# SARS-CoV-2 outbreak in immune-mediated inflammatory diseases: the Euro-COVIMID multicentre cross-sectional study

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## Summary

**Background** The COVID-19 pandemic has raised numerous questions among patients with immune-mediated inflammatory diseases regarding potential reciprocal effects of COVID-19 and their underlying disease, and potential effects of immunomodulatory therapy on outcomes related to COVID-19. The seroprevalence of SARS-CoV-2 and factors associated with symptomatic COVID-19 in patients with immune-mediated inflammatory diseases are still unclear. The Euro-COVIMID study aimed to determine the serological and clinical prevalence of COVID-19 among patients with immune-mediated inflammatory diseases, as well as factors associated with COVID-19 occurrence and the impact of the pandemic in its management.

**Methods** In this multicentre cross-sectional study, patients aged 18 years or older with a clinical diagnosis of rheumatoid arthritis, axial spondyloarthritis, systemic lupus erythematosus, Sjögren's syndrome, or giant cell arteritis were recruited from six tertiary referral centres in France, Germany, Italy, Portugal, Spain, and the UK. Demographics, comorbidities, treatments, and recent disease flares, as well as information on COVID-19 symptoms, were collected through a questionnaire completed by participants. SARS-CoV-2 serology was systematically tested. The main outcome was the serological and clinical prevalence of COVID-19. Factors associated with symptomatic COVID-19 were assessed by multivariable logistic regression, and incidence of recent disease flares, changes in treatments for underlying disease, and the reasons for treatment changes were also assessed. This study is registered with ClinicalTrials.gov, NCT04397237.

**Findings** Between June 7 and Dec 8, 2020, 3136 patients with an immune-mediated inflammatory disease answered the questionnaire. 3028 patients (median age 58 years [IQR 46–67]; 2239 [73·9%] women and 789 [26·1%] men) with symptomatic COVID-19, serological data, or both were included in analyses. SARS-CoV-2 antibodies were detected in 166 (5·5% [95% CI 4·7–6·4]) of 3018 patients who had serology tests. Symptomatic COVID-19 occurred in 122 (4·0% [95% CI 3·4–4·8]) of 3028 patients, of whom 24 (19·7%) were admitted to hospital and four (3·3%) died. Factors associated with symptomatic COVID-19 were higher concentrations of C-reactive protein (odds ratio 1·18, 95% CI 1·05–1·33; p=0·0063), and higher numbers of recent disease flares (1·27, 1·02–1·58; p=0·030), whereas use of biological therapy was associated with reduced risk (0·51, 0·32–0·82; p=0·0057). At least one disease flare occurred in 654 (21·6%) of 3028 patients. Over the study period, 519 (20·6%) of 2514 patients had treatment changes, of which 125 (24·1%) were due to the pandemic.

**Interpretation** This study provides key insights into the epidemiology and risk factors of COVID-19 among patients with immune-mediated inflammatory diseases. Overall, immunosuppressants do not seem to be deleterious in this scenario, and the control of inflammatory activity seems to be key when facing the pandemic.

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## Introduction

Despite the onset of the COVID-19 pandemic in Europe by March, 2020, no large-scale nationwide European seroprevalence studies have been published so far, except in Spain, where the prevalence of antibodies against SARS-CoV-2 in the general population was only 5% by May, 2020.[1] The burden of COVID-19 has been reported to be higher in specific at-risk populations, including people with chronic conditions such as diabetes and cardiovascular disease. Many concerns have been raised regarding COVID-19 in patients with immune-mediated inflammatory diseases, which affect an estimated 4·5% of the global population.[2] Patients with immune-mediated inflammatory diseases are known to be at higher risk of severe infections, not only due to their baseline immune dysfunction but also as a consequence of immuno-suppressant therapy. Pooled data from seven case-control studies estimated the risk of symptomatic COVID-19 in

