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

Anja Strangfeld, Martin Schäfer, Milena A Gianfrancesco, Saskia Lawson-Tovey, Jean W Liew, Lotta Ljung, Elsa F Mateus, Christophe Riché, Maria J Santos, Gabriela Schmajuk, Carlo A Scirè, Emily Sirotich, Jeffrey A Sparks, Paul Sufka, Thierry Thomas, Laura Trupin, Zachary S Wallace, Sarah Al-Adely, Javier Bachiller-Corral, Suleman Bhana, Patrice Cacoub, Loreto Carmona, Ruth Costello, Wendy Costello, Laure Gossec, Rebecca Grainger, Eric Hachulla, Rebecca Hasseli, Jonathan S Hausmann, Kimme L Hyrén, Zara Izadi, Lindsay Jacobsohn, Patricia Katz, Lianne Kearsley-Fleet, Philip C Robinson, Jinoos Yazdany, Pedro M Machado

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...
We used data collected on or before 1 July 2020. Further details of this registry have been described elsewhere. 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 mofetil/mycophenolic acid, tacrolimus) as recommended by Isaacs and Burmester; 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 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.
Epidemiology

Disease groups and diseases included

Inflammatory Joint Diseases (UD)
- Rheumatoid arthritis (RA)
- Axial and peripheral spondyloarthritis (SpA)
- Psoriatic arthritis (PsA)
- Oligoarticular/polyarticular 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
- Behçet’s disease
- Polymyalgia rheumatica
- Kawasaki disease
- Other vasculitis

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

Medication groups and medications included

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

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

Targeted synthetic DMARDs (tsDMARDs)
- Apremilast
- JAK inhibitors

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

Glucocorticoids
- Prednisone-equivalent dose

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.

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. 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 participating 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.

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 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 cDMARDs 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%), PaA (440/3729, 11.8%) and other non-IJD (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.
Epidemiology

