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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

Key messages

What is already known about this subject?

- To date, most available data on outcomes for people with rheumatic diseases infected with SARS-CoV-2 come from single centre or single country case series or from one large international registry; the COVID-19 Global Rheumatology Alliance (GRA) physician registry.
- The first GRA publication identified factors associated with higher odds of COVID-19 hospitalisation, including older age, presence of comorbidities and higher dosages of glucocorticoids (≥10 mg/day of prednisolone equivalent).
- Clinical outcome information on patients with COVID-19 who have rheumatic disease therefore remains limited, particularly with regard to factors associated with COVID-19-related death.

What does this study add?

- In this analysis of 3729 patients with rheumatic diseases, older age, male sex, and cardiovascular and chronic lung disease were associated with COVID-19-related death.
- Disease-specific factors, namely, moderate/high disease activity and certain medications (rituximab, sulfasalazine and immunosuppressants (as opposed to immunomodulators like disease-modifying anti-rheumatic drugs (DMARDs)) were also associated with COVID-19-related death.

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.

of adequate disease control with DMARDs, preferably without increasing glucocorticoid dosages. Caution may be required with rituximab, sulfasalazine and some immunosuppressants.

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.[1–3]

Whether people with rheumatic diseases belong to a vulnerable, higher risk population for SARS-CoV-2 infection and have poorer outcomes is unclear.[1–8] In general, this population seems to have similar or only slightly poorer outcomes compared with those without rheumatic disease.[7–9] 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 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 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.[11–13] 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 antirheumatic 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[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.

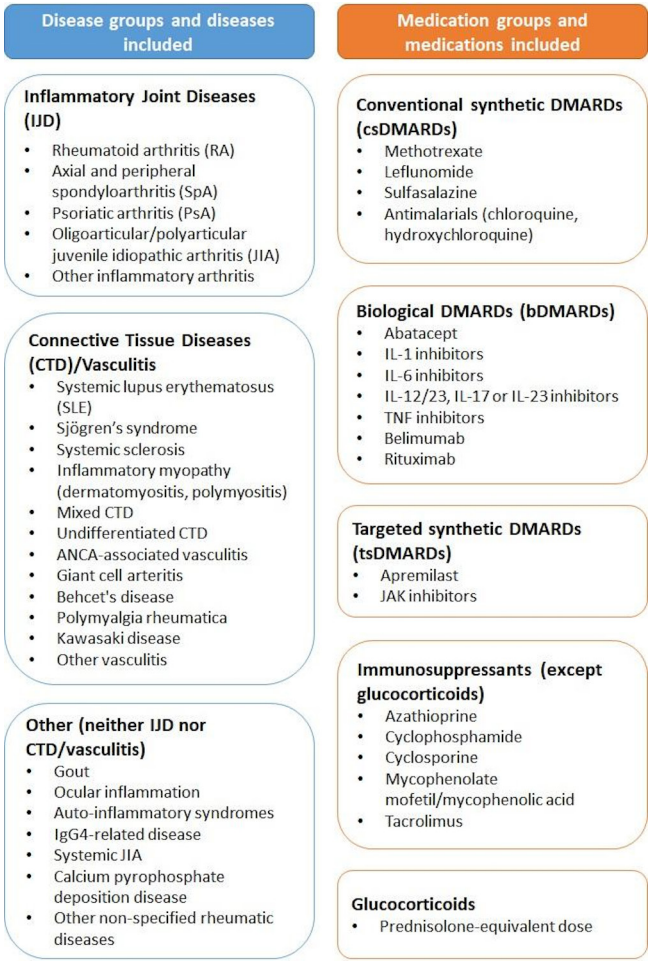

Figure 1 Disease and medication groups. ANCA, anti-neutrophil cytoplasm antibodies; DMARD, disease-modifying antirheumatic drugs; IgG, immunoglobulin; IL, interleukin; JAK, Janus kinase; TNF, tumour necrosis factor.

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.[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 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.[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 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.

