rheumatic diseases and severe COVID-19 in detail, where the composite outcome was the dependent variable. We used several approaches to building the models: (1) using the *allsets* command, (2) automatic backward stepwise starting with a full model with all variables with a p value <0.25 in the bivariable and (3) a manual stepwise method, keeping cohort and confounding variables in the model. The best model was selected on the basis of the Akaike information criterion and the Bayesian information criterion, and the area under the receiver operating characteristic (ROC) curve and predictive capacity of the best model estimated as described.[17] All analyses were done in Stata V.12.

All data were anonymised.

RESULTS

The total sample was 456, evenly distributed into 228 patients per cohort. The diagnoses of patients with rheumatic diseases were IA (n=136, 60%): RA (n=65, 29%), SpA (n=35, 16%), PsA (n=36, 15%) and CTD (92, 40%) as detailed in online supplementary table S1. The mean duration of the rheumatic disease was 10 years (SD 8.3) with no differences across diseases.

Table 1 shows a description of both cohorts. These were matched in terms of age and sex, and well balanced regarding most other variables. However, clinician-reported only refers to obesity, and cardiovascular disease were more frequent among patients with rheumatic diseases versus controls.

Regarding treatments previously used by patients with rheumatic diseases that could predispose them to infection, most patients were on csDMARDs (57%), followed by GCs (40%), biologic agents (23%), mostly TNF-α antagonists and 12% on other immunosuppressants (table 2) before the onset of COVID-19 symptoms. In most patients (86%) on any immunosuppressant therapy but GC, including methotrexate and leflunomide among csDMARD or any ts/bDMARD (n=125 with this information available), it was withdrawn either at symptom onset or at hospital admission. Physician-reported activity of the different rheumatic diseases (active or on remission) by diagnostics is described in online supplementary table S1.

Table 3 Description of evolution and therapy of COVID-19 in the compared cohorts

COVID-19 evolution	n	Non-rheumatic n=228	Rheumatic n=228	P value
No days before PCR+*	428	7.9±6.0	7.0±6.4	0.117
Radiographic pneumonia	443	183 (83.2)	154 (69.1)	<0.001
Hospitalisation	455	175 (77.1)	162 (71.1)	0.142
Duration of hospital stay*	267	12.6±10.0	12.0±8.7	0.626
Respiratory insufficiency	455	143 (62.7)	128 (56.4)	0.169
ICU admission	453	16 (7.1)	15 (6.7)	0.882
Respiratory category	453			0.103
No oxygen was necessary		96 (42.1)	100 (44.4)	
Oxygen by nasal cannula		99 (43.4)	103 (45.8)	
Oxygen with reservoir		14 (6.1)	3 (1.3)	
Non-invasive ventilation		13 (5.7)	11 (4.9)	
Invasive ventilation		6 (2.6)	8 (3.6)	
Significant complications	452	55 (24.1)	63 (28.1)	0.333
Heart failure	448	4 (1.8)	11 (5.0)	0.056
Encephalopathy	449	8 (3.5)	3 (1.4)	0.140
Thrombotic event	448	6 (2.6)	6 (2.7)	0.962
Kidney failure	449	32 (14.0)	30 (13.6)	0.888
Septic shock	447	11 (4.8)	15 (6.9)	0.361
Death	455	30 (13.2)	41 (18.1)	0.150
Days from first symptom*	431	52.0±17.9	47.6±19.5	0.191
Severe COVID-19†	456	64 (28.1)	72 (31.6)	0.413
Laboratory tests (peak value)*				
C reactive protein (mg/dL)	386	12.5±12.0	11.0±10.1	0.199
IL-6 (µg/mL)	87	496±1990	134±8535	0.268
Lymphocytes (cells/µL)	386	903±480	993±1586	0.445
D-dimer (µg/L)	291	2356±5605	2505±10 769	0.883
Serum creatinine (mg/dL)	375	1.0±0.7	1.2±1.1	0.030
Lactate dehydrogenase (U/L)	355	390±210	377±174	0.558
Ferritin (µg/L)	207	1056±1098	1201±2244	0.551
COVID-19 therapy				
Hydroxychloroquine	450	172 (76.1)	157 (70.1)	0.150
Azithromycin	450	128 (56.6)	103 (46.0)	0.024
Antivirals				
Lopinavir/ritonavir	449	94 (41.8)	86 (38.4)	0.464
Remdesivir	450	2 (0.9)	2 (0.9)	0.685
Glucocorticoids	449	53 (23.5)	57 (25.6)	0.603
Anticytokines	456	24 (10.5)	16 (7.1)	0.185
IL-6 inhibitors	448	22 (9.8)	15 (6.7)	0.241
IL-1 inhibitors	449	2 (0.9)	3 (1.4)	0.684
Jakinibs	450	1 (0.4)	1 (0.5)	1.000
Intravenous immunoglobulin	449	–	1 (0.5)	0.314

