Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry

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ABSTRACT

Objectives To determine factors associated with COVID-19-related death in people with rheumatic diseases.

Methods Physician-reported registry of adults with rheumatic disease and confirmed or presumptive COVID-19 (from 24 March to 1 July 2020). The primary outcome was COVID-19-related death. Age, sex, smoking status, comorbidities, rheumatic disease diagnosis, disease activity and medications were included as covariates in multivariable logistic regression models. Analyses were further stratified according to rheumatic disease category.

Results Of 3729 patients (mean age 57 years, 68% female), 390 (10.5%) died. Independent factors associated with COVID-19-related death were age (66–75 years: OR 3.00, 95% CI 2.13 to 4.22; >75 years: 6.18, 4.47 to 8.53; both vs ≤65 years), male sex (1.46, 1.11 to 1.91), hypertension combined with cardiovascular disease (1.89, 1.31 to 2.73), chronic lung disease (1.68, 1.26 to 2.25) and prednisolone-equivalent dosage >10 mg/day (1.69, 1.18 to 2.41; vs no glucocorticoid intake). Moderate/high disease activity (vs remission/low disease activity) was associated with higher odds of death (1.87, 1.27 to 2.77). Rituximab (4.04, 2.32 to 7.03), sulfasalazine (3.60, 1.66 to 7.78), immunosuppressants (azathioprine, cyclophosphamide, ciclosporin, mycophenolate or tacrolimus: 2.22, 1.43 to 3.46) and not receiving any disease-modifying anti-rheumatic drug (DMARD) (2.11, 1.48 to 3.01) were associated with higher odds of death, compared with methotrexate monotherapy. Other synthetic/biological DMARDs were not associated with COVID-19-related death.

Conclusion Among people with rheumatic disease, COVID-19-related death was associated with known general factors (older age, male sex and specific comorbidities) and disease-specific factors (disease activity and specific medications). The association with moderate/high disease activity highlights the importance of specific treatment approaches.
INTRODUCTION

There is a lack of robust data to inform our understanding of outcomes following SARS-CoV-2 infection in patients with inflammatory rheumatic diseases, leading to uncertainties regarding chronic disease management, especially for those taking immunosuppressant or immunomodulatory drugs.\(^1\)\(^\text{–}^3\)

Whether people with rheumatic diseases belong to a vulnerable, higher risk population for SARS-CoV-2 infection and have poorer outcomes is unclear.\(^4\)\(^\text{–}^6\) In general, this population seems to have similar or only slightly poorer outcomes compared with those without rheumatic disease.\(^7\)\(^\text{–}^9\) However, important confounding disease-related factors, such as disease activity or treatments, have previously not been addressed.

Medications commonly used to treat rheumatic diseases have been used or are being tested for the prevention and/or treatment of COVID-19 and its complications,\(^10\) raising questions about the impact of these treatments on the outcomes of SARS-CoV-2 infection. Continuation of immunomodulatory or immunosuppressive therapy is essential for controlling rheumatic disease activity, avoiding disease progression and preventing joint or organ-damage related to sustained inflammation. Withdrawal of effective treatments should be based on sound evidence, even during a pandemic.

To generate more granular data relevant to rheumatic diseases, a global network of rheumatologists, data scientists and patients developed a COVID-19 physician-reported case registry in March 2020.\(^11\)\(^\text{–}^12\) Analysis of the first 600 patients revealed that older age and comorbidities were associated with hospitalisation,\(^13\) similar to results in the general population.\(^8\)\(^\text{–}^14\) More robust data on the risk of poor outcomes, in particular risk of death, are required.

The aim of this study was to investigate factors associated with COVID-19-related death in patients with rheumatic diseases and to analyse these associations by disease group.

METHODS

Data source

The COVID-19 Global Rheumatology Alliance (C19-GRA) physician-reported registry is an observational registry launched on 24 March 2020. Data are entered voluntarily by rheumatologists or under supervision of rheumatologists; patients are eligible for inclusion if they have a pre-existing rheumatic disease and a COVID-19 diagnosis. Data are entered either directly into the global or European data entry systems or transferred from national registries (France, Germany, Italy, Portugal and Sweden).