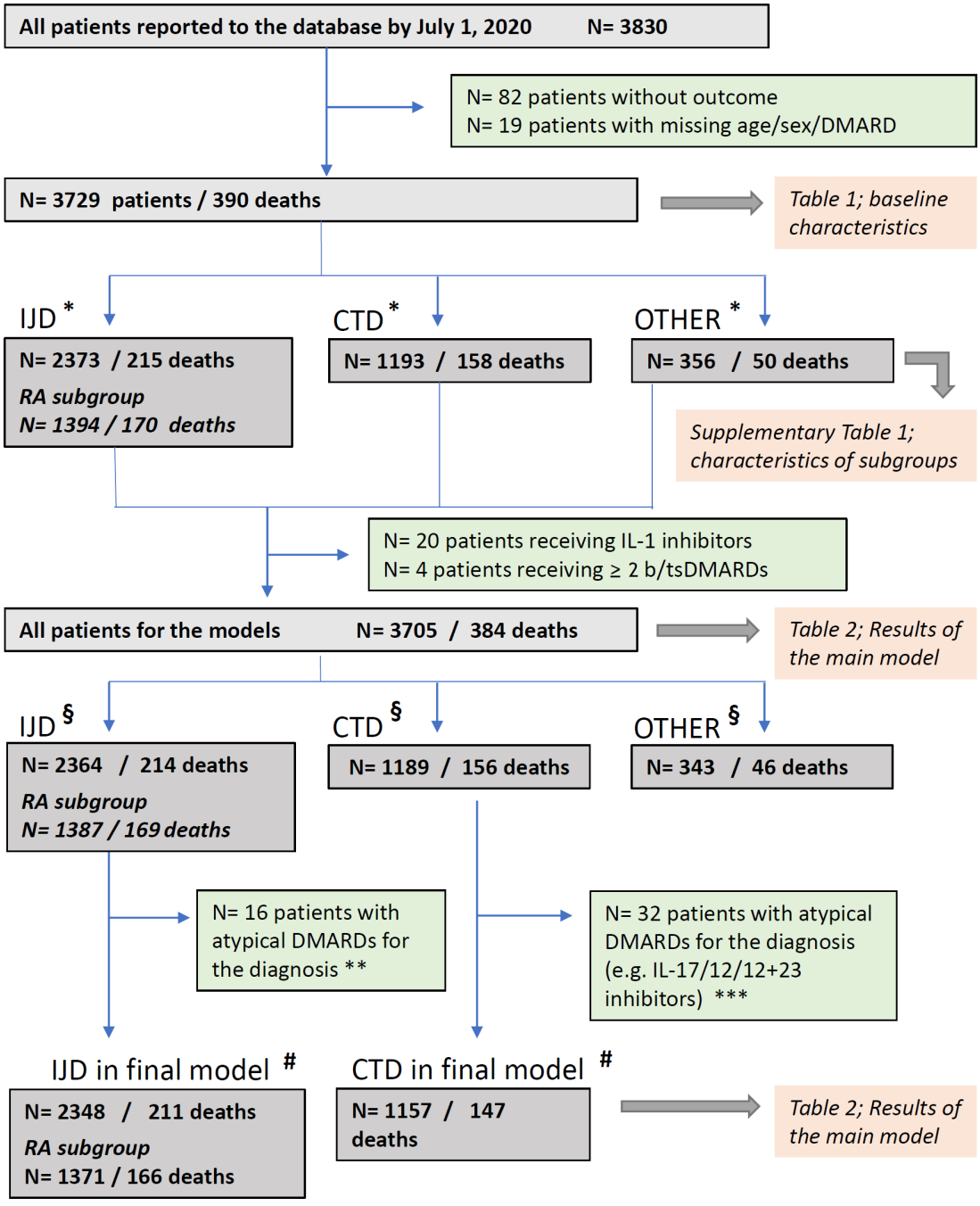

Figure 2 Patient flowchart. Some patients had diagnoses in multiple groups; as a result, the sum of patients in each group is greater than the total number of patients. (*) Patients belonging to more than one diagnosic group: IJD and CTD: N=78 (10 deaths); IJD and other: N=70 (12 deaths); CTD and other: N=50 (13 deaths); IJD and CTD and other: N=5 (2 deaths). (§) Patients belonging to more than one diagnosic group: IJD and CTD: N=77 (10 deaths); IJD and other: N=70 (12 deaths); CTD and other: N=49 (12 deaths); IJD and CTD and other: N=5 (2 deaths). (#) Patients belonging to more than one diagnosic group: IJD and CTD: N=59 (7 deaths). (**) Non-typical DMARDs for IJD and RA: immunosuppressants and belimumab; non-typical DMARDs for RA: IL-17/IL-23/IL-12+23 inhibitors. (***) Non-typical DMARDs for CTD: abatacept, IL-17/IL-23/IL-12+23 inhibitors, sulfasalazine, leflunomide and tsDMARDs. b/tsDMARDs, biological/targeted synthetic disease-modifying antirheumatic drugs; CTD, connective tissue disease/vasculitis; DMARDs, disease-modifying anti-rheumatic drugs; IJD, inflammatory joint disease; IL, interleukin; RA, rheumatoid arthritis.

