EPIDEMIOLOGICAL SCIENCE

Prevalence of hospital PCR-confirmed COVID-19 cases in patients with chronic inflammatory and autoimmune rheumatic diseases

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ABSTRACT

Background The susceptibility of patients with rheumatic diseases and the risks or benefits of immunosuppressive therapies for COVID-19 are unknown.

Methods We performed a retrospective study with patients under follow-up in rheumatology departments from seven hospitals in Spain. We matched updated databases of rheumatology patients with severe acute respiratory syndrome coronavirus 2-positive PCR tests performed in the hospital to the same reference populations. Rates of PCR+ confirmed COVID-19 were compared among groups.

Results Patients with chronic inflammatory diseases had 1.32-fold higher prevalence of hospital PCR+ COVID-19 than the reference population (0.76% vs 0.58%). Patients with systemic autoimmune or immune-mediated disease (AI/IMID) showed a significant increase, whereas patients with inflammatory arthritis (IA) or systemic lupus erythematosus did not. COVID-19 cases in some but not all diagnostic groups had older ages than cases in the reference population. Patients with IA on targeted-synthetic or biological disease-modifying antirheumatic drugs (DMARDs), but not those on conventional-synthetic DMARDs, had a greater prevalence despite a similar age distribution.

Conclusion Patients with AI/IMID show a variable risk of hospital-diagnosed COVID-19. Interplay of ageing, therapies and disease-specific factors seem to contribute. These data provide a basis to improve preventive recommendations to rheumatic patients and to analyse the specific factors involved in COVID-19 susceptibility.

Key messages

What is already known about this subject?

- The susceptibility of patients with rheumatic diseases and the risks or benefits of immunosuppressive therapies for COVID-19 are unknown.

What does this study add?

- This study shows that there is an increased rate of hospital COVID-19 cases associated with some but not all chronic inflammatory or autoimmune conditions compared with the reference population.
- The risks seem to depend on age, the specific disease and previous therapies; remarkably increased rates were observed in biologic or targeted synthetic but not in conventional disease-modifying antirheumatic drug-treated patients.

How might this impact on clinical practice or future developments?

- These data may be translated to current recommendations regarding alert on infection risk and prevention measures in rheumatic patients.
- The observed differences will hopefully contribute to future studies to identify the risk factors for COVID-19 in different patients' groups.

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INTRODUCTION

The severe lung and systemic inflammatory manifestations observed in severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) infection have led to the hypothesis of a hyperinflammatory mechanism, more dependent on the host response than on direct viral cellular damage.[1 2] Certain parallelisms with other cytokine storm situations, such as macrophage activation syndrome or chimeric antigen receptor T-cell-associated systemic inflammatory syndromes have been invoked in support. This hypothesis has prompted the rapid introduction of anti-inflammatory and immunomodulatory agents approved for rheumatic diseases in the therapeutic strategies to combat SARS-CoV-2 infection.

The prevalence of severe SARS-CoV-2 infection in patients with previous autoimmune or inflammatory diseases is unknown. This group of patients is not represented in the largest Chinese series as a specific risk factor for susceptibility or severity of COVID-19.[3 4] An excess of morbimortality associated with the previous use of conventional or

targeted immunosuppressive drugs has neither been reported. However, in an Italian series of 1591 patients with severe COVID-19 admitted to the ICU, the most prevalent comorbidity in patients under 40 years old was a miscellanea of patients that included inflammatory and immunosuppressed patients.[5]

A potential preventive or therapeutic effect of certain immunomodulatory therapies in these patients has been hypothesised. Among them, antimalarials, colchicine, corticosteroids, jakinibs and interleukin (IL)-6 or IL-1 antagonists are being used under special conditions or clinical trials with weak evidence.[6] However, the risks of these drugs in the context of viral infections without concomitant antiviral therapies are not negligible.[7–9] Whether immunosuppressants put patients with rheumatic disease at an increased or decreased risk for severe COVID-19 is unknown, and evidence is urgently needed to guide prevention and therapy.[10 11]

Since timely obtaining methodologically rigorous data on the prevalence of severe SARS-CoV-2 infection in our patients under different therapies is challenging at this moment,[8] we have performed an exploratory analysis of the relative prevalence of hospital-diagnosed COVID-19 in large multicentric cohorts of rheumatic patients under follow-up.