We used data collected on or before 1 July 2020. Further details of this registry have been described elsewhere.\(^11\)\(^\text{–}^13\) Countries were assigned to the six WHO regions (www.who.int); the ‘Americas’ was further divided into north and south. Given the registry collects anonymous data, the UK Health Research Authority and the University of California San Francisco Institutional Review Board considered it exempt from patient consent.

Patient stratification into diagnostic groups

Rheumatic diseases differ regarding the disease-modifying anti-rheumatic drugs (DMARDs) approved for their treatment. To minimise the impact of this heterogeneity on the associations of interest, in addition to the main analysis with all patients, diagnostic categories were defined (figure 1) and stratified analyses were undertaken for patients with (1) inflammatory joint diseases (IJD), (2) rheumatoid arthritis (a subset of the IJD subgroup) and (3) connective tissue diseases (CTD)/vasculitis.

COVID-19 reporting and outcome

Both confirmed and presumptive cases of COVID-19 were reported. The method of COVID-19 diagnosis was specified: PCR, CT scan, metagenomic testing, laboratory assays or based on symptoms only.

For analysis, patients were subsequently categorised into (1) confirmed or high likelihood of COVID-19 (chest imaging (CT or chest X-ray) showing bilateral infiltrates and/or symptoms after close contact with a known laboratory-confirmed COVID-19 positive patient) or (2) presumptive cases based on symptoms alone.

The primary outcome was COVID-19-related death.

Treatment prior to COVID-19

Antirheumatic medications used prior to COVID-19 diagnosis were categorised into groups shown in figure 1. Immunomodulatory drugs (conventional synthetic (cs)/biological (b)/targeted synthetic (ts) DMARDs) were distinguished from immunosuppressive drugs (azathioprine, cyclophosphamide, ciclosporin, mycophenolate moletil/mycophenolic acid, tacrolimus) as recommended by Isaacs and Burmester\(^15\); glucocorticoids are also immunosuppressive but they were examined separately and categorised by prednisolone-equivalent dosage (1–10 mg/day and >10 mg/day). Methotrexate monotherapy was adopted as the medication reference group; methotrexate is the anchor drug in multiple rheumatic diseases\(^16\) and it represents the largest medication category in the registry.

Statistical analyses

Descriptive tables were produced for the whole cohort and then by diagnostic group, country (for the six countries with the highest number of cases: France, Germany, Italy, Spain, UK and USA) and medication. Independent associations between demographic and disease features and COVID-19-related death were estimated using multivariable logistic regression and reported as OR and 95% CI. Covariates included in the model were age, sex, key comorbidities (hypertension alone or cardiovascular disease (CVD) alone, hypertension combined with CVD, chronic lung disease, chronic kidney disease (CKD) and diabetes), smoking status (ever vs never), rheumatic disease diagnostic group, disease activity as per the physician’s global assessment (severe/high or moderate disease activity vs minimal/low disease activity or remission), rheumatic disease treatment prior to COVID-19 diagnosis and prednisolone-equivalent glucocorticoid use.

Key messages

How might this impact on clinical practice or future developments?

- There is differential risk of COVID-19-related death according to disease activity and treatments in patients with rheumatic disease, highlighting the need for adequate disease control with DMARDs, preferably without increasing the glucocorticoid dosage.
one of the following diseases were grouped according to the following hierarchy: systemic lupus erythematosus (SLE) > vasculitis > other CTD > RA > psoriatic arthritis (PsA) > (other) spondyloarthritis (SpA) > other IJD > other non-IJD/non-CTD rheumatic disease. Patients receiving multiple csDMARDs or immunosuppressants (except glucocorticoids) were grouped according to the following hierarchy: immunosuppressants > sulfasalazine > antimalarials > leflunomide > methotrexate. Patients receiving a b/tsDMARD were considered solely in the b/tsDMARD group. Patients treated with more than one b/tsDMARD (N=4), patients receiving IL-1 inhibitors (N=20) and patients receiving DMARDs atypical for their disease subgroup (N=48) were excluded from analysis due to very low numbers (figure 2). Patients were excluded from a particular analysis if the medication they received provided ≤20 patients for that analysis or if there were no deaths reported for that specific medication.