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

Parameter	Not deceased	Deceased	Total
N	**3339**	**390**	**3729**
General			
Age (years)	55.5 (15.2)	69.7 (14.6)	57.0 (15.7)
≤30	197 (5.9)	9 (2.3)	206 (5.5)
31–50	1012 (30.3)	31 (7.9)	1043 (28)
51–65	1255 (37.6)	82 (21)	1337 (35.9)
66–75	536 (16.1)	109 (27.9)	645 (17.3)
>75	339 (10.2)	159 (40.8)	498 (13.4)
Male sex	1031 (30.9)	164 (42.1)	1195 (32)
Ever smoker	664 (23.3) (*N=2854*) (*Missing=485*)	112 (36.1) (*N=310*) (*Missing=80*)	776 (24.5) (*N=3164*) (*Missing=565*)
Regions			
African region	14 (0.4)	2 (0.5)	16 (0.4)
Eastern Mediterranean region	83 (2.5)	11 (2.8)	94 (2.5)
European region	2040 (61.1)	275 (70.5)	2315 (62.1)
North American region	1024 (30.7)	81 (20.8)	1105 (29.6)
South American region	112 (3.4)	10 (2.6)	122 (3.3)
South-East Asian region	11 (0.3)	0	11 (0.3)
Western Pacific region	55 (1.6)	11 (2.8)	66 (1.8)
Inflammatory joint diseases			
Rheumatoid arthritis	1224 (36.7)	170 (43.6)	1394 (37.4)
Spondyloarthritis	416 (12.5)	15 (3.8)	431 (11.6)
Psoriatic arthritis	420 (12.6)	20 (5.1)	440 (11.8)
Juvenile idiopathic arthritis (poly, oligo, not systemic)	21 (0.6)	4 (1)	25 (0.7)
Other inflammatory arthritis	90 (2.7)	8 (2.1)	98 (2.6)
Total Inflammatory joint diseases	2158 (64.6)	215 (55.1)	2373 (63.6)
Connective tissue diseases/Vasculitis			
Systemic lupus erythematosus	355 (10.6)	36 (9.2)	391 (10.5)
Connective tissue diseases (other than SLE)	473 (14.2)	60 (15.4)	533 (14.3)
Vasculitis	258 (7.7)	68 (17.4)	326 (8.7)
Total CTD	1035 (31)	158 (40.5)	1193 (32.0)
Other RMDs			
Total	306 (9.2)	50 (12.8)	356 (9.5)
Disease activity	*N=2464* (*Missing=875*)	*N=294* (*Missing=96*)	*N=2758* (*Missing=971*)
Remission	799 (32.4)	94 (32)	893 (32.4)
Minimal/low disease activity	1202 (48.8)	107 (36.4)	1309 (47.5)
Moderate disease activity	388 (15.7)	60 (20.4)	448 (16.2)
Severe/high disease activity	75 (3)	33 (11.2)	108 (3.9)
Other outcomes			
Hospitalised	1368 (43.3) (*N=3162*) (*Missing=177*)	371 (96.6) (*N=384*) (*Missing=6*)	1739 (49) (*N=3546*) (*Missing=183*)
Invasive ventilation	67 (2.5) (*N=2701*) (*Missing=638*)	120 (40.8) (*N=294*) (*Missing=96*)	187 (6.2) (*N=2995*) (*Missing=734*)
Comorbidities	*N=3314* (*Missing=25*)	*N=386* (*Missing=4*)	*N=3700* (*Missing=29*)
Hypertension	1095 (33)	212 (54.9)	1307 (35.3)
Cardiovascular disease	318 (9.6)	124 (32.1)	442 (11.9)
Cerebrovascular disease	89 (2.7)	20 (5.2)	109 (2.9)
Chronic lung disease	581 (17.5)	138 (35.8)	719 (19.4)
Chronic kidney disease	181 (5.5)	77 (19.9)	258 (7)