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## Research in context

### Evidence before this study

Since the beginning of the COVID-19 pandemic, many concerns have been raised regarding the risks of COVID-19 in patients with immune-mediated inflammatory diseases. Patients with these diseases are known to be at higher risk of severe infections, not only due to their baseline immune dysfunction but also as a consequence of immunosuppressant therapy. Heterogeneous pooled data have estimated that the risk of COVID-19 in patients with immune-mediated inflammatory diseases is higher than in the general population and that immunosuppressants might be associated with an increased risk of death due to COVID-19. However, these data were from studies in which SARS-CoV-2 serology testing was not done, meaning that mild and asymptomatic cases were likely to be missed, and resulting in an underestimation of the prevalence of COVID-19 and an overestimation of its severity. We searched PubMed, Embase, ScienceDirect, and Google Scholar for peer-reviewed English-language epidemiological studies published up to Feb 1, 2021, using the terms "seroprevalence", "serology", "SARS-CoV-2", "COVID-19", "immune-mediated disease", "autoimmune disease", "rheumatoid arthritis", "axial spondyloarthritis", "systemic lupus erythematous", "Sjögren's syndrome", and "giant cell arteritis". Large-scale seroprevalence studies in patients with immune-mediated inflammatory diseases have not been done so far.

### Added value of this study

We determined the prevalence of COVID-19 among 3028 patients with immune-mediated inflammatory diseases (rheumatoid arthritis, axial spondyloarthritis, systemic lupus erythematosus, Sjögren's syndrome, and giant cell arteritis) across six European countries using a systematic serological assessment. We found that the overall seroprevalence and severity of SARS-CoV-2 infection in these patients over the study period resembled that of the general population. In addition, increased systemic inflammation in patients with immune-mediated inflammatory diseases (higher C-reactive protein concentrations and a higher number of disease flares) was associated with symptomatic COVID-19. Symptomatic SARS-CoV-2 infection occurred less frequently among patients with immune-mediated inflammatory diseases treated with biological drugs.

### Implications of all the available evidence

An understanding of the true prevalence of COVID-19 in patients with immune-mediated inflammatory diseases and reliable risk stratification could be useful in the design of prioritisation strategies when carrying out mass vaccination. Immunosuppressants do not seem to be deleterious with regard to susceptibility to and severity of COVID-19, and the control of inflammatory activity could be a primary goal in the management of patients with immune-mediated inflammatory disease during the pandemic.

patients with an immune-mediated inflammatory disease at two times higher than that in the general population.[3] Several factors might affect the risk and disease severity in this heterogeneous group of patients. It was postulated that the severity of COVID-19 would increase with higher degrees of immunosuppression, as use of a combination of immunosuppressants has been associated with higher risk of hospital admission and death due to COVID-19.[3] Conversely, considering the immune-mediated mechanisms underlying severe COVID-19,[4] inflammation-dampening treatments might actually confer protection against severe COVID-19 to some patients.

Another consequence of COVID-19 in patients with immune-mediated inflammatory diseases is the substantial risk of untimely discontinuation of immunomodulating agents by themselves or their treating physicians due to fear that these agents could predispose them to COVID-19, despite reassuring international guidelines.[5,6] The effect of COVID-19 on the control of disease, including a possible risk of flares, in these patients is another key question. There has been a paucity of data addressing these issues, and whether disease activity, immunomodulatory therapy, or both might have an effect on COVID-19 remains unclear.

The Euro-COVIMID study was designed to assess the seroprevalence of SARS-CoV-2 in patients in Europe with immune-mediated inflammatory diseases, and the effect

of COVID-19 on the underlying disease. Our main goal was to provide a more reliable estimate of the exposure to SARS-CoV-2 in this population.

## Methods

### Study design and participants

We did a multicentre cross-sectional study (Euro-COVIMID) of patients followed up in six tertiary referral centres in Île-de-France (France), Nordrhein-Westfalen (Germany), Emilia Romagna (Italy), Centro (Portugal), Comunidad de Madrid (Spain), and London (UK). Eligible individuals had to be older than 18 years and have a definite clinical diagnosis of rheumatoid arthritis, axial spondyloarthritis, systemic lupus erythematosus, Sjögren's syndrome, or giant cell arteritis diagnosed by experienced rheumatologists and fulfilling the respective international classification criteria.[7–11] Patients who refused to participate, did not speak or read the local language, or were unwilling to undergo routine blood collection during the study period were excluded. The study protocol was implemented according to the Declaration of Helsinki and was approved by the Institutional Review Board from each centre. Patients agreed to participate through either informed oral or written consent based on the requirements of each local ethics committee. A patient partner (G von Krause, based in Paris, France) was involved in the study design and in

the development of the patient questionnaire, following the rules proposed by the European League Against Rheumatism and Outcome Measures in Rheumatology Clinical Trials.[12,13] Patients and the public were not involved in conducting, reporting, or in the dissemination plans of this research.