PATIENTS AND METHODS

We performed a retrospective observational study with patients under follow-up in rheumatology departments from reference hospitals in Spain. We selected seven centres pertaining to a public Research network for the Investigation of Inflammation and Rheumatic Diseases (RIER), by the availability of updated medical records ID lists of adult patients under follow-up in rheumatology departments, diagnosed with chronic inflammatory arthritis (IA) or systemic autoimmune or immune-mediated disease (AI/IMID), including: rheumatoid arthritis (RA), psoriatic arthritis (PsA), spondyloarthritis (SpA), systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), systemic sclerosis (SSc), polymyalgia rheumatica or giant cell arteritis (PMR-GCA) and other diseases (including systemic vasculitis, Behcet's syndrome, sarcoidosis and inflammatory myopathies). We also obtained updated ID lists of patients with IA on therapy with only conventional synthetic disease-modifying antirheumatic drugs (csDMARD), specifically methotrexate or leflunomide, or with targeted synthetic disease-modifying antirheumatic drug (tsDMARD) or biological disease-modifying antirheumatic drug (bDMARD), including jakinibs or any biological agent. Not all groups have databases of all diagnostic or therapeutic categories. Only complete datasets allowing calculation of incident/total number of cases in a particular category were included for the aggregated analysis.

Selected centres were also microbiology reference centres where all SARS-CoV-2 PCR diagnostic tests in the covered adult population were performed. Patients' medical record IDs were matched against central SARS-CoV-2+ PCR hospital registers between 7 and 17 April, after the incidence peak of SARS-CoV-2 infection had been reached in Spain. Medical records were reviewed to confirm clinical COVID-19 diagnosis. Since SARS-CoV-2 PCR availability was limited, these registries include only patients attending referral hospitals and exclude the less severe community cases that did not require hospitalisation nor referral to hospitals emergency departments.

Data are reported as rates in the different groups and compared with the rates in the general reference population by ORs with 95% CIs and χ^2 tests. Median age in the different groups was compared by non-parametric tests.

RESULTS

The reference population in the participating hospitals was 2.9 million people, with a global prevalence of PCR+ SARS-CoV-2 of 0.58%. In the different centres, it varied from 0.23% to 1.16%, consistently with the reported prevalence in the different regions of Spain (https://cnecovid.isciii.es/covid19/). We screened a total of 26.131 patients under follow-up in rheumatology departments for hospital positive SARS-CoV-2 PCR results in their reference hospitals and found a higher prevalence of PCR+ cases (0.76%; OR 1.3, CI 1.15% to 1.52%) compared with the reference population, with a similar regional variation from 0.23% to 1.24%. Although we cannot calculate the age-adjusted rates due to lack of age information of PCR-negative cases, PCR+ cases in a representative sample (n=3800) of the reference population had a median younger age than rheumatic disease cases (55 vs 65 years old, p<0.0001). Age and sex distributions are shown in table 1.

Patients with IA (RA, PsA and SpA) showed a prevalence similar to that in the reference population, but in the SpA subset, it was increased by 1.54-fold (CI 1.11 to 2.13). Among this group, patients with IA on therapy with csDMARD (methotrexate or leflunomide) also showed a similar prevalence, whereas patients on tsDMARD/bDMARD therapy showed a 1.60-fold (CI 1.23 to 2.10) increased prevalence of COVID-19 compared with the reference population (table 1 and figure 1).

All aggregated groups of patients with AI/IMID showed higher rates of COVID-19, and analyses of the different groups confirmed increased prevalence in all diagnostic groups but SLE, where it was remarkably lower than those in the other groups and similar to that in the reference population (table 1 and figure 1).