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% (165/386) 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Not deceased</th>
<th>Deceased</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.5 (15.2)</td>
<td>69.7 (14.6)</td>
<td>57.0 (15.7)</td>
</tr>
<tr>
<td>≤30</td>
<td>197 (5.9)</td>
<td>9 (0.3)</td>
<td>206 (5.5)</td>
</tr>
<tr>
<td>31–50</td>
<td>1012 (30.3)</td>
<td>31 (7.9)</td>
<td>1043 (28.9)</td>
</tr>
<tr>
<td>51–65</td>
<td>1255 (37.6)</td>
<td>82 (2.1)</td>
<td>1337 (35.9)</td>
</tr>
<tr>
<td>66–75</td>
<td>536 (16.1)</td>
<td>109 (27.9)</td>
<td>645 (17.3)</td>
</tr>
<tr>
<td>&gt;75</td>
<td>339 (10.2)</td>
<td>159 (40.8)</td>
<td>498 (13.4)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1031 (30.9)</td>
<td>164 (42.1)</td>
<td>1195 (32)</td>
</tr>
<tr>
<td>Ever smoker</td>
<td>664 (23.3)</td>
<td>112 (36.1)</td>
<td>776 (24.5)</td>
</tr>
<tr>
<td><strong>Regions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African region</td>
<td>14 (0.4)</td>
<td>2 (0.5)</td>
<td>16 (0.4)</td>
</tr>
<tr>
<td>Eastern Mediterranean region</td>
<td>83 (2.5)</td>
<td>11 (2.8)</td>
<td>94 (2.5)</td>
</tr>
<tr>
<td>European region</td>
<td>2040 (61.1)</td>
<td>275 (70.5)</td>
<td>2315 (62.1)</td>
</tr>
<tr>
<td>North-American region</td>
<td>1024 (30.7)</td>
<td>81 (20.8)</td>
<td>1105 (29.6)</td>
</tr>
<tr>
<td>South-American region</td>
<td>112 (3.4)</td>
<td>10 (2.6)</td>
<td>122 (3.3)</td>
</tr>
<tr>
<td>South-East Asian region</td>
<td>11 (0.3)</td>
<td>0</td>
<td>11 (0.3)</td>
</tr>
<tr>
<td>Western Pacific region</td>
<td>55 (1.6)</td>
<td>11 (2.8)</td>
<td>66 (1.8)</td>
</tr>
<tr>
<td><strong>Inflammatory joint diseases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1224 (36.7)</td>
<td>170 (43.6)</td>
<td>1394 (37.4)</td>
</tr>
<tr>
<td>Spondyloarthritis</td>
<td>416 (12.5)</td>
<td>15 (3.8)</td>
<td>431 (11.6)</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>420 (12.6)</td>
<td>20 (5.1)</td>
<td>440 (11.8)</td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis (poly, oligo, not systemic)</td>
<td>21 (0.6)</td>
<td>4 (1)</td>
<td>25 (0.7)</td>
</tr>
<tr>
<td>Other inflammatory arthritis</td>
<td>90 (2.7)</td>
<td>8 (2.1)</td>
<td>98 (2.6)</td>
</tr>
<tr>
<td><strong>Connective tissue diseases/Vasculitis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>355 (10.6)</td>
<td>36 (9.2)</td>
<td>391 (10.5)</td>
</tr>
<tr>
<td>Connective tissue diseases (other than SLE)</td>
<td>473 (14.2)</td>
<td>60 (15.4)</td>
<td>533 (14.3)</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>258 (7.7)</td>
<td>68 (17.4)</td>
<td>326 (8.7)</td>
</tr>
<tr>
<td>Total CTD</td>
<td>1035 (31)</td>
<td>158 (40.5)</td>
<td>1193 (32.0)</td>
</tr>
<tr>
<td><strong>Other RMDs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>306 (9.2)</td>
<td>50 (12.8)</td>
<td>356 (9.5)</td>
</tr>
<tr>
<td><strong>Disease activity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>799 (24.2)</td>
<td>94 (23.2)</td>
<td>893 (24.4)</td>
</tr>
<tr>
<td>Minimal/low disease activity</td>
<td>1202 (48.8)</td>
<td>107 (26.4)</td>
<td>1309 (47.5)</td>
</tr>
<tr>
<td>Moderate disease activity</td>
<td>388 (15.7)</td>
<td>60 (20.4)</td>
<td>448 (16.2)</td>
</tr>
<tr>
<td>Severe/high disease activity</td>
<td>75 (3)</td>
<td>33 (11.2)</td>
<td>108 (3.9)</td>
</tr>
<tr>
<td><strong>Other outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalised</td>
<td>1368 (43.3)</td>
<td>371 (96.6)</td>
<td>1739 (49)</td>
</tr>
<tr>
<td>Invasive ventilation</td>
<td>67 (2.3)</td>
<td>120 (40.8)</td>
<td>187 (6.2)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>1202 (48.8)</td>
<td>107 (26.4)</td>
<td>1309 (47.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1095 (33)</td>
<td>212 (54.9)</td>
<td>1307 (35.3)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>318 (9.6)</td>
<td>124 (32.1)</td>
<td>442 (11.9)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>89 (2.7)</td>
<td>20 (5.2)</td>
<td>109 (2.9)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>581 (17.5)</td>
<td>138 (35.8)</td>
<td>719 (19.4)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>181 (5.5)</td>
<td>77 (19.9)</td>
<td>258 (7.7)</td>
</tr>
<tr>
<td>Obesity (BMI ≥30)</td>
<td>539 (16.3)</td>
<td>58 (15)</td>
<td>597 (16.1)</td>
</tr>
<tr>
<td>Morbid obesity (BMI ≥40)</td>
<td>106 (3.2)</td>
<td>16 (4.1)</td>
<td>122 (3.3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>410 (12.4)</td>
<td>95 (24.6)</td>
<td>505 (13.6)</td>
</tr>
<tr>
<td>Cancer</td>
<td>165 (5)</td>
<td>49 (12.7)</td>
<td>214 (5.8)</td>
</tr>
</tbody>
</table>

Continued
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.

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 2.25) 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, 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 antimalarials, leflunomide or methotrexate) was considered separately (data not shown).