## Data collection and definitions

During 7 months of the pandemic in Europe (from June to December, 2020), consecutive patients with an immune-mediated inflammatory disease followed up in the outpatient clinic or through phone consultations were invited to participate. Patients who agreed were interviewed by health professionals, who filled in a centralised and anonymised electronic case report form, which included patients' demographic information, comorbidities, clinical history, and number of disease flares (from Feb 1, 2020, until the date of inclusion). The case report form also included data on current use of immunosuppressant and immunomodulatory drugs during the same period, along with dose changes and the reasons for these changes (related or not to the pandemic). Stable measures (ie, no major changes from previous values) of C-reactive protein available from the past 24 weeks were recorded.

Information regarding contact with someone known to be infected with SARS-CoV-2, compliance to quarantine, and clinical course were recorded, as well as the onset and duration of COVID-19 symptoms. In the event of death, the date and cause of death were retrieved from medical records and family members. For all living patients, serological tests for SARS-CoV-2 were added to their routine blood collection within 4 weeks of filling in the case report form. These tests could be done either at the tertiary centre or at the patient's usual external laboratory, provided that one of the following high-accuracy tests were used: Abbott's IgG test (Abbott Park, IL, USA), which detects the SARS-CoV-2 nucleocapsid protein; Roche's total antibody test (Basel, Switzerland), which detects the SARS-CoV-2 nucleocapsid protein; Siemens' total antibody test (New York, NY, USA), which detects the SARS-CoV-2 spike protein S1 receptor-binding domain; DiaSorin's IgG test (Saluggia, Italy), which detects the SARS-CoV-2 spike protein S1 or S2; or Beckman-Coulter's IgG test (Brea, CA, USA), which detects the SARS-CoV-2 spike protein S1 receptor-binding domain.

The number of flares were assessed, and their severity was defined according to the requirement for treatment changes or hospital admission as follows: very mild, if no medical attention was sought and no treatment intensification was needed; mild, if medical attention was sought and no or slight treatment intensification was needed; moderate, if a hospital stay in a medical ward was required; and severe, if intensive care treatment was required. A COVID-19 diagnosis was considered as confirmed if typical clinical symptoms were accompanied by either a positive SARS-CoV-2 PCR or serological test.

COVID-19 severity was categorised using the WHO ordinal scale for clinical improvement.[14] This scale takes into account the worst clinical status and the highest level of support needed throughout the disease course as follows: (1) ambulatory, no limitation of activities; (2) ambulatory, with limitation of activities; (3) hospitalised, no oxygen therapy; (4) hospitalised, oxygen by mask or nasal prongs; (5) hospitalised, oxygen by non-invasive ventilation or high-flow oxygen; (6) intubation and mechanical ventilation; (7) mechanical ventilation with additional organ support (ie, vasopressors, dialysis, or extracorporeal membrane oxygenation); (8) death.

## Outcomes

The main outcome was the serological and clinical prevalence of COVID-19 in a large sample of patients with immune-mediated inflammatory diseases in Europe. Secondary outcomes included the assessment of COVID-19 severity, factors associated with COVID-19 occurrence, incidence and severity of recent flares of the underlying disease, and changes in treatments and the reasons underlying these changes.

## Statistical analysis

Assuming a prevalence of SARS-CoV-2 antibodies of 5%,[15] a sample size of 323 produces an exact two-sided 95% CI of 0·05. Thus, we aimed to recruit 100 patients per country and per disease to ensure a sufficient precision in the estimations (ie, a total of at least 3000 patients).

We included all patients with available serological or clinical COVID-19 data in analyses. Serological and clinical COVID-19 prevalence was estimated with two-sided 95% CIs. We also computed prevalence estimates according to countries and underlying disease. To compare the prevalence of symptomatic COVID-19 in patients with immune-mediated inflammatory diseases with that of the general population, we estimated the prevalence of COVID-19 cases for each region throughout the recruitment period by taking values from the UK and European dashboards[16,17] and using those to calculate number of cases per 100 inhabitants.

