Ther Adv Musculoskel Dis
2022, Vol. 14: 1–16
DOI: 10.1177/1759720X221090296

Mortality related to COVID-19 in patients with rheumatic and musculoskeletal diseases, first wave of the outbreak: a single-center study

Dalifer Freites Nuñez, Leticia Leon, Alfredo Madrid Garcia, Jose Ignacio Colomer Arce, Arkaitz Mucientes, Benjamin Gutierrez-Fernandez, Luis Rodriguez, Inés Pérez San Cristóbal, Paula Álvarez, Cristina Martinez Prada and Lydia Abasolo

Abstract

Objectives: The aim of this study was to assess the cause-specific mortality rate related to COVID-19 (CMR) in patients with rheumatic and musculoskeletal diseases (RMDs) and COVID-19 and to analyze the role of the different RMDs in their mortality risk.

Methods: An observational longitudinal study was conducted during the first pandemic wave in our center. Patients with the diagnosis of RMDs and COVID-19 were included. Main outcome is the death related to COVID-19. Independent variable – type of RMDs: autoimmune rheumatic diseases (ARD), such as chronic inflammatory arthritis (CIA) and connective tissue diseases (CTD) and non-autoimmune Rheumatic Diseases (non-ARD). Survival techniques were used to estimate the CMR per 1000 patients-month with a 95% confidence interval (CI), and Cox multivariate regression analysis was run to examine the effect of ARD compared to non-ARD on mortality risk adjusted by confounders. Results were expressed by Hazard Ratio (HR) and CI.

Results: Overall, 405 patients were included (642.5 patients-month). During the study period, 44 (10.86%) deaths were recorded. CMR was 68.48 (50.96–92.01). After adjusting for confounders, HR of mortality in ARD compared to non-ARD did not achieve statistical significance [HR: 1.15 (0.64–2.07)], neither CTD *versus* CIA nor CTD *versus* non-ARD. Age and certain comorbidities which are being diagnosed in March compared to April or May [HR: 2.43 (1.1–5.55)] increased the mortality risk. Glucocorticoids and disease-modifying antirheumatic drugs (DMARDs) dropped from the final model.

Conclusion: In patients with RMDs and COVID-19, CMR was 6.8% patients-month. This study shows that mortality risk is higher in males, older patients, and similar between CTD, CIA, and non-ARD. COVID-19 management improved after the first month of pandemic.

Plain Language Summaries

Mortality related to the outbreak of COVID-19 in patients with rheumatic and musculoskeletal diseases

Why was this study done?

- To report the COVID-19-specific mortality rate in patients with a variety of RMDs during the first pandemic peak in a tertiary hospital in Madrid and to analyze the role of specific types of ARD and other possible factors in the risk of death related to COVID-19.

Correspondence to:
Leticia Leon
Health Research Institute (IdISSC), Hospital Clínico San Carlos, c\Prof. Martín Lagos s/n, 28040 Madrid, Spain
Health Sciences, Camilo Jose Cela University, Madrid, Spain
lleon@salud.madrid.org

Dalifer Freites Nuñez
Inés Pérez San Cristóbal
Paula Álvarez
Cristina Martinez Prada
Rheumatology Department, Hospital Clínico San Carlos, Madrid, Spain

Alfredo Madrid Garcia
Jose Ignacio Colomer Arce
Arkaitz Mucientes
Lydia Abasolo
Health Research Institute (IdISSC), Hospital Clínico San Carlos, Madrid, Spain

Benjamin Gutierrez-Fernandez
Luis Rodriguez
Rheumatology Department, and Health Research Institute (IdISSC), Hospital Clínico San Carlos, Madrid, Spain

What did the researchers do?

- We performed a retrospective observational study during the first wave of the COVID-19 pandemic in Madrid, Spain.

What did the researchers find?

- In this study, neither the different diagnoses of RMDs, including CIA, CTD, or non-ARD disease or its treatment were not implicated as a potential risk of death related to COVID-19
- In consonance with other studies, RMDs patients and COVID-19, older age, male sex, and certain comorbidities implied more mortality risk
- Our data reflect COVID-19 severity in a particular context, time, and population. In times of the absence of COVID-19 vaccine, healthcare, social, and political measures taken to contain the coronavirus outbreak have worked properly.

What do the findings mean?

- The presence of comorbidities in RMDs patients represents a greater risk than the different types of RMDs themselves, in the development of COVID-19 fatal outcome. It is important to integrate the control of comorbidities in the daily management.

Keywords: autoimmune disease, COVID-19, epidemiology, mortality, rheumatic diseases

Received: 17 December 2021; revised manuscript accepted: 10 March 2022.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the novel acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has triggered a global health crisis.[1,2] Currently, the cumulative number of confirmed COVID-19 cases worldwide has exceeded 370 million.[3] The spectrum of symptomatic infection ranges from mild to critical; fortunately, most infections are not severe and have good prognosis.[4–9] In general population, the proportion of severe or fatal disease occurs predominantly in patients with certain risk factors, such as advanced age, male sex, and with underlying comorbidities[4,8,10–20]

Individuals with rheumatic and musculoskeletal diseases (RMDs), especially those with ARD, have a higher risk to be infected with SARS-CoV2 and develop COVID-19 than the general population.[21–24] Concretely, the significance of ARD and their therapies, with respect to the course of COVID-19, is in a constant update of evidence, with preliminary findings suggesting that a poorly controlled systemic autoimmune condition and certain comorbidities increased the risk of hospital admission,[25] whereas most disease-modifying antirheumatic drugs (DMARDs) were not associated with hospital admission.[21,26–31] Regarding DMARDs, it has been recently published that the use of rituximab and Janus kinase (JAK) inhibitors seems to increase the disease severity.[32,33] In addition, in patients with RMDs hospitalized with COVID-19, certain features might determine critical or fatal disease.[4,9]

Thus, individuals with RMDs and infected with COVID-19 require special consideration because the underlying immune conditions or other factors could affect the clinical prognostic. In this regard, several publications have raised with controversial results. In a meta-analysis of Wang *et al.*,[5] they did not find that ARD had a higher risk of death due to COVID-19. Whereas in the meta-analysis of Xu *et al.*,[34] the fatality rate was higher in rheumatic diseases, although age, gender and comorbidity were not matched. We have to note the heterogeneity found in different rheumatic diseases, reference population, geographic location or time period included in both meta-analyses.