The following sensitivity analyses were performed to examine the robustness of our findings to procedures for handling missing data: (1) excluding patients from France (no disease activity data available); (2) complete case analysis. Further sensitivity analyses were conducted to assess the stability of the results: (1) limited to patients with confirmed or highly likely COVID-19; (2) using the alternative outcome ‘death or invasive ventilation’; (3) using a reduced number of covariates to assess the risk of overfitting; (4) analysis explicitly controlling for country, using data from the top six reporting countries; (5) analysis stratified for several binary key variables (age >65 or not, sex, ever smoked vs not, high/moderate/severe disease activity vs remission/low disease activity, CVD, chronic lung disease, glucocorticoid use) to assess the possibility of interactions.

Data were considered statistically significant for p values <0.05. All analyses were conducted in SAS (V.9.4) and R (V.3.6.3).

RESULTS

As of 1 July 2020, 3830 patients were in the registry, of whom 3729 had no missing values for death, age, sex and DMARD therapy (table 1, results for all patients; online supplemental table 1, results stratified by diagnostic subgroup; online supplemental table 2, results stratified by country; online supplemental table 3, results stratified by medication of interest).

Patient characteristics and outcomes of COVID-19

Mean age was 57 (15.7) years and most patients were ≤65 years (2586/3729, 69.3%) and female (2534/3729, 68%). The most common disease was RA (1394/3729, 37.4%), followed by CTDs other than SLE (533/3729, 14.3%), SLE (391/3729, 10.5%), PsA (440/3729, 11.8%) and other SpA (431/3729, 11.6%).

Patients were primarily from Europe (2315/3729, 62.1%) or North America (1105/3729, 29.6%). Nearly half (1309/2758, 47.5%) had minimal or low disease activity and one-third (893/2758, 32.4%) were in remission before COVID-19. One-quarter of all patients (776/3164, 24.5%) were ever smokers.

Most patients had a laboratory-confirmed diagnosis of COVID-19 (2897/3729, 77.7%); 2.4% (91/3729) had a high likelihood of infection based on imaging or confirmed COVID-19 contacts.

Death occurred in 10.5% (390/3729) of patients; 68.7% (268/390) of those who died were >65 years. Nearly half of all patients (1739/3546, 49.0%) were hospitalised. Invasive ventilation was reported in 6.2% (187/2995) of patients, but in 40.8% (120/294) of those who died.

All patients with confirmed or presumptive COVID-19 were included in the main analyses. Patients with missing primary outcome (N=82) or missing values for age, sex and DMARD (N=19) were excluded from analysis. Missing values for comorbidities, smoking status, glucocorticoid therapy and disease activity were derived by multiple imputation using full conditional specification.17 Results of the logistic regression analyses for 10 imputed datasets were pooled by Rubin’s rules. As disease activity was missing for all French patients, country-level life expectancy was used in the imputation model to explain potential structural differences in disease activity between countries not accounted for in the patient-level data (data from 2018, source: http://hdr.undp.org/).

To account for pronounced heterogeneity between participant countries regarding both healthcare systems and infection dynamics, countries were implicitly considered as data clusters in the regression analysis by assuming that the data arose from a cluster sample design; this was done by applying a Taylor series linearisation in the variance estimation.18 For patients listed as having more than one rheumatic disease or being treated with more than one of the medications of interest, we created a hierarchy based on clinical expertise to categorise patients. This process creates disjoint categories, allowing a clear reference group for interpretation of the regression models and avoiding collinearities. Patients with more than

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**Epidemiology**

### Disease groups and medications included

#### Inflammatory Joint Diseases (JD)
- Rheumatoid arthritis (RA)
- Axial and peripheral spondyloarthritis (SpA)
- Psoriatic arthritis (PsA)
- Oligoarticular/polyparticular juvenile idiopathic arthritis (JIA)
- Other inflammatory arthritis

#### Connective Tissue Diseases (CTD)/Vasculitis
- Systemic lupus erythematosus (SLE)
- Sjögren’s syndrome
- Systemic sclerosis
- Inflammatory myopathy (dermatomyositis, polymyositis)
- Mixed CTD
- Undifferentiated CTD
- ANCA-associated vasculitis
- Giant cell arteritis
- Behcet’s Disease
- Polymyalgia rheumatica
- Kawasaki disease
- Other vasculitis