Continuous variables are presented as medians with IQRs and were compared between groups using the Wilcoxon rank-sum test. Categorical variables are presented with counts and percentages and were compared using $\chi^2$ tests with continuity correction or Fisher exact tests as appropriate. We used multiple logistic regressions with a random effect on the country to determine a set of variables independently associated with symptomatic COVID-19. All factors significantly associated with symptomatic COVID-19 were considered in the regression model. A backward procedure with a stopping rule on p values of less than 0·05 was applied. Odds ratios (ORs) with two-sided 95% CIs were estimated. We did sensitivity analyses to check the consistency of results using a generalised linear model with penalised maximum likelihood, and to assess the
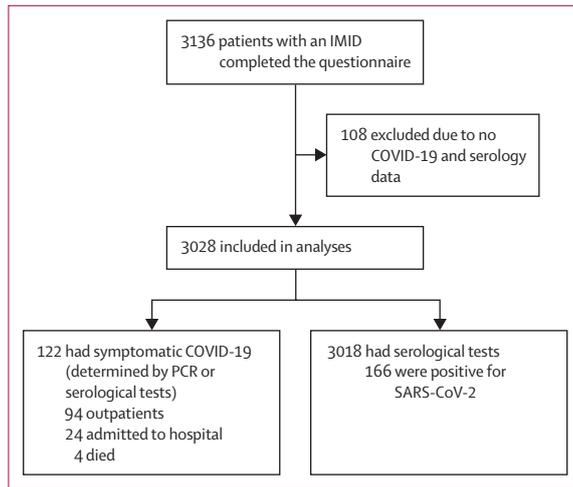
**Figure 1:** COVID-19 prevalence in the Euro-COVIMID study population
IMID=immune-mediated inflammatory disease.

effect of missing data using multiple imputation by chained equation. All tests were two-sided, and a p value below 0·05 was considered as significant. Analyses were done with R statistical platform software (version 4.0.3).

This study is registered with ClinicalTrials.gov, NCT04397237.

### Role of the funding source
The funder of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit the paper for publication.

### Results
Between June 7 and Dec 8, 2020, 3136 patients with an immune-mediated inflammatory disease completed the questionnaire (figure 1). Of these patients, 3028 (96·6%) had available COVID-19 data, serological data, or both (median age 58 years [IQR 46–67]; 2239 [73·9%] women and 789 [26·1%] men; table 1). Enrolment rate was constant throughout the study period. Median duration of immune-mediated inflammatory disease was 8·7 years (IQR 3·3–17·4) at enrolment, and median C-reactive protein concentration was 3·0 mg/L (2·0–4·5; table 1). One or more comorbidities were observed in 1624 (53·6%) of 3028 patients and included mainly hypertension (899 [29·7%] of 3028), dyslipidaemia (411 [13·6%]), obesity (245 [8·1%]), depression (218 [7·2%]), diabetes (200 [6·6%]), and cancer history (196 [6·5%]; appendix p 2). 1303 (48·2%) of 2076 patients received an influenza vaccine in 2019, and 946 (36·0%) of 2629 patients received a pneumococcal vaccine in the past 5 years. 992 (32·8%) patients were taking prednisone (median daily dose 5 mg [IQR 3–6]), with 1645 (54·3%) receiving at least one conventional synthetic disease-modifying antirheumatic drug (DMARD) and 1086 (35·9%) receiving at least one biological DMARD (table 1; appendix pp 3–5).

Of the 3028 included patients, all but ten had a serological test (table 2), and the most used test kits were those from Abbott (1293 [48·4%] of 2674; data missing for 344 patients) and Roche (302 [11·3%]). A positive serology result was found in 166 patients (5·5% [95% CI 4·7–6·4]). Differences were observed among countries, with a lower proportion of seropositive patients in Germany (5 [0·8%] of 624), Portugal (6 [1·1%] of 526), and Italy (8 [1·5%] of 522) than in France (42 [7·1%] of 593), Spain (70 [13·4%] of 524), and the UK (35 [14·6%] of 239; appendix pp 6–8). The characteristics of patients with immune-mediated inflammatory diseases according to SARS-CoV-2 serology are detailed in the appendix (pp 9–14). In patients with detectable SARS-CoV-2 antibodies, C-reactive protein concentrations were higher and the proportion of current smokers was lower. No significant differences were observed between seropositive and seronegative patients with regard to patient demographics, comorbidities, and medications for underlying disease.