Certainly, the epidemiological situation and disease severity after the introduction of COVID-19 vaccine have resulted in a better scenario;[35–38] however, to understand how the pandemic is evolving, it is a matter of interest to know more about the severity of the disease and mortality rates of COVID-19 in patients with RMDs under non-vaccination conditions. The aim of our study is to report the COVID-19-specific mortality rate in patients with a big variety of RMDs, during the first pandemic peak in a tertiary hospital in Madrid. Moreover, we analyze the role of specific types of ARD and other possible factors, including the month of COVID-19 diagnosis in the risk of death related to COVID-19.

Methods

Setting, study design, and patients

It was conducted in a public reference tertiary hospital, Hospital Clínico San Carlos (HCSC), in Madrid, Spain. The catchment area is almost 400,000 people.

We performed a retrospective observational study during the first wave of the COVID-19 pandemic from 1 March (when our health area had the first hospital admission related to COVID-19) to 20 May 2020. We preselected all the patients attended at our rheumatology outpatient clinic during the study period whose data were recorded in our departmental electronic health record (EHR Penelope). The inclusion criteria were patients older than 16 years of age with a medical diagnosis of RMD [according to International Classification of Diseases (ICD-10)] and diagnosed with COVID-19 according to a medical diagnosis and confirmed with a positive SARS-CoV-2 polymerase chain reaction (PCR) diagnostic test. All patients were included since the date of COVID-19 diagnosis until death or end of the study (20 May).

Patient data were obtained during routine daily clinical practice. The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice, and HCSC Ethics Review Board approval was obtained (Approval No. 20/268-E_BS).

Data source

Sociodemographic, clinical, and laboratory data of the RMDs patients were obtained through EHR Penelope.

Patients infected by COVID-19 were detected by different ways: (a) phone contact: warning calls to our rheumatologists or nurses or *via* routine telephone consultation; (b) through their sick leave forms due to COVID-19; (c) SARS-CoV-2 PCR diagnostic assays obtained from the microbiology/infectious service of HCSC; and (d) admissions due to COVID-19 obtained from HCSC Central Services. In addition, deaths due to COVID-19 were obtained from HCSC Central Services, and last report received was on 20 May 2020.

Variables

The main outcome was mortality related to COVID-19 in patients with RMDs. The independent variable was the type of RMD: (a) ARD, including (a1) chronic inflammatory arthritis (CIA) and (a2) connective tissue diseases (CTD) and (b) non-ARD (Table 1).

The co-variables recorded at the baseline were the following: (1) sociodemographic characteristics, including sex, age, and RMD duration. (2) Disability (using a seven-ordinal level scale from 1 = *perfect health* to 7 = *unable to get out of the bed*) from the Rosser Classification Index (RCI).[39] (3) Comorbid conditions, including hypertension, dyslipidemia, depression, diabetes mellitus, smoking habit, chronic renal insufficiency, chronic liver disease, lung diseases (chronic obstructive pulmonary disease and interstitial lung disease), thyroid disease, heart disease (valve disease, arrhythmias, cardiomyopathy, heart failure and pericarditis), ischemic vascular disease (stroke, cardiovascular and peripheral vascular disease), venous thromboembolism (pulmonary embolism and deep vein thrombosis), and cancer. (4) Erythrocyte sedimentation rate (ESR) as a surrogate variable of disease activity (mean value, at least 3 months prior to COVID-19 infection). (5) Stable treatments for RMDs – (a) non-steroidal anti-inflammatory drugs (NSAIDs); (b) glucocorticoids (mean dose during the previous month of COVID-19 infection); (c) conventional synthetic disease-modifying antirheumatic drugs (csDMARDs): antimalarials (hydroxychloroquine and chloroquine), azathioprine, cyclophosphamide, cyclosporine, colchicine, leflunomide, methotrexate, mycophenolate mofetil/mycophenolic acid, and sulfasalazine; (d) targeted synthetic/biologic DMARDs (b/tsDMARDs), including (d1) anti-tumor necrosis factor (TNF)-alpha drugs (infliximab, adalimumab, etanercept, certolizumab, and golimumab); (d2) other biologics: anti-interleukin (IL)-6 (tocilizumab and

Table 1. Type of diagnoses by RMD groups.

			***N* (%)**
ARD *N* = 162 (40%)	CIA *N* = 107 (26%)	Rheumatoid arthritis	65 (61)
		Undifferentiated inflammatory polyarthritis	9 (8.4)
		Psoriatic arthritis	8 (7.5)
		Axial spondyloarthritis or other spondyloarthritis	25 (33.1)
	CTD *N* = 55 (14%)	Polymyalgia rheumatica	9 (16.4)
		Mixed connective tissue disease	8 (14.6)
		Systemic sclerosis	4 (7.3)
		Sjogren's syndrome	10 (18.2)
		Vasculitis	4 (7.3)
		Raynaud's phenomenon	3 (5.4)
		Polymyositis	1 (1.8)
		Polychondritis	1 (1.8)
		Behçet's disease	2 (3.6)
		Antiphospholipid syndrome	2 (3.6)
		Systemic lupus erythematosus	11 (20)
Non-ARD *N* = 243 (60%)	Musculoskeletal mechanical diseases *N* = 157(38.8%)	Back pain	26 (16.6)
		Neck pain	8 (5.1)
		Sciatica	13 (8.3)
		Peripheral neuropathy	5 (3.2)
		Disorders of muscles including fibromyalgia	22 (14)
		Osteoarthritis	50 (31.8)
		Osteoporosis	10 (6.4)
		Other soft tissue disorders, including internal knee pain	23 (14.6)
	Inflammatory non-autoimmune diseases *N* = 86 (21.2%)	Microcrystalline arthritis	15 (17.4)
		Disorders of synovium and tendon	71 (82.6)

sarilumab), rituximab, abatacept, belimumab, anti-IL-17/23, anti-IL-17 (ustekinumab, ixekizumab, and secukinumab); and (d3) JAK inhibitors (tofacitinib and baricitinib). All treatments were considered stable in terms of prescription and dose at least 1 month prior to the diagnosis of COVID-19. (6) COVID-19 diagnosis date (calendar time by month intervals).

Statistical analysis

A descriptive analysis was performed for the sociodemographic and clinical characteristics of the study population and for the main outcome. Continuous variables were expressed as mean [and standard deviation (SD)] or median values [and interquartile ranges (IQR)]. Categorical variables were expressed as frequencies. Continuous variables were compared using a two-sample *t*-test for continuous normally distributed variables or Mann–Whitney U test for continuous non-normally distributed variables. Categorical variables were compared using chi-squared tests. The case fatality rate was calculated as the number of deaths related to COVID-19 divided by the number of confirmed cases of COVID-19. Survival techniques were used to estimate the cause-specific mortality rate related to COVID-19 (CMR), expressed per 1000 patients-month with a 95% confidence interval (CI). Survival over time was evaluated using Kaplan–Meier curves.