#### Other (neither JD nor CTD/vasculitis)
- Gout
- Ocular inflammation
- Auto-inflammatory syndromes
- IgG4-related disease
- Systemic JIA
- Calcium pyrophosphate deposition disease
- Other non-specified rheumatic diseases

#### Conventional synthetic DMARDs (csDMARDs)
- Methotrexate
- Leflunomide
- Sulfasalazine
- Antimalarials (chloroquine, hydroxychloroquine)

#### Biological DMARDs (bDMARDs)
- Abatacept
- IL-1 inhibitors
- IL-6 inhibitors
- IL-12/23/23-17 or IL-23 inhibitors
- TNF inhibitors
- Bevacizumab
- Rituximab

#### Targeted synthetic DMARDs (tsDMARDs)
- Apremilast
- JAKInhibitors

#### Immunosuppressants (except glucocorticoids)
- Azathioprine
- Cyclophosphamide
- Cyclosporine
- Mycophenolate mofetil/mycophenolic acid
- Tacrolimus

#### Glucocorticoids
- Prednisone-equivalent dose

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**Figure 1** Disease and medication groups. ANCA, anti-neutrophil cytoplasm antibodies; DMARD, disease-modifying antirheumatic drugs; IgG, immunoglobulin; IL, interleukin; JAK, Janus kinase; TNF, tumour necrosis factor.
Comorbidities

Most patients (2582/3700, 69.8%) had at least one comorbidity, and 20.5% (760/3700) had more than three. The most frequent were hypertension (1307/3700, 35.3%), chronic lung disease (719/3700, 19.4%), obesity (BMI ≥30; 597/3700, 16.1%), diabetes (505/3700, 13.6%), other CVD (442/3700, 11.9%) and CKD (258/3700, 7.0%). Among deceased patients, the proportion of those with comorbidities was higher, with 42.7% (212/386) having ≥3 comorbidities, namely, 54.9% (212/386) with hypertension, 35.8% (138/386) with chronic lung disease, 24.6% (95/386) with diabetes, 32.1% (124/386) with other CVD and 19.9% (77/386) with CKD.

Treatments

At the time of COVID-19 diagnosis, 40.6% (1514/3729) of patients were treated only with csDMARDs, immunosuppressants or combinations of these; 35.7% (1331/3729) received
### Table 1  Patient demographic and clinical characteristics

| Parameter | Not deceased | Deceased | Total |
|-----------|--------------|----------|-------|
| N         | 3339         | 390      | 3729  |

**General**

- **Age (years)**
  - ≥30: 197 (9.9)
  - 31–50: 1012 (30.3)
  - 51–65: 1255 (37.6)
  - 66–75: 536 (16.1)
  - >75: 339 (10.2)
- **Male sex**: 1031 (30.9)
- **Ever smoker**: 664 (23.3)
- **Hypertension**: 1095 (33)
- **Diabetes**: 410 (12.4)

**Other outcomes**

- **Chronic lung disease**: 581 (17.5)
- **Cerebrovascular disease**: 82 (2.4)
- **Cancer**: 165 (5)

**Immunological diseases**

- **Systemic lupus erythematosus**: 355 (10.6)
- **Rheumatoid arthritis**: 1224 (36.7)
- **Spondyloarthritis**: 416 (12.3)
- **Psoriatic arthritis**: 420 (12.6)
- **Juvenile idiopathic arthritis (poly, oligo, not systemic)**: 21 (0.6)
- **Other inflammatory arthritis**: 90 (2.7)

**Disease activity**

- **N=2464 (Missing=875)**
- **Remission**: 799 (32.4)
- **Minimal disease activity**: 1202 (48.8)
- **Moderate disease activity**: 388 (15.7)
- **Severe/high disease activity**: 75 (3)

**Other RMDs**

- **Hospitalisation**: 1368 (41.3)
- **Invasive ventilation**: 67 (2.3)
- **Comorbidities**: 3109 (91.7)
- **Hypertension**: 1095 (33)
- **Cardiovascular disease**: 318 (9.6)
- **Cerebrovascular disease**: 89 (2.7)
- **Chronic lung disease**: 581 (17.5)
- **Chronic kidney disease**: 181 (5.5)
- **Obesity (BMI ≥30)**: 539 (16.3)
- **Morbid obesity (BMI ≥40)**: 106 (3.2)
- **Diabetes**: 410 (12.4)
- **Cancer**: 165 (5)

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Factors associated with death

In multivariable analyses (table 2, figure 3), patients between 66 and 75 years of age were more likely to have died (OR 3.00, 95% CI 2.13 to 4.22) than those ≤65 years. The association was even more pronounced in patients over 75 years (6.18, 4.47 to 8.53; vs ≤65 years). Male sex was also associated with higher odds of death (1.46, 1.11 to 1.91). Current or former smoking was only associated with death in the RA subgroup (1.45, 1.02 to 2.04).