Obesity (BMI ≥30)	539 (16.3)	58 (15)	597 (16.1)
Morbid obesity (BMI ≥40)	106 (3.2)	16 (4.1)	122 (3.3)
Diabetes	410 (12.4)	95 (24.6)	505 (13.6)
Cancer	165 (5)	49 (12.7)	214 (5.8)
Other comorbidities	771 (23.3)	126 (32.6)	897 (24.2)
Number of comorbities	1.3 (1.3)	2.5 (1.6)	1.4 (1.3)
No comorbidity	1090 (32.9)	28 (7.3)	1118 (30.2)
One comorbidity	1032 (31.1)	83 (21.5)	1115 (30.1)
Two comorbidities	597 (18)	110 (28.5)	707 (19.1)
≥3 comorbidites	595 (18)	165 (42.7)	760 (20.5)
DMARD therapies			
csDMARDs monotherapy	592 (17.7)	59 (15.1)	651 (17.5)
csDMARDs combination therapy	692 (20.7)	61 (15.6)	753 (20.2)
Methotrexate monotherapy	531 (15.9)	47 (12.1)	578 (15.5)
Methotrexate combination therapy	607 (18.2)	52 (13.3)	659 (17.7)
Leflunomide monotherapy	61 (1.8)	12 (3.1)	73 (2)
Leflunomide combination therapy	120 (3.6)	10 (2.6)	130 (3.5)
Sulfasalazine monotherapy	51 (1.5)	16 (4.1)	67 (1.8)
Sulfasalazine combination therapy	129 (3.9)	26 (6.7)	155 (4.2)
Antimalarial monotherapy	287 (8.6)	17 (4.4)	304 (8.2)
Antimalarial combination therapy	322 (9.6)	39 (10)	361 (9.7)
Immunosuppressants monotherapy	149 (4.5)	26 (6.7)	175 (4.7)
Immunosuppressants combination therapy	147 (4.4)	21 (5.4)	168 (4.5)
Mycophenolate mofetil monotherapy	68 (2)	14 (3.6)	82 (2.2)
Mycophenolate mofetil combination therapy	81 (2.4)	15 (3.8)	96 (2.6)
Azathioprine monotherapy	63 (1.9)	7 (1.8)	70 (1.9)
Azathioprine combination therapy	51 (1.5)	3 (0.8)	54 (1.4)
Cyclophosphamide monotherapy	10 (0.3)	3 (0.8)	13 (0.3)
Cyclophosphamide combination therapy	5 (0.1)	5 (1.3)	10 (0.3)
Tacrolimus monotherapy	5 (0.1)	2 (0.5)	7 (0.2)
Tacrolimus combination therapy	11 (0.3)	0	11 (0.3)
Ciclosporin monotherapy	3 (0.1)	0	3 (0.1)
Ciclosporin combination therapy	11 (0.3)	1 (0.3)	12 (0.3)
bDMARDs monotherapy	675 (20.2)	48 (12.3)	723 (19.4)
bDMARDs combination therapy	562 (16.8)	46 (11.8)	608 (16.3)
TNF inhibitors monotherapy	434 (13)	13 (3.3)	447 (12)
TNF inhibitors combination therapy	340 (10.2)	17 (4.4)	357 (9.6)
Abatacept monotherapy	28 (0.8)	4 (1)	32 (0.9)
Abatacept combination therapy	46 (1.4)	5 (1.3)	51 (1.4)
B-cell-targeted bDMARDs monotherapy	71 (2.1)	25 (6.4)	96 (2.6)
B-cell-targeted bDMARDs combination therapy	106 (3.2)	18 (4.6)	124 (3.3)
Rituximab monotherapy	66 (2)	25 (6.4)	91 (2.4)
Rituximab combination therapy	85 (2.5)	17 (4.4)	102 (2.7)
Belimumab monotherapy	5 (0.1)	0	5 (0.1)
Belimumab combination therapy	22 (0.7)	1 (0.3)	23 (0.6)
IL-6 inhibitors monotherapy	51 (1.5)	3 (0.8)	54 (1.4)
IL-6 inhibitors combination therapy	34 (1)	2 (0.5)	36 (1)