Regarding the age distribution of COVID-19 cases in the different IA and AI/IMID, some but not all diagnostic groups were older compared with the reference population (table 1). The age of PCR-negative cases was not available in all cohorts. A partial sample from two centres showed that the proportion of rheumatic patients older than 65 doubled that in the reference population (40% vs 20%). The relative prevalence in older (>65 years) versus younger individuals was similar in rheumatic patients (OR 1.77, CI 1.20 to 2.60, n=8270) and in the reference population (OR 1.86, CI 1.73 to 1.99, n=372 000).

DISCUSSION

Our systematic approach identified a significant number of patients with different rheumatic conditions and immunomodulatory therapies with SARS-CoV-2 PCR-confirmed diagnosis that allowed us to describe the prevalence of hospital COVID-19 and to identify differences between diagnostic and therapeutic groups. The observed differences can be considered to identify specific factors associated with susceptibility to COVID-19 in rheumatic patients.

Patients with RA or PSA showed similar rates compared with the reference population despite their older age, but specific groups of IA, including patients with SpA and those on tsDMARD/bDMARD seem at higher risk. This suggests that these specific immunomodulators may increase the risk for COVID-19, similarly as for other viral infections.[7 12]

In patients with different systemic AI/IMID, a variably greater prevalence among specific disease groups was detected. It is remarkable the relatively low rate in patients with SLE, despite an expected greater use of corticosteroids and immunosuppressants. A possible explanation is the frequent use of antimalarials, which might have played a protective role as proposed according

Table 1 Rates of hospital PCR-confirmed COVID-19 cases in patients with different rheumatic diseases

	n	COVID-19 prevalence % (CI)	OR (CI) versus reference§	Median age of cases (IQR)	Sex (female, %)
Reference population	2 899 935	0.58 (0.57 to 0.59)	–	55(43-69)†	44†
All rheumatic diseases	26 131	0.76 (0.66 to 0.87)	1.32 (1.15–1.52)*	65 (53–78)*	56
Inflammatory arthritis	19 975	0.63 (0.53 to 0.75)	1.06 (0.0.91–1.30)‡	63 (53–75)*	50
Arthritis csDMARD	7558	0.53 (0.38 to 0.72)	1.10 (0.80–1.50)‡	69 (52–79)*	39
Arthritis tsDMARD/ bDMARD	5802	0.94 (0.71 to 1.22)	1.60 (1.23–2.10)**	60 (51–70)***	53
RA	10 927	0.57 (0.44 to 0.73)	0.98 (0.76–1.26)‡	67 (56–79)*	56
PsA	4777	0.57 (0.37 to 0.82)	0.97 (0.67–1.43)‡	57 (51–78)‡	48
SpA	4268	0.89 (0.63 to 1.22)	1.54 (1.11–2.13)***	59 (49–69)‡	43
AI/IMID	4781	1.11 (0.83 to 1.45)	1.92 (1.47–2.53)*	60 (51–73)***	68
AI/IMID non-SLE	2528	1.54 (1.10 to 2.10)	2.69 (1.96–3.69)*	60 (54–76)*	65
SLE	2253	0.62 (0.34 to 1.04)	1.07 (0.63–1.80)‡	51 (42–66)*	77
PMR-CGA	1378	1.45 (0.89 to 2.23)	2.53 (1.62–3.93)*	84 (75–86)**	57

*P<0.0001, **p<0.001, ***p<0.01.
†Calculated in a subset of reference population cases (n 3,800).
‡Non-significant difference.
§Odds ratio (OR) with 95% confidence intervals (CI), and all comparisons were between each group and the reference population.
AI/IMID, autoimmune or immune-mediated disease; bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional-synthetic disease-modifying antirheumatic drug; PMR-CGA, polymyalgia rheumatica or giant cell arteritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SpA, spondyloarthritis; tsDMARD, targeted-synthetic disease-modifying antirheumatic drug.

to their in vitro antiviral effects, but this will require further analyses.[13] This relatively low prevalence contrasts with the significant increase observed in all other AI/IMID diseases. In most groups, ageing is an expected associated risk factor, but somewhat surprisingly, in the PMR-GCA group, hospital COVID-19 prevalence does not seem higher compared with other groups of AI/IMID. The real risk in PMR-CGA might have been underestimated, considering the difficult access to the hospital of aged and institutionalised patients and merits further analysis.