Other factors associated with death included chronic lung disease (1.68, 1.26 to 2.23) and CVD combined with hypertension (1.89, 1.31 to 2.73), whereas hypertension or CVD alone did not show a significant association. CKD was significantly associated with death in patients with CTD or vasculitis (2.30, 1.37 to 3.88) but not in other disease subgroups.

Across all diagnostic groups, treatments with leflunomide, antimalarials, antimalarial, TNF inhibitors, abatacept, belimumab, IL-6 inhibitors, IL-17/IL-23/IL-12+23 inhibitors and tsDMARDs were not associated with death, as compared with methotrexate monotherapy. In the overall model, not receiving DMARD treatment was associated with death (2.11, 1.48 to 3.01) compared with methotrexate monotherapy. This was also seen in the IJD, RA and CTD subgroups.

Compared with methotrexate monotherapy, treatments associated with a higher odds of death were rituximab (4.04, 2.32 to 7.03, in the overall model; 5.42, 2.77 to 10.61, in the IJD subgroup; 4.99, 2.43 to 10.26, in the RA subgroup; 3.72, 1.21 to 11.48, in the CTD/vasculitis subgroup), sulfasalazine (3.60, 1.66 to 7.78, in the overall model and consistent across all subgroups) and immunosuppressants (azathioprine, cyclophosphamide, ciclosporin, mycophenolate or tacrolimus: 2.22, 1.43 to 3.46, in the overall model; 2.44, 1.06 to 5.65, in the CTD/vasculitis subgroup; not applicable to other subgroups).

An additional analysis indicated that the association of sulfasalazine with an increased odds for death was mainly driven by the larger group of sulfasalazine monotherapy and persisted even when sulfasalazine combination treatment (plus either antimalarial, leflunomide or methotrexate) was considered separately (data not shown).

Treatment with higher dosages of glucorticoids (>10 mg/day prednisolone-equivalent dose vs no use) was also found to be associated with death (1.69, 1.18 to 2.41), particularly in the CTD/vasculitis subgroup (1.93, 1.11 to 3.36).

Higher disease activity at COVID-19 diagnosis was consistently associated with death across all disease groups. Patients with high/moderate/severe disease activity had higher odds of death (1.87, 1.27 to 2.77) than patients with low disease activity or in remission (overall model and consistent across all subgroups).

Sensitivity analyses

Results were largely consistent in our sensitivity analyses (online supplemental tables 4–9). In the complete case analysis (online supplemental table 5), the association between sulfasalazine and death was no longer statistically significant. In stratified analyses (online supplemental tables 10–16), sulfasalazine use was not associated with death among patients who never smoked, with the OR among ever smokers being almost threefold than among non-smokers (online supplemental table 12).

Table 1

| Parameter | Not deceased | Deceased | Total |
|-----------|--------------|----------|-------|
| IL-1 inhibitors monotherapy | 10 (0.3) | 2 (0.5) | 12 (0.3) |
| IL-1 inhibitors combination therapy | 4 (0.1) | 4 (1) | 8 (0.2) |
| IL-17, IL-23, IL-12/23 inhibitors monotherapy | 79 (2.4) | 1 (0.3) | 80 (2.1) |
| IL-17, IL-23, IL-12/23 inhibitors combination therapy | 36 (1.1) | 0 | 36 (1) |
| tsDMARDs monotherapy | 61 (1.8) | 5 (1.3) | 66 (1.8) |
| tsDMARDs (**) combination therapy | 71 (2.1) | 10 (2.6) | 81 (2.2) |
| JAK inhibitors monotherapy | 54 (1.6) | 4 (1) | 58 (1.6) |
| JAK inhibitors combination therapy | 67 (2) | 9 (2.3) | 76 (2) |
| Apremilast monotherapy | 7 (0.2) | 1 (0.3) | 8 (0.2) |
| Apremilast combination therapy | 3 (0.1) | 1 (0.3) | 4 (0.1) |
| No DMARD therapies | 615 (18.4) | 124 (31.8) | 739 (19.8) |