Treatment with higher dosages of glucocorticoids (>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 that never smoked, with the OR among ever smokers being almost threefold than among never-smokers (online supplemental table 12).

Table 1

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

Further therapies

<table>
<thead>
<tr>
<th>Glucocorticoids (¶)</th>
<th>N=3254</th>
<th>Missing=85</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10 mg/day</td>
<td>1106 (33)</td>
<td>(N=320)</td>
</tr>
<tr>
<td>&gt;10 mg/day</td>
<td>217 (67)</td>
<td>(N=380)</td>
</tr>
<tr>
<td>Glucocorticoids 1–10 mg/day</td>
<td>1273 (39)</td>
<td>(N=3682)</td>
</tr>
<tr>
<td>≥10 mg/day</td>
<td>983 (30)</td>
<td>(N=3677)</td>
</tr>
<tr>
<td>Glucocorticoids 12–23 mg/day</td>
<td>220 (6)</td>
<td>(N=3617)</td>
</tr>
<tr>
<td>23+/IL-17</td>
<td>638 (19)</td>
<td>(N=3449)</td>
</tr>
</tbody>
</table>

Data are N (column %) for categorical variables or mean (SD) for continuous variables. The table includes patients with a missing glucocorticoid dosage. (¶) Includes patients with a missing glucocorticoid dosage. (†) Includes patients with a missing glucocorticoid dosage. (§) Includes patients with a missing glucocorticoid dosage. (¶) Includes patients with a missing glucocorticoid dosage. (¶) Includes patients with a missing glucocorticoid dosage.
### Table 2  Multivariable logistic regression analysis of factors associated with COVID-19-related death in patients with rheumatic diseases (all patients)

<table>
<thead>
<tr>
<th>N deaths/patients (%)</th>
<th>All</th>
<th>OR (95% CI)</th>
<th>Patients with inflammatory joint disease (JDs)</th>
<th>OR (95% CI)</th>
<th>Only patients with rheumatoid arthritis</th>
<th>OR (95% CI)</th>
<th>Patients with connective tissue disease (CTDs) or vasculitis</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤ 65</td>
<td>118/2556</td>
<td>1.0</td>
<td>Reference</td>
<td>55/1657</td>
<td>1.0</td>
<td>Reference</td>
<td>40/840</td>
<td>1.0</td>
</tr>
<tr>
<td>Age &gt; 75</td>
<td>157/2406</td>
<td>6.18</td>
<td>4.47 to 8.53</td>
<td>85/265</td>
<td>8.21</td>
<td>5.54 to 12.18</td>
<td>71/27</td>
<td>7.30</td>
</tr>
<tr>
<td>Male (sex 6 vs female)</td>
<td>161/1188</td>
<td>1.46</td>
<td>1.11 to 1.91</td>
<td>82/788</td>
<td>1.31</td>
<td>0.95 to 1.8</td>
<td>55/345</td>
<td>1.17</td>
</tr>
<tr>
<td>Ever smoked (yes)</td>
<td>140/922</td>
<td>1.21</td>
<td>0.94 to 1.57</td>
<td>84/607</td>
<td>1.06</td>
<td>0.93 to 1.72</td>
<td>71/385</td>
<td>1.45</td>
</tr>
</tbody>
</table>

### Comorbidities

- Hypertension alone or CVD alone
  - Age ≤ 65: 151/150 (OR: 1.19, 95% CI: 0.89 to 1.59)
  - Age > 75: 157/496 (OR: 1.68, 95% CI: 1.26 to 2.25)
  - Hypertension and CVD: 154/170 (OR: 1.31, 95% CI: 1.21 to 2.73)
  - Chronic lung disease: 136/721 (OR: 1.68, 95% CI: 1.26 to 2.25)
  - Chronic kidney disease: 76/259 (OR: 1.67, 95% CI: 0.99 to 2.9)
  - Diabetes mellitus: 96/508 (OR: 1.38, 95% CI: 0.85 to 2.29)

- Rheumatic disease
  - Rheumatoid arthritis: 160/1326 (OR: 1.0, 95% CI: n.a.)
  - Systemic lupus erythematosus: 36/391 (OR: 1.2, 95% CI: 0.3 to 2.04)
  - Vasculitis: 67/295 (OR: 0.8, 95% CI: 0.2 to 1.98)