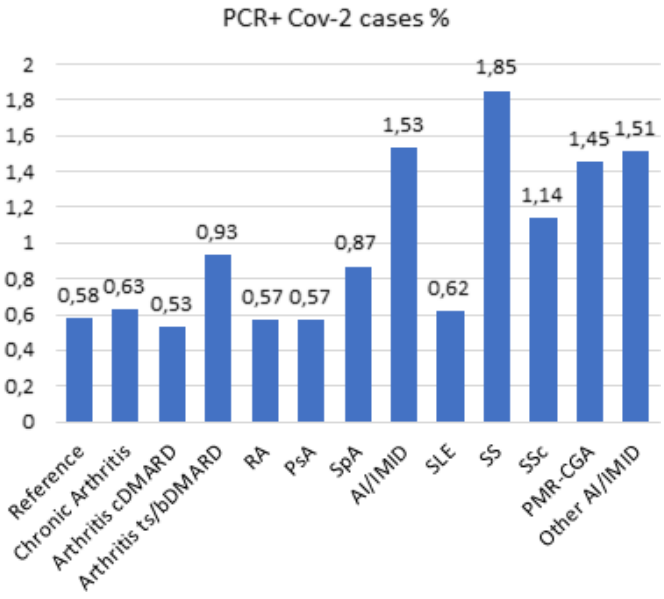

Figure 1 Rates of hospital COVID-19 in patients with chronic arthritis, autoimmune diseases and reference population. Prevalence of hospital PCR-confirmed cases of COVID-19 infection in patients with chronic IA or AI/IMID diseases (n=26 131) in seven reference hospitals in Spain, compared with that in the reference population of the same hospitals (n=2.9 million). The AI/IMID group includes all diagnoses but PMR-CGA, and other AI/IMID of the less frequent diseases as indicated in the Patients and methods section. AI/IMID, autoimmune or immune-mediated disease; ts/bDMARD, targeted synthetic or biological disease-modifying antirheumatic drug; cDMARD, conventional disease-modifying antirheumatic drug; csDMARD, conventional-synthetic disease-modifying antirheumatic drug; IA, inflammatory arthritis; PMR-CGA, polymyalgia rheumatica or giant cell arteritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SpA, spondyloarthritis; SS, Sjögren's syndrome; SSc, systemic sclerosis.

Several considerations have to be taken to interpret these results. We have only identified cases requiring attention in hospital emergency departments and often hospitalisation. Since severity, but not prevalence, increases with age, a higher rate of severe cases among rheumatic patients' cohorts was expected.[14 15] However, only in some groups, hospital COVID-19 cases have an older age than the reference population. Therefore, although older age is a clear risk factor, disease or therapy-related factors also seem to modify the risk for hospital COVID-19 cases in the different rheumatic patients' groups. Although authorities' recommendations for hospital attendance were based on severity rather than on pre-existing potential risk conditions, a bias towards different PCR testing in rheumatic patients cannot be excluded. We are aware of a still unknown but important number of rheumatic patients with milder SARS-CoV-2 disease whose detection was based on self-reporting and phone consultations but not confirmed by PCR testing. The real prevalence of severe and non-severe cases among rheumatic patients, but also in the non-rheumatic reference population, could be only reliably estimated by future serological testing.

With these limitations, we conclude that different chronic inflammatory or autoimmune diseases, and different therapies have a different impact on the risk of COVID-19. Our data on specific groups should be translated to current recommendations regarding alert on infection risk and prevention measures in rheumatic patients. Ongoing studies of the specific factors potentially involved in the observed differences will hopefully contribute to understand the impact of the SARS-CoV-2 pandemics in different risk groups.

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