Continued

Table 1 Continued

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 (#)	1056 (32) (*N=3302*) (*Missing=37*)	217 (57.1) (*N=380*) (*Missing=10*)	1273 (34.6) (*N=3682*) (*Missing=47*)
Glucocorticoids 1–10 mg/day	833 (25.6) (*N=3254*) (*Missing=85*)	150 (41.3) (*N=363*) (*Missing=27*)	983 (27.2) (*N=3617*) (*Missing=112*)
Glucocorticoids>10 mg/day	171 (5.3) (*N=3254*) (*Missing=85*)	49 (13.5) (*N=363*) (*Missing=27*)	220 (6.1) (*N=3617*) (*Missing=112*)
NSAIDs	600 (19.3) (*N=3103*) (*Missing=236*)	38 (11.0) (*N=345*) (*Missing=45*)	638 (18.5) (*N=3448*) (*Missing=281*)

Data are N (column %) for categorical variables or mean (SD) for continuous variables. The table includes all 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 parenthesis, for the applicable variables. (*) Includes one patient on a study medication (Lenabasum). (#) Includes patients with a missing glucocorticoid dosage.
bDMARD, biological disease-modifying antirheumatic drug; BMI, body mass index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CTD, connective tissue diseases; DMARD, disease-modifying antirheumatic drug; IL, interleukin; JAK, Janus kinase; JIA, juvenile idiopathic arthritis; N, number; NSAID, non-steroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus; TNF, tumour necrosis factor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

bDMARDs 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.

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 non-smokers (online supplemental table 12).

DISCUSSION

With global cooperation, the C19-GRA physician-reported registry is the largest collection to date of patients with rheumatic

Table 2 Multivariable logistic regression analysis of factors associated with COVID-19-related death in patients with rheumatic diseases (all patients)