Cox regression analysis was conducted to determine the risk factors of death related to COVID-19. Cox bivariate analyses were done to assess the differences between COVID-19 mortality risk and covariates. Cox multivariate regression model (adjusted for age, sex, comorbidity related to COVID-19, and calendar time) was run in a stepwise manner to examine the possible influence of the types of RMDs on survival. The model also included DMARDs and all other variables with a $p < 0.2$ from the bivariate regression analysis. Results were expressed by hazard ratio (HR) and CI. Proportional hazard assumption was tested using Schoenfeld residuals and the scaled Schoenfeld residuals.

All analyses were performed using STATA software version 13 (Stata Corp, College Station, TX, USA). A two-tailed *p*-value less than 0.05 was considered to indicate statistical significance. Data were anonymized. The reporting of this study conforms to the strengthening the reporting of observational studies in epidemiology (STROBE) statement (Supplementary Material 1).[40]

Results

Patient characteristics

During the study period, 405 patients with RMDs were diagnosed with COVID-19. The most common RMD was the non-ARD in 243 patients, followed by CIA in the ARD group (26%), including 65 Rheumatoid arthritis (RA) patients (Table 1).

Table 2 outlines the baseline demographic and clinical characteristics of ARD and non-ARD patients. From the total, 69.14% were women with a mean age of 59.37 years, without differences between diagnosis groups. The mean RMDs duration at the time of COVID-19 infection was different according to the condition with a mean of 11.48, 11.64, and 5.03 years for CIA, CTD, and non-ARD, respectively.

Regarding comorbidity, it was present in 34% of the patients at baseline, being highest in those with CTD. The most frequent were the traditional cardiovascular risk factors. The presence of any type of comorbidity related to COVID-19 severity (see footnote Table 2) was reported in 26% of the patients and results higher in CTD, followed by CIA and non-ARD with statistical significance between them. Specifically, by the types of comorbidities, there were no differences between RMD groups except for chronic liver disease that was lower in non-ARD.

Hospital admission due to COVID-19 was required in 146 patients. This percentage was primarily at the expense of CTD. Concerning RMDs chronic treatments, in CTD, the use of NSAIDs was less frequent, whereas exposure to glucocorticoids was more frequent compared to other RMDs groups. The median dose of glucocorticoids was 5 mg with a minimum of 2.5 mg and a maximum of 30 mg. Methotrexate was the most commonly used csDMARD followed by antimalarials. Among b/tsDMARDs, anti-TNF drugs were the most widely used.

Case fatality rate for COVID-19

We found 44 deaths related to COVID-19 during the study period. The case fatality rate was 10.86%, being 12.7%, 12.15%, and 9.88% for CTD, CIA, and non-ARD, respectively, ($p = 0.7$). Death cases reported 54.55% were women with a mean age of 81.61 (7.29) years. ARD was present in 45.45%, including nine patients with RA. Almost two-thirds of the patients (70.45%) had at least one baseline comorbidity and the most prevalent was hypertension (45%). All cases had a positive SARS-CoV-2 PCR diagnostic test, and most of deaths (88%) occurred during hospital admission. Concerning treatments, 43.18% individuals were exposed previously to glucocorticoids with a mean (SD) prednisone equivalent dose of 5.78 (2.5) mg/day. Regarding DMARDs, five patients were receiving methotrexate, two

Table 2. Baseline demographic and clinical characteristics of patients with RMDs and COVID-19.

Variable	COVID-19 patients (*N* = 405)	ARD		Non-ARD (*N* = 243)	*p*
		CIA (*N* = 107)	CTD (*N* = 55)		
Female gender, *n* (%)	280 (69.14)	70 (65.42)	41 (74.55)	169 (69.55)	0.48
Age (years), M (SD)	59.37 (15.26)	58.92 (15.09)	62.57 (15.3)	58.84 (15.32)	0.24
Time since RMD diagnosis (years), M (SD)	7.62 (8.39)	11.48 (9.29)	11.64 (8.83)	5.03 (6.74)	0.000
COVID-19 diagnosis date, *n* (%)					
March	262 (64.69)	67 (62.62)	32 (57.14)	163 (67.08)	
April	129 (31.85)	38 (34.91)	20 (36.36)	71 (29.22)	0.44
May	14 (3.46)	1 (0.93)	3 (5.45)	9 (3.70)	
Disability, *n* (%) Moderate or severe	92 (22.72)	21 (19.63)	13 (23.64)	58 (23.87)	0.6
PCR diagnostic test, *n* (%)					
Negative	19 (4.69)	6 (5.61)	1 (1.82)	12 (4.94)	
Positive	185 (45.68) 201	44 (41.12)	31 (56.36)	110 (45.27)	0.43
Not performed	(49.63)	57 (53.27)	23 (41.82)	121 (49.79)	
Active smoking habit, *n* (%)	12 (2.96)	3 (2.80)	2 (3.64)	7 (2.88)	0.9
Comorbidity, *n* (%)	138 (34.10)	41 (38.32)	26 (47.27)	71 (29.22)	0.2
Heart disease	34 (8.40)	11 (10.28)	7 (12.73)	16 (6.58)	0.19
Ischemic vascular disease	16 (3.95)	4 (3.74)	3 (5.45)	9 (3.70)	0.71
Hypertension	87 (21.48)	29 (27.10)	9 (16.36)	49 (20.16)	0.22
Diabetes mellitus	29 (7.16)	8 (7.48)	7 (12.73)	14 (5.76)	0.19
Dyslipidemia	67 (16.54)	18 (16.82)	4 (7.27)	45 (18.52)	0.123
Obesity	17 (4.20)	6 (5.61)	2 (3.64)	9 (3.70)	0.63
Lung disease	39 (9.63)	11 (10.28)	10 (18.18)	18 (7.41)	0.052
Chronic liver disease	13 (3.21)	6 (5.61)	4 (7.27)	3 (1.23)	0.011
Chronic renal insufficiency	12 (2.96)	3 (2.80)	4 (7.27)	5 (2.06)	0.125
Cancer	22 (5.43)	2 (1.87)	5 (9.09)	15 (6.17)	0.076
Venous thromboembolism	7 (1.73)	4 (3.74)	1 (1.82)	2 (0.82)	0.102
Peptic ulcer disease	10 (2.47)	5 (4.67)	1 (1.82)	4 (1.65)	0.25
Neurological disease	16 (3.95)	1 (0.93)	3 (5.45)	12 (4.94)	0.154
Thyroid disease	30 (7.41)	10 (9.35)	7 (12.73)	13 (5.35)	0.144
Depression	26 (6.42)	9 (8.41)	0	17 (7)	0.063