- Other connective tissue diseases
  - Scleroderma: 50/123 (OR: 0.75, 95% CI: 0.58 to 0.97)

- Other inflammatory arthritis or non-systemic RA
  - Psoriasis: 19/429 (OR: 0.75, 95% CI: 0.53 to 1.07)
  - Ankylosing spondylitis: 15/423 (OR: 0.72, 95% CI: 0.34 to 1.54)

### Medication

- Methotrexate: 47/595 (OR: 1.0, 95% CI: n.a.)
  - No DMARD therapy: 124/739 (OR: 2.11, 95% CI: 1.48 to 3.01)
  - Leflunomide: 1290 (OR: 1.56, 95% CI: 0.92 to 2.77)
  - Antimalarials: 233426 (OR: 0.99, 95% CI: 0.66 to 1.46)
  - Sulfasalazine: 33144 (OR: 3.6, 95% CI: 1.66 to 7.78)
  - Immunosuppressants: 38276 (OR: 2.22, 95% CI: 1.43 to 3.46)
  - TNF inhibitors: 30803 (OR: 0.85, 95% CI: 0.52 to 1.36)
  - Rituximab: 47182 (OR: 4.0, 95% CI: 2.32 to 7.03)
  - Belimumab: 127 (OR: 0.71, 95% CI: 0.39 to 1.38)
  - Galectin-3 inhibitors: 590 (OR: 0.83, 95% CI: 0.38 to 1.84)
  - IL-6 inhibitors: 1115 (OR: 0.25, 95% CI: 0.03 to 2.04)
  - toDMARDs: 15145 (OR: 1.60, 95% CI: 0.91 to 2.8)

- Glucocorticoids (GCs)
  - No GCs: 165/2411 (OR: 1.0, 95% CI: n.a.)
  - GCs ≤ 10 mg/day: 170/1082 (OR: 1.43, 95% CI: 0.98 to 2.09)

- Other:

  | GCs 2–20 mg/day: 77/2735 | OR: 1.36, 95% CI: 0.76 to 2.45 |
  | GCs 21–100 mg/day: 78/464 | OR: 1.34, 95% CI: 0.66 to 2.74 |
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-aminosalicylic acid (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
Epidemiology

Figure 3  Results of the main logistic regression analysis. Shown are multivariable-adjusted ORs for the outcome COVID-19-related death with 95% CIs, assessing the association with (A) general patient characteristics, (B) comorbidities, (C) rheumatic disease diagnoses (RMD) and (D) rheumatic disease medications. ORs are shown for four groups: all patients (black), patients with inflammatory joint disease (red), patients with rheumatoid arthritis (orange), and patients with a connective tissue disorder or vasculitis (blue). For (C), only ORs for all patients are shown. The reference categories are as follows: (A) ≤65 years, females, never smoked, remission or low disease activity; (B) the non-presence of the specific comorbidities (for all effects); (C) rheumatoid arthritis (for all effects); (D) methotrexate monotherapy (for all effects except for glucocorticoids), no glucocorticoids (for glucocorticoid dosage groups). 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; glucocorticoids were examined separately and categorised by prednisolone-equivalent dosage (1–10 mg/day and >10 mg/day). bDMARD, biological disease-modifying anti-rheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CTD, connective tissue disease; CVD, cardiovascular disease; JIA, juvenile idiopathic arthritis; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drug.

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.25 26 Their 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.27 28 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) do 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.