	All			Patients with inflammatory joint diseases (IJDs)			Only patients with rheumatoid arthritis			Patients with connective tissue diseases (CTDs) or vasculitis		
	384/3705 (10.4%)			211/2348 (9.0%)			166/1371 (12.1%)			147/1157 (12.7%)		
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												
Age≤65	118/2565	1	Reference	55/1657	1	Reference	40/840	1	Reference	56/779	1	Reference
65years<Age≤75	109/644	**3**	**2.13 to 4.22**	71/426	**3.63**	**2.55 to 5.15**	55/314	**3.10**	**1.68 to 5.72**	33/187	**2.29**	**1.34 to 3.93**
Age>75	157/496	**6.18**	**4.47 to 8.53**	85/265	**8.21**	**5.54 to 12.18**	71/217	**7.30**	**4.42 to 12.06**	58/191	**4.08**	**2.27 to 7.36**
Male sex (vs female)	161/1188	**1.46**	**1.11 to 1.91**	82/788	1.31	0.95 to 1.8	55/345	1.17	0.78 to 1.76	63/296	1.66	0.96 to 2.86
Ever smoked (vs never)	140/922	1.21	0.94 to 1.57	84/607	1.26	0.93 to 1.72	71/385	**1.45**	**1.02 to 2.04**	42/248	1.11	0.67 to 1.86
Comorbidities												
Hypertension alone or CVD alone	155/1150	1.19	0.89 to 1.59	79/690	1.04	0.74 to 1.46	66/454	1.11	0.74 to 1.67	69/406	**1.56**	**1.06 to 2.29**
Hypertension and CVD	89/301	**1.89**	**1.31 to 2.73**	53/168	**2.29**	**1.25 to 4.23**	38/118	**2.03**	**1.03 to 3.97**	28/106	1.57	0.78 to 3.16
Chronic lung disease	136/721	**1.68**	**1.26 to 2.25**	76/406	**1.52**	**1.04 to 2.21**	63/293	1.44	0.99 to 2.09	54/285	**2.05**	**1.47 to 2.85**
Chronic kidney disease	76/259	1.67	0.99 to 2.8	27/111	1.09	0.54 to 2.21	21/83	1.01	0.46 to 2.24	41/124	**2.30**	**1.37 to 3.88**
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	0.64 to 3
Rheumatic disease												
Rheumatoid arthritis	160/1326	1	Reference	166/1373	1	Reference		n.a.			n.a.	
Systemic lupus erythematosus	36/391	1.2	0.70 to 2.04		n.a.			n.a.		32/378	1	Reference
Vasculitis	67/325	0.8	0.60 to 1.08		n.a.			n.a.		64/318	0.81	0.49 to 1.33
Other connective tissue diseases	53/473	**0.75**	**0.58 to 0.97**		n.a.			n.a.		51/461	0.78	0.39 to 1.54
Psoriasis arthritis	19/429	0.75	0.53 to 1.07	19/437	0.82	0.55 to 1.22		n.a.			n.a.	
Spondyloarthritis	15/423	0.72	0.34 to 1.54	15/424	0.82	0.4 to 1.69		n.a.			n.a.	
Other inflammatory arthritis or non-systemic JIA	10/109	0.79	0.46 to 1.34	11/114	0.76	0.43 to 1.36		n.a.			n.a.	
Other rheumatic diseases (not IJDs/CTDs/vasculitis)	24/229	**0.51**	**0.35 to 0.73**		n.a.			n.a.			n.a.	
High/moderate/severe disease activity (DA) vs remission/low DA	109/722	**1.87**	**1.27 to 2.77**	54/453	**1.6**	**1.13 to 2.26**	44/274	**1.60**	**1.03 to 2.47**	51/230	**2.45**	**1.49 to 4.02**
Medication												
Methotrexate	47/595	1	Reference	41/487	1	Reference	34/354	1	Reference	6/94	1	Reference
No DMARD therapy	124/739	**2.11**	**1.48 to 3.01**	38/239	**2.08**	**1.38 to 3.14**	25/110	**2.12**	**1.34 to 3.37**	67/353	**3.18**	**1.61 to 6.27**
Leflunomide	12/90	1.56	0.9 to 2.7	10/83	1.37	0.69 to 2.73	9/68	1.43	0.71 to 2.86		n.a.	
Antimalarials	27/426	0.99	0.66 to 1.48	17/167	1.14	0.65 to 2	17/141	1.24	0.7 to 2.19	11/271	1.38	0.48 to 4.02
Sulfasalazine	33/144	**3.6**	**1.66 to 7.78**	31/137	**3.40**	**1.46 to 7.93**	21/85	**2.62**	**1.21 to 5.68**		n.a.	
Immunosuppressants	38/276	**2.22**	**1.43 to 3.46**		n.a.			n.a.		32/247	**2.44**	**1.06 to 5.65**
TNF inhibitors	30/803	0.85	0.52 to 1.36	26/764	0.77	0.42 to 1.41	16/292	0.82	0.39 to 1.76	4/39	2.00	0.36 to 11.2
Abatacept	9/81	1.20	0.61 to 2.34	9/75	1.3	0.62 to 2.71	9/68	1.4	0.65 to 2.99		n.a.	
Rituximab	42/192	**4.04**	**2.32 to 7.03**	22/90	**5.42**	**2.77 to 10.61**	21/86	**4.99**	**2.43 to 10.26**	22/104	**3.72**	**1.21 to 11.48**
Belimumab	1/27	0.71	0.19 to 2.68		n.a.			n.a.		1/27	1.07	0.21 to 5.37
IL-6 inhibitors	5/90	0.83	0.38 to 1.84	1/68	0.25	0.03 to 2.43	1/63	0.25	0.03 to 2.33	4/23	2.69	0.88 to 8.19
IL-17/IL-23/IL-12+23 inhibitors	1/115	0.25	0.03 to 2.04	1/112	0.26	0.03 to 2.06		n.a.			n.a.	
tsDMARDs	15/145	1.60	0.91 to 2.8	15/142	1.75	0.99 to 3.12	13/118	1.57	0.75 to 3.27		n.a.	
Glucocorticoids (GCs)												
No GCs	165/2417	1	Reference	109/1721	1	Reference	78/863	1	Reference	38/551	1	Reference
GCs 1–10mg/day	170/1062	1.43	0.98 to 2.09	89/567	1.36	0.76 to 2.45	78/464	1.34	0.66 to 2.74	75/469	**1.69**	**1.11 to 2.57**