(continued)

Table 2. (continued)

Variable	COVID-19 patients (*N* = 405)	ARD		Non-ARD (*N* = 243)	*p*
		CIA (*N* = 107)	CTD (*N* = 55)		
Comorbidity[a]	105 (25.93)	31 (28.97)	26 (47.27)	48 (19.75)	0.000
Hospital admission, *n* (%)	146 (36.05)	38 (35.51)	32 (58.18)	76 (31.28)	0.001
NSAIDs, *n* (%)	109 (26.91)	29 (27.10)	6 (10.91)	74 (30.45)	0.013
Glucocorticoids, *n* (%)	82 (20.25)	47 (43.93)	29 (52.73)	6 (2.47)	0.000
Colchicine, *n* (%)	23 (5.68)	2 (1.87)	5 (9.09)	16 (6.58)	0.087
csDMARDs, *n* (%)	122 (30.12)	86 (80.37)	33 (58.18)	3 (1.23)	0.000
Methotrexate	70 (17.28)	55 (51.40)	15 (25.86)	0	–
Leflunomide	17 (4.20)	16 (14.95)	1 (1.82)	0	–
Sulfasalazine	13 (3.21)	12 (11.21)	1 (1.82)	0	–
Antimalarials	40 (9.88)	26 (24.30)	11 (20.00)	3 (1.23)	0.000
Azathioprine	11 (2.72)	1 (0.93)	10 (18.18)	0	–
Mofetil/mycophenolic	1 (0.25)	0	1 (1.82)	0	–
Cyclophosphamide	1 (0.25)	0	1 (1.82)	0	–
b/tsDMARDs, *n* (%)	36 (8.89)	29 (27.10)	7 (12.73)	0	–
Anti-TNF	25 (6.17)	23 (21.50)	2 (3.64)	0	–
Infliximab	3 (0.74)	2 (1.87)	1 (1.82)	0	–
Golimumab	2 (0.49)	2 (1.87)	0	0	–
Adalimumab	12 (2.96)	11 (10.28)	1 (1.82)	0	–
Etanercept	4 (0.99)	4 (3.74)	0	0	–
Certolizumab	4 (0.99)	4 (3.74)	0	0	–
Other biologic agents	10 (2.47)	5 (4.67)	5 (9.09)	0	–
Abatacept	1 (0.25)	1 (0.93)	0	0	–
Tocilizumab	4 (0.99)	2 (1.87)	2 (3.64)	0	–
Belimumab	1 (0.25)	0	1 (1.82)	0	–
Rituximab	4 (0.99)	2 (1.87)	2 (3.64)	0	–
JAKi	1 (0.25)	1 (0.93)	0	0	–

Anti-TNF, tumor necrosis factor-alpha inhibitor; ARD, autoimmune rheumatic diseases; b/tsDMARDs, biologic/target synthetic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; JAKi, JAK inhibitor; PCR, polymerase chain reaction; RMDs, rheumatic and musculoskeletal diseases; SD, standard deviation. Heart disease: arrhythmias, valve disease, cardiomyopathy, and heart failure. Ischemic vascular disease: stroke, cardiovascular, and peripheral vascular disease. Lung disease: the presence of chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD). Disability: moderate–severe: level of disability $\geqslant 3$.
[a]Comorbidity related to COVID-19: presence of at least one of the following: diabetes mellitus, heart disease (arrhythmias, valve disease, cardiomyopathy, and heart failure), ischemic vascular disease (stroke, cardiovascular, and peripheral vascular disease), chronic liver disease and renal insufficiency, pulmonary embolism, and lung disease (ILD and COPD).

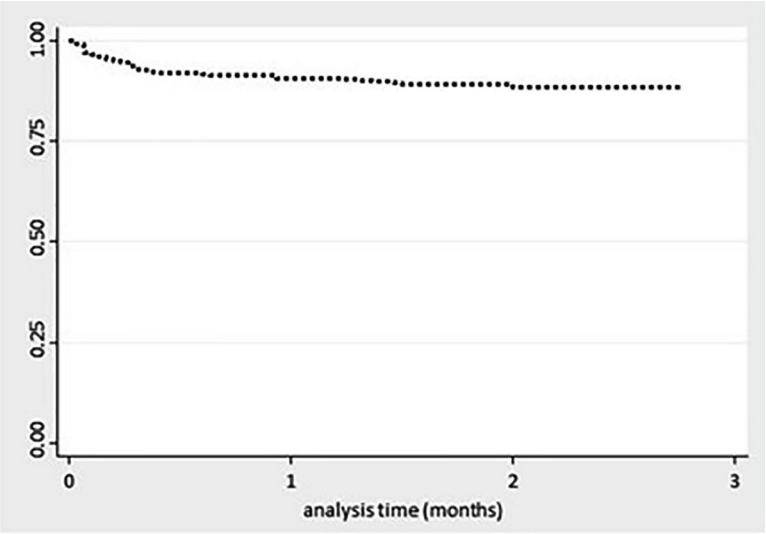

Figure 1. Cumulative incidence of deaths related to COVID-19 over time in patients with RMD during the study period. Kaplan–Meier survival estimate curve.

patients anti-TNF, and one patient JAK inhibitors. None was previously received on regular treatment with NSAIDs or other biological agents.

CMR for COVID-19

In individuals with RMDs, the CMR was estimated in 68.48 cases per 1000 patients-month (95% CI: 50.96–92.01). Figure 1 represents cumulative incidence of deaths related to COVID-19, showing that deaths occurred early soon after the diagnosis. In the 44 death cases recorded, the median lag time from diagnosis to death was 6.5 (2–15) days, 75% occur within 12 days. In those patients who required hospital admission, the median lag time was 5 (2–11) days and 75% occur within 10 days.

Table 3 shows CMR by different patient's characteristics. CMR resulted higher in male sex, in older patients, in those with a baseline comorbidity related to COVID-19, and in those with higher levels of disability. Concerning to different RMDs groups explored, CMR was somewhat higher for CTD. Assessing specific type of RMD, it was higher especially for RA, vasculitis, polymyalgia rheumatic, and MCTD patients. Interestingly, the CMR was higher in those patients diagnosed in March compared from those in April or May.