Values in cells represent n (%) unless otherwise indicated.
*Mean±SD.
†Death, ICU admission or serious COVID-19 complication.
ICU, intensive care unit; IL, interleukin.

No patient in the non-rheumatic cohort was taking any of these drugs, except for a patient who was taking GC at a dose of 5 mg/day for other reasons.

The evolution of the COVID-19 disease and its comparison between cohorts are described in table 3. The bivariable analysis shows a larger proportion of radiographic pneumonia in the non-rheumatic cohort and a non-statistically larger proportion of heart failure and higher peak serum creatinine in the rheumatic cohort. All other variables measured were similar between groups, which were also treated with similar COVID-19 drugs, with the exception of a non-statistically significant larger use of azithromycin in the non-rheumatic cohort.

Table 4 Analysis of individual risk factors for poor outcome: total and by cohort

Variable	Relative risk (95% CI) Non-rheumatic cohort	Rheumatic cohort	P value*
Age over 60 years	**3.70 (1.99 to 6.93)**	**4.04 (2.30 to 7.08)**	0.841
Male sex	**2.16 (1.39 to 3.35)**	**1.58 (1.09 to 2.29)**	0.286
Obesity	1.22 (0.72 to 2.06)	**1.62 (1.10 to 2.36)**	0.393
Diabetes	0.95 (0.53 to 1.70)	**1.93 (1.34 to 2.79)**	0.038
Hypertension	**1.64 (1.07 to 2.53)**	**2.27 (1.49 to 3.46)**	0.290
CV disease	1.44 (0.90 to 2.33)	**2.92 (2.04 to 4.17)**	0.020
Lung disease	**1.57 (1.00 to 2.46)**	**1.74 (1.19 to 2.55)**	0.723

Bold values indicate statistically significant associations with outcome.
*From a Mantel-Haenszel test of homogeneity. If p<0.01, the cohort of origin is modifying the effect.
CV, cardiovascular.

The risk of a severe COVID-19 was 28.1% in the non-rheumatic cohort and 31.6% in the rheumatic cohort, that is, a risk difference of 3.5% (95% CI −4.9% to 11.9%), a risk ratio of 1.13 (95% CI 0.84 to 1.49), an attributable fraction of the exposed of 11.1% and in the population of 5.9% (p=0.413).

Table 4 shows the relative risk of variables common to both cohorts, by cohort. Age ≥60 years and all comorbid variables were associated with outcome in the rheumatic cohort, but only age, hypertension and lung disease in the non-rheumatic cohort. No clear effect modification of the cohort on the associations was present, as by the results of the homogeneity test.

The results of the bivariable and multivariable logistic regression analysis are shown in table 5. Variables with very low observations were not analysed or combined into meaningful categories. The best model was the stepwise automatic one, in which specific variables were forced in (obesity, diabetes, heart failure and GCs) to adjust results for, and its results are shown in the right part of the table and in figure 1. The model correctly classified 72.23% of the patients (area under the ROC curve=0.753).