The prevalence of symptomatic COVID-19 among the 3028 patients was 4·0% (95% CI 3·4–4·8); specific symptoms are detailed in the appendix (p 1). Symptomatic COVID-19 occurred in 122 patients (112 with serology data [92 positive, 20 negative], ten without serology data); 24 (19·7%) required hospital admission and four (3·3%) died (table 2). Asymptomatic infection was noted in 74 (44·6%) of 166 people with detectable antibodies against SARS-CoV-2. The occurrence of symptomatic COVID-19 was associated with higher C-reactive protein concentrations (p=0·038), median daily dose of prednisone (p=0·0058), and number of disease flares (p=0·0018), but lower use of biological DMARDs (p=0·0009) and lower prevalence of current smoking (p=0·0085; table 1). No differences were observed in the occurrence of symptomatic COVID-19 with respect to age and comorbidities (table 1; appendix p 2).

All factors significantly associated with symptomatic COVID-19 in the univariate analysis were considered in the multivariable logistic regression model. The factors associated with the occurrence of symptomatic COVID-19 in multivariate analysis were higher levels of C-reactive protein (OR for each 10 mg/L increment 1·18 [95% CI 1·05–1·33], p=0·0063) and higher number of recent disease flares (OR for each additional flare 1·27 [1·02–1·58], p=0·030). By contrast, use of biological or targeted synthetic DMARDs was associated with a reduced occurrence of symptomatic COVID-19 (OR 0·51 [95% CI 0·32–0·82], p=0·0057; figure 2).

The prevalence of symptomatic COVID-19 based on the Euro-COVIMID data was higher than the reported local prevalence in the UK, whereas prevalence based on the Euro-COVIMID data was lower than the reported local prevalence in all other countries (appendix p 15).

At least one disease flare was reported by 654 (21·6%) of 3028 patients, of which 309 (47·2%) were very mild, 303 (46·3%) were mild, 40 (6·1%) were moderate, and