Respecting drug exposure, glucocorticoids presented more CMR, whereas the use of b/tsDMARDs had lower CMR both compared to non-exposure. Regarding csDMARDs, patients on these drugs did not differ in their CMR from those without them. Specifically in patients on MTX, and antimalarials, the CMR was estimated in 43.6 [18.1–104.7], and in 82.05 [34.1–197.14], respectively.

Role of an ARD diagnosis and factors associated to death related to COVID-19

In the bivariate analysis (Table 4), comparison of ARD with non-ARD did not achieve statistical significance [HR: 1.31 (0.72–2.37), $p = 0.36$], neither CTD *versus* CIA nor CTD *versus* non-ARD. Concerning covariates, age, gender, time of evolution of the RMD, month of COVID-19 diagnosis, disability, and presence of comorbidity were associated to mortality with statistical significance. Exposure to glucocorticoids increased the risk of mortality, whereas exposure to DMARDs of any type did not.

Multivariate regression model is shown in Table 5. The HR of mortality in ARD compared to non-ARD did not achieve statistical significance (HR: 1.15 (0.64–2.07), $p = 0.64$), neither CTD *versus* CIA nor CTD *versus* non-ARD. Older age and comorbidity related to COVID-19 severity implied more risk of mortality, nevertheless, having hypertension dropped from the model ($p = 0.7$). Interestingly, patients diagnosed in March had independently more risk of death compared to

Table 3. COVID-19-specific mortality rate analysis per 1000 patients-month in patients with RMDs and COVID-19.

	n	Follow-up Persons-month	CMR per 1,000 Persons-month	CI 95%
Total	44	642.5	68.48	50.96–92.01
Sex				
Male	20	189.7	105.45	68.03–163.45
Female	24	452.8	52.99	35.52–79.06
Age (years), *n* (%)				
<50	0	185.7	0	–
50–59	1	223.9	4.47	0.63–31.70
60–74	5	154.9	32.28	13.44–77.55
>75	38	78	487.18	354.49–669.53
ARD	20	245.17	81.58	52.63–126.45
CIA	13	163.83	79.59	46.2–137.1
Rheumatoid arthritis	9	99.7	90.27	46.97–173.49
Polyarthritis[a]	1	13.8	72.45	10.2–514.4
Psoriatic arthritis	0	11.6	0	–
Spondyloarthritis	3	35.16	85.30	27.15–264.5
CTD	7	81.83	85.50	40.77–179.42
Polymyalgia rheumatica	3	10.37	289.39	93.33–897.27
MCTD	1	14.1	70.92	9.99–503.48
Systemic sclerosis	0	6	0	–
Sjogren's syndrome	1	15.3	64.37	9.06–457.02
Vasculitis	2	2.03	983.61	246–3932.89
Raynaud's phenomenon	0	2.3	0	–
Polymyositis	0	1.5	0	–
Polychondritis	0	2.1	0	–
Behcet's disease	0	2.9	0	–
Antiphospholipid syndrome	0	4.3	0	–
Systemic lupus erythematosus	0	17.53	0	–
Non-ARD	24	397.4	60.39	40.48–90.10
Month of COVID-19 infection				
March	36	476.33	75.58	54.52–104.78
April	8	161	48.13	24.84–99.36

(continued)

Table 3. (continued)

	n	Follow-up Persons-month	CMR per 1,000 Persons-month	CI 95%
May	0	5.23	0	–
PCR diagnostic test				
Negative	0	25.7	0	–
Positive	31	270.7	114.52	80.54–162.84
Not performed	13	346.1	37.55	21.80–64.67
Comorbidity[b]				
Yes	26	144.7	179.60	122.28–263.78
No	18	497.8	36.15	22.78–57.39
Disability level				
None or mild	20	515.87	38.77	25.01–60.09
Moderate or severe	24	126.7	189.42	126.96–282.61
Hospital admission required				
Yes	39	198.1	196.87	143.8–269.4
No	5	444.4	11.25	4.68–27.07
Glucocorticoids				
Yes	19	110.7	171.53	109.4–268.9
No	25	531.8	47.01	31.7–69.57
csDMARDs				
No	31	454.0	68.3	48.01–97.07
Yes	13	188.5	69.9	40.04–118.71
b/tsDMARDs				
Yes	3	54.5	54.98	17.73–170.47
No	41	588	69.7	51.34–94.69
Anti-TNF	2	38.93	51.37	12.85–205.40
Other biological agents	0	15.6	0	–
JAKi	1	0.07	–	–

Anti-TNF, tumor necrosis factor-alpha inhibitor; ARD: autoimmune rheumatic diseases; b/tsDMARDs, biologic/target synthetic disease-modifying antirheumatic drug; CI, confidence interval; CIA, chronic inflammatory arthritis; csDMARD, conventional synthetic disease-modifying anti rheumatic drug; CMR, cause-specific mortality rate; CTD, connective tissue diseases; JAKi, Janus Kinase inhibitors; MCTD, Mixed connective tissue disease; PCR, polymerase chain reaction; RMDs, rheumatic and musculoskeletal diseases.
Other biological agents including abatacept, rituximab, tocilizumab, and belimumab. csDMARDs, including methotrexate, leflunomide, antimalarials, azathioprine, sulfasalazine, cyclophosphamide, and azathioprine.
[a]Polyarthritis: Undifferentiated inflammatory polyarthritis.
[b]Comorbidity related to COVID-19: presence of at least one of the following: diabetes mellitus, heart disease (arrhythmias, valve disease, cardiomyopathy, and heart failure), ischemic vascular disease (stroke, cardiovascular, and peripheral vascular disease), chronic liver disease, and renal insufficiency, pulmonary embolism, lung disease (ILD and COPD).

Table 4. Risk factors of death related to COVID-19 in patients with RMDs: bivariate analysis.