Author affiliations
1Epidemiology and Health Care Research, German Rheumatism Research Center (DRFZ Berlin), Berlin, Germany
2Division of Rheumatology, Department of Medicine, University of California, San Francisco, CA, USA
3Centre for Genetics and Genomics Versus Arthritis, Centre for Musculoskeletal Research, University of Manchester, Manchester, UK
4National Institute of Health Research Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK
5Section of Rheumatology, Department of Medicine, Boston University School of Medicine, Boston, MA, USA
6Department of Public Health and Clinical Medicine/Rheumatology, Umeå University, Umeå, Sweden
7Clinical Epidemiology Section, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden
8Portuguese League Against Rheumatic Diseases (LPCDR), Lisbon, Portugal
9European League Against Rheumatism (EULAR) Standing Committee of People with Arthritis/Rheumatism in Europe (PARE), Klinke, Switzerland
10Club Rhumatismes et Inflammation (CRI) and Immune-Mediated Inflammatory Disease Alliance for Translational and Clinical Research Network (IMIDATE), Bordeaux, France
11Rheumatology Department, Hospital Garcia de Orta, Almada, Portugal
12Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina de Lisboa, Lisboa, Portugal
13Rheumatology Diseases Portuguese Register (Reuma.pt), Portuguese Society of Rheumatology (SPR), Lisboa, Portugal
14Epidemiology Unit, Italian Society for Rheumatology (SIR), Milan, Italy and Rheumatology Unit, Department of Medical Sciences, University of Ferrara, Ferrara, Italy
15Division of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada
16Canadian Arthritis Patient Alliance, Toronto, ON, Canada
17Division of Rheumatology, Immunology, and Immunology, Brigham and Women’s Hospital, Boston, MA, USA
18Healthpartners, St. Paul, MN, USA
19Société française de Rhumatologie (SFR), Saint-Etienne, France
20Department of Rheumatology, Hôpital Nord, CHU Saint-Etienne, Saint-Etienne, France
21INSERM U1059, Université de Lyon-Université Jean Monnet, Saint-Etienne, France
22Clinical Epidemiology Program and Rheumatology Unit, Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
23Centre for Epidemiology Versus Arthritis, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK
24Hospital Universitario Ramón y Cajal, Madrid, Spain
25Instituto de Investigación IRYCIS, Universidad de Alcalá, Madrid, Spain
26Crystal Run Healthcare, Middletown, NY, USA
27Département de Médecine Interne et Immunologie Clinique, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Paris, France
28Sorbonne Universités, UPMC Univ Paris 06, UMR 7211; Inflammation-Immunopathology-Biotherapy Department (DHU I2B), Paris, France
29Société Nationale Française de Médecine Interne (SNFMI), Paris, France
30Instituto de Salud Musculoesquelética, Madrid, Spain
31Irish Children’s Arthritis Network (ICAN), Tipperary, Ireland
32Institut Pierre Louis d’Épidémiologie et de Santé Publique, INSERM, Sorbonne Université, Paris, France
33AP-HP, Sorbonne Université, Rheumatology department, Pitié-Salpêtrière hospital, Paris, France
34University of Otago, Wellington, New Zealand
35Filière des maladies Auto-Immunes et Autoinflammatoires Rares (FAI2R), Lille University, France, Lille Université, Lille, France
36Department of Rheumatology and Clinical Immunology, Campus Kerckhoff, usus-Liebig-University Giessen, Giessen, Germany
37Filiation Program in Rheumatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
38Division of Rheumatology and Clinical Immunology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
39Faculty of Medicine, University of Queensland, Brisbane, Queensland, Australia
40Royal Brisbane & Women’s Hospital, Metro North Hospital & Health Service, Herston, Queensland, Australia
41National Institute for Health Research (NIHR) University College London Hospitals Biomedical Research Centre, University College London Hospitals National Health Service (NHS) Trust, London, UK
42Department of Rheumatology, Northwick Park Hospital, London North West University Healthcare NHS Trust, London North West University Healthcare NHS Trust, London, UK
43Centre for Rheumatology & Department of Neuromuscular Diseases, University College London, London, UK

Correction notice This article has been corrected since it published Online First. The collaborator names have been updated.

Twitter Jean W Liew @rheum_cat, Carlo A Scùre @arthritis, Emily Sirotich @emily_sirotich, Zachary S Wallace @zach_wallace_md, Loreto Carmona @carmona_loreto, Jonathan S Haumann @haumannmd, Philip C Robinson @philipcrobinson and Pedro M Machado @pedrommcmachado

Acknowledgements We wish to thank all rheumatology providers who entered data into the registry.