| | All patients* (n=3028) | Patients with symptomatic COVID-19 (n=122) | Patients with asymptomatic or no COVID-19 (n=2906) | p value |
|---|---|---|---|---|
| Age, years | 58 (46–67) | 58 (48–68) | 58 (46–67) | 0·67 |
| 18–29 | 141 (4·7%) | 6 (4·9%) | 135 (4·6%) | .. |
| 30–39 | 286 (9·4%) | 11 (9·0%) | 275 (9·5%) | .. |
| 40–49 | 501 (16·5%) | 18 (14·8%) | 483 (16·6%) | .. |
| 50–59 | 764 (25·2%) | 32 (26·2%) | 732 (25·2%) | .. |
| 60–69 | 706 (23·3%) | 31 (25·4%) | 675 (23·2%) | .. |
| ≥70 | 630 (20·8%) | 24 (19·7%) | 606 (20·9%) | .. |
| Sex | .. | .. | .. | 1·00 |
| Female | 2239 (73·9%) | 90 (73·8%) | 2149 (74·0%) | .. |
| Male | 789 (26·1%) | 32 (26·2%) | 757 (26·0%) | .. |
| Body-mass index, kg/m² | 24·98 (22·04–28·28) | 24·23 (22·21–28·16) | 24·98 (22·04–28·28) | 1·00 |
| Smoking | .. | .. | .. | 0·0085 |
| Current | 483/2587 (18·7%) | 9/95 (9·5%) | 474/2492 (19·0%) | .. |
| Former | 705/2587 (27·3%) | 37/95 (38·9%) | 668/2492 (26·8%) | .. |
| Never | 1399/2587 (54·1%) | 49/95 (51·6%) | 1350/2492 (54·2%) | .. |
| At least one comorbidity | 1624 (53·6%) | 66 (54·1%) | 1558 (53·6%) | 0·99 |
| Positive SARS-CoV-2 serology* | 166 (5·5%) | 92/112 (82·1%) | 74 (2·5%) | <0·0001 |
| IMID | .. | .. | .. | 0·50 |
| Rheumatoid arthritis | 891 (29·4%) | 39 (32·0%) | 852 (29·3%) | .. |
| Axial spondylarthritis | 670 (22·1%) | 19 (15·6%) | 651 (22·4%) | .. |
| Systemic lupus erythematous | 605 (20·0%) | 28 (23·0%) | 577 (19·9%) | .. |
| Sjögren's syndrome | 511 (16·9%) | 21 (17·2%) | 490 (16·9%) | .. |
| Giant cell arteritis | 351 (11·6%) | 15 (12·3%) | 336 (11·6%) | .. |
| Disease duration, years | 8·7 (3·3–17·4) | 8·4 (3·4–15·7) | 8·6 (3·3–17·3) | 0·99 |
| C-reactive protein, mg/L† | 3·0 (2·0–4·5; n=2520) | 3·0 (3·0–6·4; n=96) | 3·0 (2·0–4·4; n=2424) | 0·038 |
| Number of IMID flares | .. | .. | .. | 0·0018 |
| None | 2374 (78·4%) | 82 (67·2%) | 2292 (78·9%) | .. |
| One | 516 (17·0%) | 27 (22·1%) | 489 (16·8%) | .. |
| Two | 75 (2·5%) | 9 (7·4%) | 66 (2·3%) | .. |
| Three | 32 (1·1%) | 2 (1·6%) | 30 (1·0%) | .. |
| Four or more | 31 (1·0%) | 2 (1·6%) | 29 (1·0%) | .. |
| Severity of IMID flares | .. | .. | .. | 0·73 |
| Very mild | 309/654 (47·2%) | 19/40 (47·5%) | 290/614 (47·2%) | .. |
| Mild | 303/654 (46·3%) | 17/40 (42·5%) | 286/614 (46·6%) | .. |
| Moderate | 40/654 (6·1%) | 4/40 (10·0%) | 36/614 (5·9%) | .. |
| Severe | 2/654 (0·3%) | 0 | 2/614 (0·3%) | .. |
| IMID treatments | .. | .. | .. | .. |
| No treatment | 379 (12·5%) | 17 (13·9%) | 362 (12·4%) | 0·73 |
| Non-steroidal anti-inflammatory drugs | 362 (12·0%) | 12 (9·8%) | 350 (12·0%) | 0·55 |
| Prednisone | 992 (32·8%) | 44 (36·1%) | 948 (32·6%) | 0·49 |
| Daily dose, mg | 5 (3–6; n=987) | 5 (5–8; n=44) | 5 (3–6; n=943) | 0·0058 |
| At least one conventional synthetic DMARD | 1645 (54·3%) | 73 (59·8%) | 1572 (54·1%) | 0·25 |
| At least one biological or targeted synthetic DMARD | 1086 (35·9%) | 26 (21·3%) | 1060 (36·5%) | 0·0009 |

Data are median (IQR), n (%), or n/N (%) unless otherwise specified. Percentages might not sum to 100% due to rounding. DMARD=disease-modifying antirheumatic drug. IMID=immune-mediated inflammatory disease. *Serology test result was not available for ten symptomatic patients with COVID-19. †Last stable biological parameters refer to the 24 weeks before inclusion.

*Table 1:* **Characteristics of all patients with immune-mediated inflammatory diseases and according to the presence of COVID-19 symptoms**

| | Patients (n=3028) |
|---|---|
| **SARS-CoV-2 serology*** | |
| Positive result | 166/3018 (5·5%) |
| Positive IgA | 3/3018 (0·1%) |
| Positive IgM | 11/3018 (0·4%) |
| Positive IgG | 122/3018 (4·0%) |
| Total antibodies positivity | 39/3018 (1·3%) |
| Symptomatic COVID-19 | 122 (4·0%) |
| Close contact with a confirmed COVID-19 case | 54/122 (44·3%) |
| Non-adherence to confinement | 24/122 (19·7%) |
| Health professional | 9/24 (37·5%) |
| Symptom duration, days | 10 (7–20) |
| **WHO ordinal scale for clinical improvement** | |
| No limitations of activities | 65/122 (53·3%) |
| Limitation of activities, home oxygen, or both | 29/122 (23·8%) |
| Hospitalisation without supplemental oxygen | 4/122 (3·3%) |
| Hospitalisation with low-flow oxygen | 18/122 (14·8%) |
| Non-invasive ventilation or high-flow oxygen | 1/122 (0·8%) |
| Mechanical ventilation | 1/122 (0·8%) |
| Mechanical ventilation and additional organ support | 0 |
| Death | 4/122 (3·3%) |

Data are n/N (%) or median (IQR). *Serology test result was not available for ten symptomatic patients with COVID-19.