Continued

Table 2 Continued

N deaths/patients (%)	All			Patients with inflammatory joint diseases (IJDs)			Only patients with rheumatoid arthritis			Patients with connective tissue diseases (CTDs) or vasculitis		
	384/3705 (10.4%)			211/2348 (9.0%)			166/1371 (12.1%)			147/1157 (12.7%)		
	N deaths/patients	OR	95% CI	N deaths/patients	OR	95% CI	N deaths/patients	OR	95% CI	N deaths/patients	OR	95% CI
GCs>10 mg/day	49/226	**1.69**	**1.18 to 2.41**	12/60	1.55	0.67 to 3.57	10/44	1.59	0.6 to 4.18	34/137	**1.93**	**1.11 to 3.36**

Missing values were imputed via multiple imputation, patient numbers may thus be rounded. Effects significant at level α=0.05 are marked in bold. 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.
TNF; tumour necrosis factor; CTD, connective tissue diseases; CVD, cardiovascular disease; DMARD, disease-modifying antirheumatic drugs; GC, glucocorticoids; IL, interleukin; JIA, juvenile idiopathic arthritis; N, number; n.a., not applicable; tsDMARD, targeted synthetic disease-modifying antirheumatic drugs.

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.[1] Other factors associated with death were older age, male sex and the presence of comorbidities, which is consistent with reports from the general population.[8] 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.[19] 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)).[20] 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.[21–24] 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