	HR	CI 95%	*p*
Female	0.52	0.29–0.93	0.028
Age (years)	1.13	1.11–1.15	0.000
Time since RMD diagnosis (years)	1.04	1.00–1.07	0.015
RMDs			
CTD	1	–	–
CIA	0.94	0.37–2.37	0.9
Non-ARD	0.73	0.31–1.68	0.5
COVID-19 diagnosis date (April and May *versus* March)	0.46	0.21–0.99	0.047
Comorbidity[a]	4.61	2.53–8.38	0.000
Hypertension	3.28	1.8–5.9	0.000
Presence of moderate or severe disability	4.52	2.50–8.15	0.000
Exposure to glucocorticoids (mg)	1.08	1.02–1.13	0.003
Chronic exposure to csDMARDs			
None	1	–	–
Monotherapy	1.09	0.59–2.16	0.8
Combined	0.65	0.15–2.78	0.56
Methotrexate	0.60	0.24–1.55	0.293
Antimalarials	1.18	0.47–2.98	0.724
b/tsDMARDs	0.78	0.23–2.57	0.68
Anti-TNF	0.73	0.17–3.10	0.672

Anti-TNF, tumor necrosis factor-alpha inhibitor; ARD, autoimmune rheumatic diseases; b/tsDMARDs, biologic/target synthetic disease-modifying antirheumatic drug; CI, confidence interval; CIA, chronic inflammatory arthritis; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CTD, connective tissue diseases; HR, hazard ratio; RMDs, rheumatic and musculoskeletal diseases.
[a]Comorbidity: presence of at least one of the following: diabetes mellitus, heart disease (arrhythmias, valve disease, cardiomyopathy, and heart failure), ischemic vascular disease (stroke, cardiovascular, and peripheral vascular disease), chronic liver disease and renal insufficiency, pulmonary embolism, lung disease (ILD and COPD).

those diagnosed on April or May. Mean chronic doses of prednisone ($p = 0.680$), exposure to csDMARDs ($p = 0.657$), and bDMARDs ($p = 0.257$) dropped from the final model. Proportionality of these regression models was tested with a p-value ≥ 0.45.

Discussion

This is a real-world longitudinal study conducted during the whole first wave of the COVID-19 pandemic in Madrid, giving us a general picture of the situation in a great variety of RMDs patients infected by SARS-CoV-2, in terms of mortality related to COVID-19, severity among different rheumatic diseases, and other factors associated with this CMR related to COVID-19 over time.

In this sense, two findings, considered important for the management of these patients in clinical practice, should be highlighted: on the one hand, the risk of death seemed to be similar between

Table 5. Role of RMD and other risk factors of death related to COVID-19 in patients with RMDs: multivariate analysis.

Variable	HR	CI 95%	*p*
Female	0.63	0.35–1.12	0.12
Age (years)	1.12	1.10–1.15	0.000
RMDs			
CTD	1	–	–
CIA	1.33	0.55–3.23	0.5
Non-ARD	1.03	0.46–2.32	0.9
Comorbidity[a]	2.21	1.19–4.11	0.012
COVID-19 diagnosis date			
March	1	–	–
April and May	0.41	0.18–0.90	0.028

ARD, autoimmune rheumatic diseases; CI, confidence interval; CIA, chronic inflammatory arthritis; CTD, connective tissue diseases; HR, hazard ratio; RMDs, rheumatic and musculoskeletal diseases.
[a]Comorbidities including the presence of at least one of the following: diabetes mellitus, heart disease (arrhythmias, valve disease, cardiomyopathy, and heart failure), ischemic vascular disease (stroke, cardiovascular, and peripheral vascular disease), chronic liver disease and renal insufficiency, pulmonary embolism, and lung disease (ILD and COPD).

CTD, CIA, and non-ARD regardless of other factors. As a second relevant result, in the absence of vaccine scenario, mortality risk decreased after the first month of the pandemic, this might be explained by diverse possible reasons, involving the healthcare measures applied during severe coronavirus outbreak and some psychological factors, such as the delay in consulting emergency services. This fact may also have generated selection bias in those patients who did not require hospital admission.[41–43] This pandemic had a great impact, especially in Madrid, with more than 27,000 deaths related to COVID-19 until the last week of May 2020.[44] In this study with underlying RMDs, the case fatality rate for COVID-19 was 10.86%, (12.7% for CTD and 12.15% for CIA), being similar to the reported in Spain general population and to the published in RMDs patients in the same period of time.[44] This study shows that the overall CMR in RMD is estimated in 6.8% patients-month, being an early phenomenon from the moment of infection. In fact, and in accordance with other studies, most of the deaths relate to COVID-19 occurred during the first 15 days since the time of SARS-CoV-2 infection.[45,46]

In this study, the CMR for COVID-19 was somewhat higher in patients with ARD compared to non-ARD, and subtly more in CTD without statistical significance, in accordance with the results published by the French RMD COVID-19 cohort.[47] Moreover, regarding clinical outcomes, our findings are in consonance with those found in the recent meta-analysis conducted by Wang *et al.*[21] An added value for our study is that we have adjusted for several important aspects that influence mortality related to COVID-19.

Consistent with other studies, our data show that CMR for COVID-19 resulted higher in males, older patients, and in the presence of certain comorbid conditions[14,47–49] Specifically, particular clinical conditions, such as diabetes mellitus, heart disease, ischemic vascular disease, chronic liver disease, renal insufficiency, pulmonary embolism, and lung disease implied more risk of mortality. Comorbidities previously identified as a risk for severe COVID-19 in RMDs by the Global Rheumatology Alliance registry and different representative cohorts.[33,47,48]

Nevertheless, in our study, hypertension had no statistical association with death in the final model. This may suggest that the final effect of the cardiovascular continuum as implied by ischemic vascular disease, chronic kidney failure on fatal outcome was more relevant than the presence of hypertension. We found no deaths reported between obesity and smoking; however, these were only reported in few patients in our cohort, Interestingly in our data, less than 30% of patients with COVID-19 diagnosis and none of reported deaths were taking NSAIDs as regular treatment, being not able to stablish robust conclusions from these observational findings; however, our results may be cautiously in line with the findings, where in SARS-CoV-2 positive patients, exposure to NSAIDs was not associated with an excessive risk of hospital admission, death, or serious outcomes and similar to a recently published systematic review and meta-analysis, which concludes that the theoretical risks of NSAIDs in SARS-CoV-2 infection were not confirmed by observational data.[50,51]

The role of exposure to different RMD treatments in the severity of COVID-19 has received special focus during the pandemic. In consonance with previous reports, csDMARDs or anti-TNF drugs do not seem to be at higher risk of death related to COVID-19.[47,48] Although, according to

the insufficient number of patients taking other biologics rather than anti-TNF drugs or JAK inhibitors, we cannot consider these drugs in this assertion. In our study, glucocorticoid's exposure was associated COVID-19-related death in the bivariate analysis; however, it dropped from the final model. Perhaps, the way this variable was collected may have influenced the results, taking into account that previous researches have demonstrated that long-term corticosteroid use increased the risk of severe COVID-19 infection and death,[29,48,52–54] benefit effect of corticosteroid in COVID-19 is a matter of time though, as is demonstrated by the RECOVERY study.[55]

This study has some limitations, the main ones are those that affect any observational retrospective study in a single center. In this sense, data regarding rheumatic disease activity analytical data or treatment dosages were not available, variables that could potentially be related to the risk of death from COVID-19.[25,48] We collected ESR as a surrogate variable of disease activity, but we had almost 60% of missing data, not being possible to use this data. Besides, SARS-CoV-2 PCR diagnostic test should be required as a part of the inclusion criteria definition. However, at that time PCR was only available at the hospitals, in this sense if we had not included the milder cases, mortality rate would be overestimated. In addition, there was a percentage of admitted patients without tests due to a lack of available tests and extreme healthcare overload at that time, all of these reflected the critical situation in which we were immersed.