*Table 2:* Information on SARS-CoV-2 serology and symptomatic COVID-19 for patients with immune-mediated inflammatory diseases

| | Patients |
|---|---|
| Treatment changes during the pandemic (June–December, 2020) | 519/2514 (20·6%) |
| Due to the pandemic | 125/519 (24·1%) |
| Not related to the pandemic | 394/519 (75·9%) |
| Change in corticosteroids | 219/992 (22·1%) |
| Dose increase | 102/219 (46·6%) |
| Dose decrease | 90/219 (41·1%) |
| Interruption | 27/219 (12·3%) |
| Change in conventional synthetic DMARDs | 199/1645 (12·1%) |
| Dose increase | 83/199 (41·7%) |
| Dose decrease | 46/199 (23·1%) |
| Interruption | 70/199 (35·2%) |
| Change in biological or targeted synthetic DMARDs | 193/1086 (17·8%) |
| Dose increase | 40/193 (20·7%) |
| Dose decrease | 72/193 (37·3%) |
| Interruption | 81/193 (42·0%) |

Data are n/N (%). 379 patients received no treatment, and data on treatment changes were unavailable for 135 patients. DMARDs=disease-modifying antirheumatic drugs.

*Table 3:* Effect of the COVID-19 pandemic on treatments for immune-mediated inflammatory diseases

| | OR (95% CI) | p value |
|---|---|---|
| C-reactive protein | 1·18 (1·05–1·33) | 0·0063 |
| Biological or targeted synthetic DMARDs | 0·51 (0·32–0·82) | 0·0057 |
| Number of flares | 1·27 (1·02–1·58) | 0·030 |
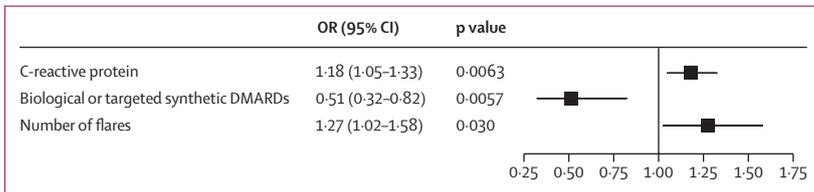


*Figure 2:* Forest plot for the odds of symptomatic COVID-19
The OR for C-reactive protein corresponds to a per 10 mg/L increase in concentration, and for number of flares it corresponds to each additional flare. DMARDs=biological disease-modifying antirheumatic drugs. OR=odds ratio.

two (0·3%) were severe (table 2). 519 (20·6%) of 2514 patients had changes in their treatment between June and December, 2020. The reason for the changes was the pandemic in 125 (24·1%) patients (table 3). Corticosteroids were the most frequently changed drug during the pandemic (219 [22·1%] of 992 patients), and more than half of therapeutic changes were a reduction or cessation of treatment rather than an increase in treatment.

## Discussion

In this multicentre cross-sectional study, we determined for the first time (to our knowledge) the prevalence of COVID-19 among patients with immune-mediated inflammatory diseases across six European countries by using a systematic serological assessment. The overall seroprevalence and effects of SARS-CoV-2 in patients with immune-mediated inflammatory diseases over the study period resembles that of the general population. Increased systemic inflammation (ie, higher C-reactive protein concentrations and disease flares) might play a part in the occurrence of symptomatic COVID-19, whereas biological and targeted synthetic DMARDs appeared to be protective. More than 20% of patients included in analyses had at least one disease flare.

A systematic serological assessment is the best way to achieve a broad understanding of distinct populations. Data from China showed a SARS-CoV-2 seropositivity rate ranging from 3·2% to 3·8% between March and April, 2020,[18] and in the largest nationwide population-based study so far in Spain, seroprevalence reached 5% by May, 2020.[1] Repeated cross-sectional analysis across all US jurisdictions have shown that less than 10% of the population had detectable SARS-CoV-2 antibodies as of September, 2020.[19] The seroprevalence is expected to increase as we approach at-risk populations, but these data are still scarce for several groups of patients. For patients on dialysis in the USA, a large nationwide analysis estimated prevalence of SARS-CoV-2 antibodies to be 8% by July, 2020.[20] We estimated a seroprevalence of 5·5% in patients with immune-mediated inflammatory diseases over the 6-month study period. In addition, as has been reported in the general population, we found differences between COVID-19 prevalence across European countries. This finding might reflect the different degrees of restrictive measures applied in each region. We could hypothesise that patients with immune-mediated inflammatory diseases from our tertiary centres were more adherent to physical distancing measures, as

patients from Germany, Italy, and Portugal had significantly less contact with people with confirmed COVID-19 than did those from the other studied countries.