Table 5 Association of risk factors with poor outcome in COVID-19

Factors	OR (95% CI) Bivariable	P value	OR (95% CI) Multivariable	P value
Rheumatic disease	1.29 (0.86 to 1.93)	0.218		
CTD	1.64 (1.02 to 2.66)	0.042	1.82 (1.00 to 3.30)	0.050
Chronic IA	0.90 (0.58 to 1.41)	0.659		
Age >60 years	6.06 (3.65 to 10.06)	<0.001	4.83 (2.78 to 8.37)	<0.001
Male sex	2.34 (1.55 to 3.53)	<0.001	1.93 (1.21 to 3.07)	0.006
Comorbidity				
Obesity	1.78 (1.13 to 2.81)	0.013	1.47 (0.86 to 2.51)	0.164
Diabetes	1.81 (1.11 to 2.95)	0.018	0.82 (0.46 to 1.46)	0.493
Hypertension	2.60 (1.72 to 3.94)	<0.001		
Heart failure	3.49 (2.21 to 5.51)	<0.001	1.57 (0.93 to 2.66)	0.092
Lung disease	2.15 (1.34 to 3.45)	0.001		
Medication				
Glucocorticoids (any dose)	2.20 (1.36 to 3.54)	0.001	1.10 (0.60 to 2.01)	0.755
HCQ	1.15 (0.51 to 2.62)	0.733		
csDMARDs	1.04 (0.64 to 1.72)	0.864		
ts/bDMARDs	0.45 (0.21 to 0.96)	0.039		
Other IS	0.99 (0.40 to 2.44)	0.981		
COVID-19 drugs used				
HCQ	2.26 (1.35 to 3.79)	0.002		
Antivirals	2.37 (1.58 to 3.59)	<0.001	2.05 (1.30 to 3.23)	<0.001

csDMARD, conventional synthetic disease-modifying antirheumatic drug; CTD, connective tissue disease; HCQ, hydroxychloroquine; IA, inflammatory arthritis; IS, immunosuppressants; ts/bDMARD, targeted synthetic or biological disease-modifying antirheumatic drug.

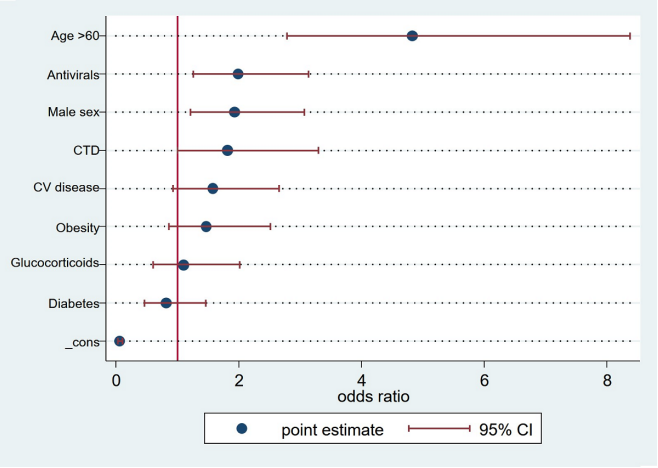

Figure 1 ORs with 95% CIs of the best fitted model to predict 'severe COVID-19', adjusted for selected comorbidities and glucocorticoids use. CV, cardiovascular; CTD, connective tissue disease.

An independent association between CTD (OR 1.82; CI 1.00 to 3.30), age (OR 4.83; CI 2.78 to 8.37) and male sex (OR 1.93; CI 1.21 to 3.07) with higher risks for the composite severe COVID-19 outcome was found, whereas all other factors such as IA, comorbidities and active antirheumatic therapies were not confirmed in the multivariable adjusted analysis. A higher use of antivirals also remained associated to severity.

Since IA, and particularly CTD, include a heterogeneous group of patients with different diagnostics, we performed a subanalysis of groups with more homogeneous categories in terms of clinical or pathophysiological characteristics. By multivariable analysis, these four groups: SpA (including PsA); RA; SLE, SS and primary antiphospholipid syndrome (PAPS); and PMR, giant cell arteritis (GCA) and vasculitis showed a similar association as IA or CTD groups where they had been included (online supplementary tables S2 and S3).

DISCUSSION

In this matched cohort study, we show that among hospital patients with chronic inflammatory rheumatic diseases, having a systemic CTD but not an IA is an independent risk factor for poor COVID-19 outcomes. Comorbidities associated with severe COVID-19 in the general population are also associated with greater risk to these patients by bivariable analyses.[1–3 15] This is of particular interest because some of them as cardiovascular disease or obesity are also associated with inflammatory disease as shown in our cohort.[16 18] However, there was no independent association between these morbidities and severity in the fully adjusted multivariable analysis, suggesting some collinearity mainly with ageing and also with inflammatory disease.