However, the main strength is that this is real-world setting study performed during the peak of pandemic in Spain. It includes a representative number of non-selected patients with a wide range of different RMD, with not standardized immunosuppressive therapy, followed-up during the whole first wave of pandemic. We were able to analyze differences between rheumatic diseases and see the effect of time in the analysis. Thus, we believe, this study contributes with gaps of knowledge until existing patient registries and administrative databases improve these data.

In conclusion, it seems that predisposition for COVID-19 fatal outcome, at expenses of age and certain comorbidities, occurs in general population, rather than types of RMDs or treatments exposed. This study shows how CMR decreased after the first month, regardless other factors. This potentially reflects that, in times of absence of COVID-19 vaccine, healthcare, social, and political measures assumed to contain the coronavirus outbreak have worked properly.

Acknowledgements

The authors thank the patients for making this study possible. The authors also thank Ana M Perez for their help in the data collection. They also specially thank all rheumatologist and nurse colleagues who contributed in the care of patients in an innovative and so involved way.

Author contribution(s)

Dalifer Freites Nuñez: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft.

Leticia Leon: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft.

Alfredo Madrid Garcia: Investigation, Methodology, Writing – review & editing.

Jose Ignacio Colomer Arce: Colomer Formal analysis, Investigation, Methodology, Writing – review & editing.

Arkaitz Mucientes: Data curation, Investigation, Writing – review & editing.

Benjamin Fernandez-Gutierrez: Conceptualization, Investigation, Project administration, Writing – review & editing.

Luis Rodriguez: Investigation, Project administration, Writing – review & editing.

Inés Pérez San Cristóbal: Data curation, Investigation, Writing – review & editing.

Paula Álvarez: Data curation, Investigation, Writing – review & editing.

Cristina Martinez: Data curation, Investigation, Writing – review & editing.

Lydia Abasolo: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship,

and/or publication of this article: This work was supported by the Instituto de Salud Carlos III (ISCIII), Ministry of Health, Spain (CP16/00916; PI18/01188; and RD16/0012/0014), and co-funded by el Fondo Europeo de Desarrollo Regional (FEDER). The funders had no role in study design, data collection, analysis, article preparation, or decision to publish.

Ethics

The study was approved by the Hospital Clínico San Carlos institutional ethics committee (Approval No. 20/268-E-BS). This study was conducted according to the principles of the Declaration of Helsinki.

ORCID iDs

Leticia Leon https://orcid.org/0000-0001-7142-0545

Alfredo Madrid Garcia https://orcid.org/0000-0002-1591-0467

Benjamin Gutierrez-Fernandez https://orcid.org/0000-0002-6126-8786

Luis Rodriguez https://orcid.org/0000-0002-2869-7861

Availability of supporting data

The datasets generated and analyzed for the present study are available from the corresponding author on reasonable request.

Supplemental material

Supplemental material for this article is available online.

References

1. World Health Organization. Coronavirus disease (COVID-19) pandemic, https://www.who.int
2. Wang C, Horby PW, Hayden FG, *et al*. A novel coronavirus outbreak of global health concern. *Lancet* 2020; 395: 470–473.
3. World Health Organization. *Coronavirus disease (COVID-2019) situation reports*. Geneva: World Health Organization, 2021.
4. Chen N, Zhou M, Dong X, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; 395: 507–513.
5. Wang D, Hu B, Hu C, *et al*. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020; 323: 1061–1069.
6. Liu K, Fang Y-Y, Deng Y, *et al*. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J* 2020; 133: 1025–1031.
7. Yang X, Yu Y, Xu J, *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; 8: 475–481.
8. Wu Z and McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020; 323: 1239–1242.
9. Huang C, Wang Y, Li X, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497–506.
10. Verity R, Okell LC, Dorigatti I, *et al*. Estimates of the severity of coronavirus disease 2019: a model-based analysis. *Lancet Infect Dis* 2020; 20: 669–677.
11. Petrilli CM, Jones SA, Yang J, *et al*. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ* 2020; 369: m1966.
12. Zhou F, Yu T, Du R, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395: 1054–1062.
13. Lighter J, Phillips M, Hochman S, *et al*. Obesity in patients younger than 60 years is a risk factor for COVID-19 hospital admission. *Clin Infect Dis* 2020; 71: 896–897.
14. Williamson EJ, Walker AJ, Bhaskaran K, *et al*. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; 584: 430–436.
15. Tartof SY, Qian L, Hong V, *et al*. Obesity and mortality among patients diagnosed with COVID-19: results from an Integrated Health Care Organization. *Ann Intern Med* 2020; 173: 773–781.
16. Liang W, Guan W, Chen R, *et al*. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020; 21: 335–337.
17. Richardson S, Hirsch JS, Narasimhan M, *et al*. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized With COVID-19 in the New York City area. *JAMA* 2020; 323: 2052–2059.