Collaborators COVID-19 Global Rheumatology Alliance Consortium: Brigham Dahou (Association Rhumatologues Algériens Privés; Algeria), Marcelo Pinheiro (Universidade Federal De São Paulo Escola Paulista de Medicina e Escola Paulista de Enfermagem; Brazil), Francinne M Ribeiro (Hospital Universitário Pedro Ernesto Universidade do Estado do Rio de Janeiro; Brazil), Anne-Marie Chassin-Trubert (Complejo Hospitalario San José; Chile), Sebastián Ibáñez (Clínica Alemana de Santiago; Chile), Lingli Dong (Tongji Hospital, China)Lui Cajas (Clinica Universitaria de Salud; Colombia), Hesham Hamoud (Al Azhar University Hospitals; Egypt), Jérôme Avouac (Rheumatology A Department, Cochin University Hospitals Paris-Centre, AP-HP, France), Véronique Belin (Department of Rheumatology, Hospital Center of Thonon-les-Bains; France), Raphaël Borie (Department of Rheumatology, Bichat Hospital, AP-HP, France), Pascal Chazerain (Department of Rheumatology and Internal Medicine, Diaconesses Croix Saint Simon Hospital, Paris, France), Xavier Chevalier (Department of Rheumatology, Henri Mondor University Hospitals, AP-HP, Créteil, France), Pascal Claudel (Department of Rheumatology, Henri Mondor University Hospitals, AP-HP, Créteil, France), Géraldine Clavel (Department of Internal Medicine, Rothschild Foundation, Paris, France), Marie-Eve Colette-Cedoz (Nord-Irse Rheumatology practice, Bourgoin-Jallieu, France), Bernard Combe (Department of Rheumatology, Lapeyronie University Hospital of Montpellier France), Elodie Constant (Department of Rheumatology, Hospital Center of Ventou; France), Nathalie Costedoat-Chalumeau (Department of Internal Medicine, Cochin University Hospitals Paris-Centre, AP-HP, France), Marie Desmurs (Department of Rheumatology, Mulhouse-South Alsace hospital group; France), Valérie Devauchelle-Pensec (Rheumatology Department, Caserne Blanche Hospital and Brest Occidentale University; France), Mathilde Devaux (Department of Internal Medicine, Intermunicipal Hospital Center of Poissy-Saint Germain; France), Robin Dhote (Department of Internal Medicine, Avicenne University Hospital, AP-HP, Paris; France), Yannick Dieudonné (Department of Internal Medicine and Clinical Immunology, Strasbourg University Hospital; France), Fanny Domont (Department of Internal Medicine and Clinical Immunology, Pitié-Salpêtrière Hospital,
Contribute to the debate on the impact of COVID-19 on rheumatic diseases in arthritis.

1. Introduction
2. Methods
3. Results
4. Discussion
5. Conclusion
6. Acknowledgments
7. References

Epidemiology

Contributors

Funding

Provenance and peer review

Ethics approval

Patient consent for publication

Supplemental material

Open access
others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: https://creativecommons.org/licenses/by/4.0/.

ORCID iDs
Anja Strangfeld http://orcid.org/0000-0002-6233-022X
Lotta Ljung http://orcid.org/0000-0001-8999-0925
Christophe Richez http://orcid.org/0000-0002-3029-8739
Maria J Santos http://orcid.org/0000-0002-7946-1365
Carlo A Sicile http://orcid.org/0000-0001-7451-0271
Javier Bachiller-Corral http://orcid.org/0000-0001-8954-209X
Loreto Carmona http://orcid.org/0000-0002-4401-2551
Russ Costello http://orcid.org/0000-0003-7297-6666
Laure Gossec http://orcid.org/0000-0002-4528-310X
Eric Hachulla http://orcid.org/0000-0001-2982-8253
Jonathan S Hausmann http://orcid.org/0000-0003-0786-8788
Kimme L Hyrich http://orcid.org/0000-0001-8242-9262
Lianne Kearsley-Fleet http://orcid.org/0000-0003-0377-1575
Philip C Robinson http://orcid.org/0000-0002-3156-3418
Pedro M Machado http://orcid.org/0000-0002-8411-7972

REFERENCES