Our data are in agreement with a previous study in a smaller COVID-19 hospitalised cohort, which identified a higher odds of intensive care admission/mechanical ventilation among hospitalised patients with rheumatic diseases versus matched controls.[9] In contrast with ours, this study combined all patients with IA and CTD. Our data illustrate how IA and CTD groups carry a different risk for severe COVID-19. Whether specific diagnostics within the heterogeneous CTD group may have a different risk cannot be ruled out. Our subanalysis of different groups such as vasculitides (including PMR/GCA) and SLE and related

conditions showed similar associations with severe COVID-19 but further analyses would be needed to more precisely evaluate the severity of specific CTD.

Concerning previous use of therapies by patients with rheumatic diseases, the use of GC was associated with poorer outcome by bivariable analysis, whereas no substantial risk was detected neither for traditional immunosuppressants nor csDMARDS (methothrexate and leflunomide), nor for ts/bDMARD (mostly anti-TNF-α). Interestingly, the use of ts/bDMARD was associated in the bivariable with lower odds of complications. They did not make it into the final models probably because of the collinearity with other variables and not being the full rheumatic sample included, thus encountering problems of statistical power.

The potential therapeutic effect of anticytokine biologicals and Jakinibs on COVID-19 is being tested through numerous observational and randomised trials.[19] Since most of these drugs have long-term immunological effects even if withdrawn, their previous use in patients with rheumatic diseases might have a different influence on COVID-19 evolution than their use as therapy for COVID-19 acute inflammatory complications in non-rheumatic patients. In our previous analysis of the prevalence of hospital PCR+cases in patients with rheumatic diseases and the general population, a higher prevalence was observed in ts/bDMARD but not csDMARD-treated patients.[8] Therefore, our observations regarding ts/bDMARD should be considered with caution because we cannot exclude the possibility of confounding by indication of the therapies in the different included diseases, that is, the preferential use of ts/bDMARD in IA. Larger cohorts of patients treated with these drugs or meta-analysis are warranted to clarify the real impact of ts/bDMARD on COVID-19 susceptibility or severity in patients with rheumatic diseases.

Our study has additional limitations. Our conclusions are limited to hospitalised cases, excluding a large proportion of patients with rheumatic diseases with less severe COVID-19. As patients with rheumatic diseases and matched controls were selected on the same date, we do not expect to have selection bias on the initial patient's and control profiles.

Also, the role of the use of antivirals remains unclear. Although it was associated with worse outcome, a strong bias by its indication for the most severe patients seems the most plausible interpretation, since the most used drug (lopinavir/ritonavir) has resulted neither efficacious nor deleterious in randomised trials.[20]

Since ageing and having a CTD are the most relevant risk factors for severe COVID-19 in patients with rheumatic disease, shared immune-pathogenetic factors that might modify defensive and inflammatory responses need to be identified. Exhaustion of adaptive T-cell responses and increased effector inflammatory responses associated to accumulation of senescent cells, termed inflammaging, have been identified in both situations.[21–23] In experimental models of murine coronavirus infection, biological ageing induced by telomere dysfunction is also associated with lethality and higher cytokine responses.[24] In our cohorts, additional differences between rheumatic and control patients in the expression of COVID-19 were not detected. Despite the proinflammatory background of patients with CTD, the biological response to the infection is similar to that of controls in most studies.[9 10] This suggests that the severity is not necessarily related to quantitative differences in the cytokines response (ie, IL-6/CRP) and additional factors should be searched for.

In conclusion, among hospitalised patients with inflammatory rheumatic diseases, having a CTD pose a significantly greater risk for poor outcomes, whereas immunosuppressive therapies do not. Previously known risk factors as ageing and male sex also apply to patients with rheumatic diseases. This observation should help to tailor recommendations to specific diagnostic and therapeutic groups of patients with rheumatic diseases during this or future coronavirus pandemics.

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Data availability statement Data are available upon reasonable request. Individual de-identified patient data will made available to researchers who provide a reasonable and methodologically sound proposal. Proposals should be directed to the corresponding author.

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