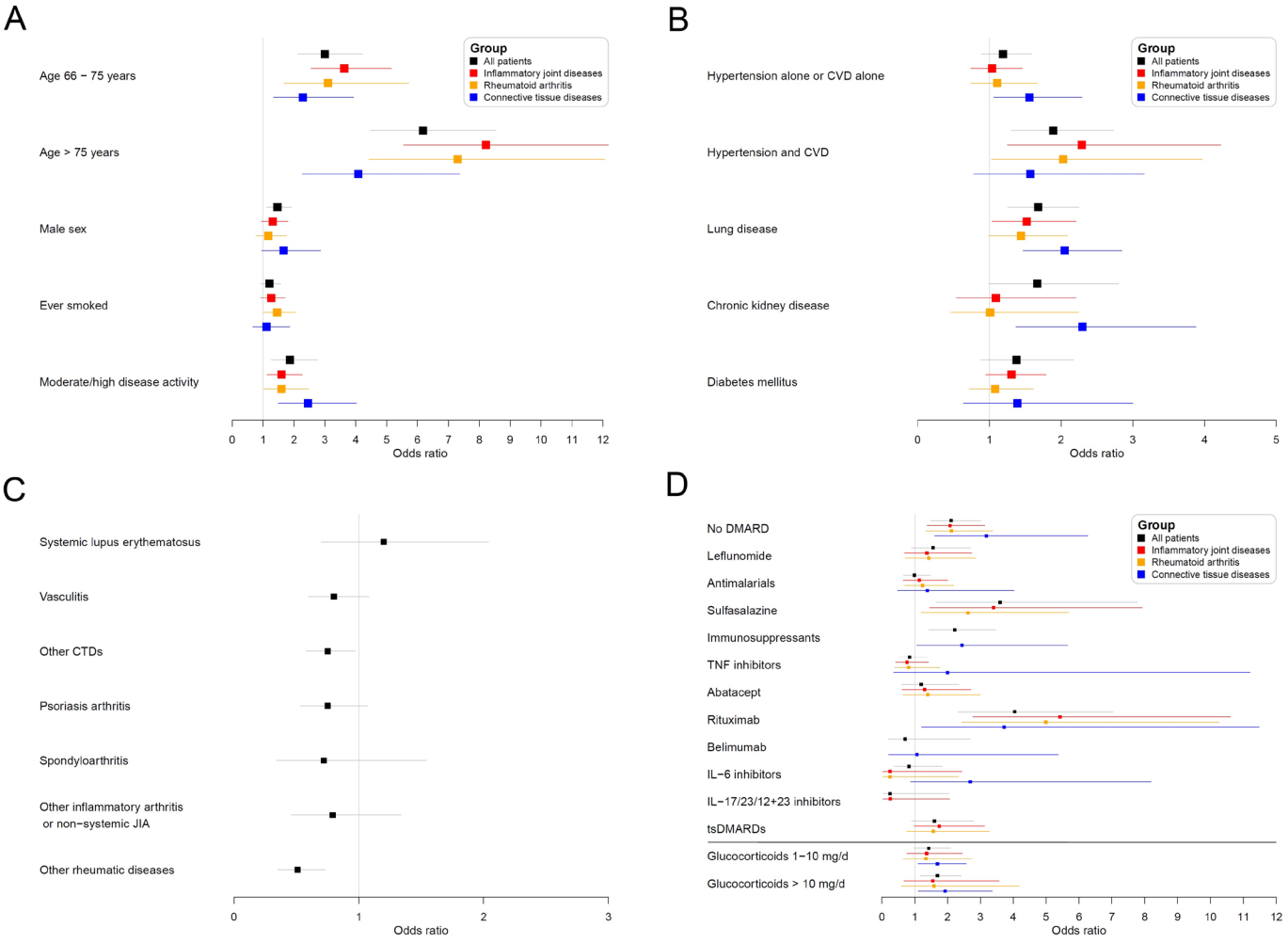

Figure 3 Results of the main logistic regression analysis. Shown are multivariable-adjusted ORs for the outcome COVID-19-related death with 95% CIs, assessing the association with (A) general patient characteristics, (B) comorbidities, (C) rheumatic disease diagnoses (RMD) and (D) rheumatic disease medications. 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 disease 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 diseases; CVD, cardiovascular disease; JIA, juvenile idiopathic arthritis; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drug.

merging of sulfasalazine combination therapy (with other csDMARDs) with sulfasalazine monotherapy; however, the increased odds for death persisted in the sulfasalazine monotherapy 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.[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.[29 30] 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.

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