The COVID-19 epidemiology in patients with immune-mediated inflammatory diseases has several biases that make the data difficult to interpret. Among the inherent selection biases from case series, overestimating disease severity is the most relevant one. In the largest worldwide case series of patients with rheumatic diseases from the COVID-19 Global Rheumatology Alliance registry, 49% of patients were admitted to hospital and 10·5% died.[21] Our study showed comparatively lower rates of hospital admission (19·7%) and deaths (3·3%) among patients with symptomatic COVID-19, which are closer to those of the general population.[22] Several studies have assessed large fixed samples;[23–25] however, the scarcity of systematic serological testing does not allow for the detection of mild and asymptomatic infections and thus undermines prevalence calculations. Our finding that 44·6% of patients with immune-mediated inflammatory diseases who had positive SARS-CoV-2 serology had asymptomatic infection makes the prevalence and severity of COVID-19 found in this population more reliable.

The mechanisms underlying the development of symptomatic COVID-19 remain unclear. Older age and comorbidities have been highlighted as key poor prognosis factors of COVID-19 in the general population,[26,27] and these associations have also been suggested for patients with immune-mediated inflammatory diseases.[3,21] However, these findings were not reproduced in our study. Notably, higher C-reactive protein concentrations and number of disease flares accounted for the main risk factors of symptomatic COVID-19. Higher disease activity at COVID-19 diagnosis has been associated with death among patients with immune-mediated inflammatory diseases in a large case series.[21] Taken together, these findings suggest that the inflammatory status might play a part in the development of COVID-19 and its outcomes. One of the most relevant issues in COVID-19 risk for patients with immune-mediated inflammatory diseases concerns the use of immunosuppressants, either because of the higher implicit risk of infections or because several DMARDs (eg, tocilizumab and baricitinib) have been proposed as treatments for severe forms of COVID-19. Higher doses of corticosteroid and DMARD combination therapy were associated with a higher mortality risk due to COVID-19 among patients with immune-mediated inflammatory diseases.[3,21] By contrast, a large retrospective survey showed that patients taking hydroxychloroquine presented a reduced risk of COVID-19[23] (although other studies have not confirmed this) and early data from the COVID-19 Global Rheumatology Alliance showed an association between the use of tumour necrosis factor inhibitors and reduced odds of hospitalisation.[28] Strikingly, use of biological or targeted synthetic DMARDs reduced the risk of symptomatic COVID-19 by almost 50% in our study. Rather than a specific biological DMARD, the

control of the overall inflammatory response seems to be key in whether a patient develops symptomatic COVID-19.

Management of patients with immune-mediated inflammatory diseases has been affected by the pandemic. Remote consultations increased as the number of face-to-face consultations decreased by up to 52%.[29] Treatment decisions were frequently postponed, and specialists were less likely to start patients on biological DMARDs during the pandemic.[30] Despite the recommendations of the European League Against Rheumatism and the American College of Rheumatology,[5,6] more than 20% of participants in our study with immune-mediated inflammatory diseases reduced or discontinued their treatment during the study period, the pandemic being the reason in 24·1% of cases. In this setting, at least one disease flare was seen in 21·6% of patients. As guidelines for management of immune-mediated inflammatory diseases during the pandemic are presented as living documents, our data are useful not only in reaffirming the safety of maintaining DMARDs, but also in estimating the rate of flares and their severity during the outbreak.

Our study has limitations. As we do not have patient-level data regarding sociodemographic data such as employment status, income, and household size, we could not weigh these components in the COVID-19 risk. Additionally, by enrolling a single tertiary referral centre per country, included patients might not fully represent the general population of patients with immune-mediated inflammatory diseases in each region.

In conclusion, this study provides key insights into the epidemiology and risk factors of COVID-19 among patients with immune-mediated inflammatory diseases. These data will help to improve the management of COVID-19 in this patient population, particularly at the time when vaccination strategies start to be widely implemented.

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