Further therapies

| Glucocorticoids (g) | 1056 (32) (N=3617) | 217 (57.1) (N=380) | 1273 (34.6) (N=3682) |
| Glucocorticoids 1–10 mg/day | 833 (25.6) (N=2345) | 150 (41.3) (N=263) | 983 (27.2) (N=3617) |
| Glucocorticoids >10 mg/day | 171 (5.3) (N=3254) | 49 (13.5) (N=263) | 220 (6.1) (N=3617) |
| NSAIDs | 600 (19.3) (N=3103) | 38 (11.0) (N=236) | 638 (18.8) (N=3449) |

Data are N (column %) for categorical variables or mean (SD) for continuous variables. The table includes patients with a non-missing outcome and non-missing values for age, sex and disease-modifying anti-rheumatic drugs (DMARDs) (101 patients excluded). Data refer to patients with non-missing values for the respective variable; total N for patients with non-missing values is given in parentheses for variables with missing values; the total number of missing values is also given in parentheses, for the applicable variables. (*) Includes one patient on a study medication (lefunasum).

hDMARDs and 3.9% (147/3729) received tsDMARDs. One-fifth (739/3729, 19.8%) were not receiving any DMARD/immunosuppressive treatment (except glucocorticoids), and this proportion was higher among deceased patients (124/390, 31.8%).

Among the patients not receiving any DMARD/immunosuppressive treatment, 39.8% (290/729) received glucocorticoids, 9.8% (70/712) with a prednisolone-equivalent dosage of >10 mg/day; the most frequent diagnostic categories being other non-specified rheumatic diseases (173/739, 23.4%), vasculitis (161/739, 21.8%), CTD other than SLE (156/739, 21.1%) and RA (110/739, 14.9%).

Country-specific differences

The majority of cases (2993/3729, 80.3%) were reported from six countries with considerable differences in reported percentages of death (online supplemental table 2). Overall, 10.5% (390/3729) of patients died, with highest proportions in the UK (91/435, 20.9%) and Italy (53/315, 16.8%). Death was reported in lower proportions in the USA (70/1005, 7.0%), Germany (15/198, 7.6%), France (62/793, 7.8%) and Spain (21/247, 8.5%). Other major differences between the countries were the distribution of rheumatic diseases and the distribution and frequency of comorbidities.
### Table 2: Multivariable logistic regression analysis of factors associated with COVID-19-related death in patients with rheumatic diseases (all patients)