18. Myers LC, Parodi SM, Escobar GJ, *et al.* Characteristics of hospitalized adults with COVID-19 in an Integrated Health Care System in California. *JAMA* 2020; 323: 2195–2198.
19. Cummings MJ, Baldwin MR, Abrams D, *et al.* Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet* 2020; 395: 1763–1770.
20. Suleyman G, Fadel RA, Malette KM, *et al.* Clinical characteristics and morbidity associated with coronavirus disease 2019 in a series of patients in metropolitan Detroit. *JAMA Netw Open* 2020; 3: e2012270.
21. Wang Q, Liu J, Shao R, *et al.* Risk and clinical outcomes of COVID-19 in patients with rheumatic diseases compared with the general population: a systematic review and meta-analysis. *Rheumatol Int* 2021; 41: 851–861.
22. Ferri C, Giuggioli D, Raimondo V, *et al.* COVID-19 and rheumatic autoimmune systemic diseases: report of a large Italian patients series. *Clin Rheumatol* 2020; 39: 3195–3204.
23. Zhong J, Shen G, Yang H, *et al.* COVID-19 in patients with rheumatic disease in Hubei province, China: a multicentre retrospective observational study. *Lancet Rheumatol* 2020; 2: e557–e564.
24. Akiyama S, Hamdeh S, Micic D, *et al.* Prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases: a systematic review and meta-analysis. *Ann Rheum Dis* 2021; 80: 384–391.
25. Hasseli R, Mueller-Ladner U, Hoyer BF, *et al.* Older age, comorbidity, glucocorticoid use and disease activity are risk factors for COVID-19 hospitalisation in patients with inflammatory rheumatic and musculoskeletal diseases. *RMD Open* 2021; 7: e001464.
26. Freites Nuñez DD, Leon L, Mucientes A, *et al.* Risk factors for hospital admissions related to COVID-19 in patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2020; 79: 1393–1399.
27. Monti S, Balduzzi S, Delvino P, *et al.* Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. *Ann Rheum Dis* 2020; 79: 667–668.
28. Haberman R, Axelrad J, Chen A, *et al.* Covid-19 in immune-mediated inflammatory diseases – case series from New York. *N Engl J Med* 2020; 383: 85–88.
29. Gianfrancesco MA, Hyrich KL, Gossec L, *et al.* Rheumatic disease and COVID-19: initial data from the COVID-19 Global Rheumatology Alliance provider registries. *Lancet Rheumatol* 2020; 2: e250–e253.
30. Michelena X, Borrell H, López-Corbeto M, *et al.* Incidence of COVID-19 in a cohort of adult and paediatric patients with rheumatic diseases treated with targeted biologic and synthetic disease-modifying anti-rheumatic drugs. *Semin Arthritis Rheum* 2020; 50: 564–570.
31. Putman M, Chock YPE, Tam H, *et al.* Antirheumatic disease therapies for the treatment of COVID-19: a systematic review and meta-analysis. *Arthritis Rheumatol* 2021; 73: 36–47.
32. Pablos JL, Galindo M, Carmona L, *et al.* Clinical outcomes of hospitalised patients with COVID-19 and chronic inflammatory and autoimmune rheumatic diseases: a multicentric matched cohort study. *Ann Rheum Dis* 2020; 79: 1544–1549.
33. D'Silva KM, Serling-Boyd N, Wallwork R, *et al.* Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: a comparative cohort study from a US hot spot. *Ann Rheum Dis* 2020; 79: 1156–1162.
34. Xu C, Yi Z, Cai R, *et al.* Clinical outcomes of COVID-19 in patients with rheumatic diseases: a systematic review and meta-analysis of global data. *Autoimmun Rev* 2021; 20: 102778.
35. Pritchard E, Matthews PC, Stoesser N, *et al.* Impact of vaccination on new SARS-CoV-2 infections in the United Kingdom. *Nat Med* 2021; 27: 1370–1378.
36. Scobie HM, Johnson AG, Suthar AB, *et al.* Monitoring incidence of COVID-19 cases, hospitalizations, and deaths, by vaccination status – 13 U.S. jurisdictions, April 4-July 17, 2021. *Morb Mortal Wkly Rep* 2021; 70: 1284–1290.
37. Sattui SE, Liew JW, Kennedy K, *et al.* Early experience of COVID-19 vaccination in adults with systemic rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance Vaccine Survey. *RMD Open* 2021; 7: e001814.
38. Moghadas SM, Vilches TN, Zhang K, *et al.* The impact of vaccination on COVID-19 outbreaks in the United States. *medRxiv*. Epub ahead of print 2 January 2021. DOI: 10.1101/2020.11.27.20240051.
39. Leon L, Rodriguez-Rodriguez L, Aguilar MD, *et al.* Validation of a quality of life instrument in Spanish patients with rheumatic diseases: the Rosser classification system. *J Clin Rheumatol* 2019; 25: 78–84.
40. von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of Observational

Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med* 2007; 4: e296.

41. Shih C-L, Huang P-J, Huang H-T, *et al.* Impact of the COVID-19 pandemic and its related psychological effect on orthopedic surgeries conducted in different types of hospitals in Taiwan. *J Orthop Surg* 2021; 29: 2309499021996072.
42. Placella G, Salvato D, Delmastro E, *et al.* CoViD-19 and ortho and trauma surgery: the Italian experience. *Injury* 2020; 51: 1403–1405.
43. Hsu C-H and Hsu N-C. Impact and strategies on joint surgery centers without lockdowns during the peak of the COVID-19 pandemic: a multicenter cross-sectional study. *J Clin Med* 2021; 10: 5392.
44. Ritchie H, Mathieu E, Rodés-Guirao L, *et al*. Mortality risk of COVID-19, https://ourworldindata.org/mortality-risk-covid?country=~ESP
45. Hyrich KL and Machado PM. Rheumatic disease and COVID-19: epidemiology and outcomes. *Nat Rev Rheumatol* 2021; 17: 71–72.
46. Zheng Z, Peng F, Xu B, *et al.* Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. *J Infect* 2020; 81: e16–e25.
47. Florence A, Nassim AA, Jean-David A, *et al.* Severity of COVID-19 and survival in patients with rheumatic and inflammatory diseases: data from the French RMD COVID-19 cohort of 694 patients. *Ann Rheum Dis* 2021; 80: 527–538.
48. Strangfeld A, Schäfer M, Gianfrancesco MA, *et al*. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis* 2021; 80: 930–942.
49. Saha S, Al-Rifai RH and Saha S. Diabetes prevalence and mortality in COVID-19 patients: a systematic review, meta-analysis, and meta-regression. *J Diabetes Metab Disord* 2021; 20: 939–950.
50. Moore N, Bosco-Levy P, Thurin N, *et al.* NSAIDs and COVID-19: a systematic review and meta-analysis. *Drug Saf* 2021; 44: 929–938.
51. Gianfrancesco M, Hyrich KL, Al-Adely S, *et al.* Characteristics associated with hospitalization for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis* 2020; 79: 859–866.
52. Sanchez-Piedra C, Diaz-Torne C, Manero J, *et al.* Clinical features and outcomes of COVID-19 in patients with rheumatic diseases treated with biological and synthetic targeted therapies. *Ann Rheum Dis* 2020; 79: 988–990.
53. Haberman RH, Castillo R, Chen A, *et al.* COVID-19 in patients with inflammatory arthritis: a prospective study on the effects of comorbidities and disease-modifying antirheumatic drugs on clinical outcomes. *Arthritis Rheumatol* 2020; 72: 1981–1989.
54. Brenner EJ, Ungaro RC, Gearry RB, *et al.* Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an International Registry. *Gastroenterology* 2020; 159: 481–491.e3.
55. Dexamethasone in hospitalized patients with covid-19. *N Engl J Med* 2021; 384: 693–704.