| N deaths/patients (%) | N deaths/patients (OR) | 95% CI | N deaths/patients (OR) | 95% CI | N deaths/patients (OR) | 95% CI | N deaths/patients (OR) | 95% CI |
|-----------------------|------------------------|--------|------------------------|--------|------------------------|--------|------------------------|--------|
| **Age, years**        |                        |        |                        |        |                        |        |                        |        |
| ≥65                   | 118/265                | 1      | Reference              | 55/165 | 1                      | Reference | 40/840                | 1      | Reference | 56/799 | 1     |
| 65 years < Age ≤75    | 109/664                | 3      | 2.13 to 4.22           | 71/426 | 3.63                   | 2.55 to 5.15 | 55/314                | 3.10   | 1.68 to 5.72 | 33/167 | 2.29 |
| ≥75                   | 157/896                | 6.18   | 4.47 to 8.53           | 85/265 | 8.21                   | 5.54 to 12.18 | 71/277                | 7.30   | 4.42 to 12.06 | 58/191 | 4.08 |
| Male sex (vs female)  | 161/1188               | 1.46   | 1.11 to 1.91           | 82/588 | 1.31                   | 0.95 to 1.8  | 55/345                | 1.17   | 0.78 to 1.76  | 63/296 | 1.66 |
| Ever smoked (vs never)| 140/922                | 1.21   | 0.94 to 1.57           | 84/607 | 1.02                   | 0.93 to 1.72 | 71/385                | 1.45   | 1.02 to 2.04  | 42/248 | 1.11 |
| **Comorbidities**     |                        |        |                        |        |                        |        |                        |        |
| Hypertension alone or CVD alone | 155/150 | 1.19 | 0.89 to 1.59 | 78/960 | 1.04 | 0.74 to 1.46 | 66/404 | 1.11 | 0.74 to 1.67 | 69/406 | 1.56 |
| Chronic lung disease  | 136/231               | 1.68   | 1.26 to 2.25           | 36/406 | 1.52                   | 1.04 to 2.21 | 63/281                | 1.44   | 0.99 to 2.09  | 54/285 | 2.05 |
| Chronic kidney disease| 76/259                | 1.67   | 0.99 to 2.8            | 27/111 | 1.09                   | 0.54 to 2.41 | 21/83                 | 1.01   | 0.46 to 2.24  | 41/24 | 2.30 |
| Diabetes mellitus     | 96/508                | 1.38   | 0.88 to 2.17           | 55/313 | 1.31                   | 0.95 to 1.79 | 39/213                | 1.08   | 0.72 to 1.61  | 32/154 | 1.39 |
| Rheumatoid arthritis  | 160/1326              | 1      | Reference              | 166/1373 | 1          | Reference | n.a.                  | n.a.   | n.a.          | n.a.   | n.a. |
| Systemic lupus erythematosus | 36/391 | 1.2  | 0.30 to 2.04 | n.a. | 0.8.7 | 0.80 to 1.08 | n.a. | 0.84 | 0.78 to 1.33 | 64/318 | 0.81 |
| Vasculitis            | 67/325                | 0.8    | 0.60 to 1.08           | n.a. | 0.75 | 0.58 to 0.97 | n.a. | 0.75 | 0.57 to 1.54 | 51/481 | 0.78 |
| No DMARD therapy      | 124/739               | 2.77   | 2.26 to 3.46           | 21/104 | 2.08                   | 1.43 to 3.06 | 22/104                | 2.44   | 1.06 to 5.65  | 32/247 | 2.44 |
| Methotrexate          | 39/595                | 1.18   | 0.88 to 1.58           | 17/141 | 1.17                   | 0.69 to 2.02 | 11/114                | 0.76   | 0.52 to 1.16  | 10/97 | 1.62 |
| TNF inhibitors        | 30/803                | 0.85   | 0.52 to 1.36           | 26/674 | 0.77                   | 0.42 to 1.41 | 16/292                | 0.82   | 0.39 to 1.76  | 49/39 | 2.00 |
| Abatacept             | 9/81                  | 0.51   | 0.35 to 0.73           | n.a. | 0.57 | 0.36 to 0.94 | n.a. | 0.56 | 0.34 to 0.93 | 12/114 | 1.28 |
| Glucocorticoids (GCs) |                       |        |                        |        |                        |        |                        |        |               |      |

*Abbreviations: CTDs, connective tissue diseases; OR, odds ratio; CI, confidence interval. The p-values are based on the Wald test.*
DISCUSSION

With global cooperation, the C19-GRA physician-reported registry is the largest collection to date of patients with rheumatic diseases and COVID-19. We found that moderate/high disease activity was significantly associated with COVID-19-related death, confirming recent recommendations regarding the importance of disease control in rheumatic diseases in the COVID-19 era. Other factors associated with death were older age, male sex and the presence of comorbidities, which is consistent with reports from the general population. Overall, compared with methotrexate monotherapy, most DMARDs were not associated with higher odds of death, although rituximab and sulfasalazine were notable exceptions. Prednisolone-equivalent dosages $>10$ mg/day and other immunosuppressive drugs (as opposed to immunomodulatory DMARDs) were also associated with COVID-19-related death.

In this cohort of patients with underlying rheumatic diseases, the COVID-19-related death rate was $10.5\%$, clearly higher than that reported in the general population in most countries. However, this study was not designed to calculate a precise point estimate for mortality. Reporting biases and population-related factors, including COVID-19 testing rates, could explain this figure and, importantly, it should not be taken as an estimate of the overall death rate among patients with rheumatic diseases and COVID-19.

The association of rituximab with poorer COVID-19-related outcomes is a previously unreported finding outside of case reports. Rituximab binds to CD20 on the surface of B-cells, effectively depleting this cell type, and interferes with antibody development. Therefore, B-cell depletion could potentially compromise antiviral immunity, including the development of SARS-CoV-2 antibodies. With our data, it was not possible to determine the exact timing of infection following rituximab infusion, although all patients were clinically judged by their rheumatologist to have been exposed to the immunological effects of the drug at the time of COVID-19 diagnosis. The association between rituximab and COVID-19-related death could have also been influenced by the typical coadministration of methylprednisolone with rituximab.

A finding that merits further research is the higher odds of death found with sulfasalazine treatment. This association has also been reported in results from an international registry of patients with inflammatory bowel disease and COVID-19, where sulfasalazine or 5-aminosalicylate (5-ASA) use was associated with severe COVID-19 (adjusted OR of 3.1 (1.3 to 7.7)). This finding is surprising as sulfasalazine is usually considered to have a low immunosuppressive effect. Prior research supports an immune regulatory effect driven by sulfasalazine or its metabolite 5-ASA against other RNA viruses. However, causal interpretation of the association between sulfasalazine and COVID-19-related death should not be made. The perceived low immunosuppressive effect of sulfasalazine may have led rheumatologists to prescribe preferentially sulfasalazine over methotrexate in patients who were perceived to be at higher risk, for example, patients with pulmonary disease, smoking or recurrent chest infections. In an observational study like ours, this could lead to unmeasured confounding. A salient difference in sulfasalazine users in our study was a higher proportion of current or former smokers, compared with non-users. In the stratified analyses for chronic lung disease, the association between death and sulfasalazine was significant in both subgroups with and without chronic lung disease, while in...
the stratified analyses for smoking, the association between death and sulfasalazine was limited to ever smokers, so the factor ‘smoking’ could potentially be an effect modifier. Another potential explanation for this finding could be the merging of sulfasalazine combination therapy (with other csDMARDs) with sulfasalazine monotherapy; however, the increased odds for death persisted in the sulfasalazine mono-therapy group and was not driven by the combination treatment (data not shown).

Despite the large overall sample size, for some therapies (eg, IL-6 and IL-17/IL-23/IL-12+23 inhibitors) the number of users was low and no firm conclusions could be made. IL-6 inhibitors have been used to counteract the hyperinflammatory state produced by COVID-19, with mostly disappointing randomised trial results. The efficacy is still being investigated in ongoing trials, but it is reassuring that they were not associated with COVID-19-related death in our analyses. Previous studies had shown an association between TNF inhibitors and a decreased risk of sepsis and mortality in patients with RA after serious infection compared with csDMARDs. We could not confirm such an association after stratification by disease and adjustment for disease activity. However, the data indicate that some associations may exist among patients diagnosed with IJD other than RA (a subgroup comprising predominantly patients with axial SpA and PsA), in whom male sex and diabetes mellitus were associated with a higher odds of death, and TNF inhibitor use was associated with a lower odds of death (univariable analysis, data not shown). Due to a small number of deceased patients in this subgroup with non-RA subtypes of IJD (n=37 deaths), these effects could not be assessed in a multivariable model and this should be
investigated in the future when higher case numbers allow a more stable assessment.

This study has limitations. As a cross-sectional, case-reporting registry, it may be subject to selection bias if more severe cases are more likely to come to the rheumatologists’ attention and therefore to be reported. There is an absence of a population-based comparator, and we are unable to make comparisons between those with and without COVID-19. Moreover, we caution against interpreting our estimates causally. There is likely unmeasured confounding dependent on the particularities of health systems and case reporting differences. We tried to address this by limiting the research questions to those that could be answered with this dataset and by accounting for potential confounders in our analyses. The high number of variables compared with outcome events in the subgroup models may result in biased estimates. However, the consistency between the main model and the sensitivity analyses (including using a lower number of variables) does not indicate an issue with overfitting.

In conclusion, people with rheumatic diseases with higher disease activity have higher odds of COVID-19-related death, highlighting the importance of disease control, preferably by managing DMARDs effectively without increasing glucocorticoids. Future studies should address the observed association of rituximab and sulfasalazine with poor outcomes. Finally, as in the general population, older age, male sex and/or the presence of comorbidities increase the odds of COVID-19-related death.

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