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Hospital admissions in inflammatory rheumatic diseases during the peak of COVID-19 pandemic: incidence and role of disease-modifying agents

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Abstract

Aims: In this pandemic, it is essential for rheumatologists and patients to know the relationship between COVID-19 and inflammatory rheumatic diseases (IRDs). We wanted to assess the role of targeted synthetic or biologic disease-modifying antirheumatic drugs (ts/bDMARDs) and other variables in the development of moderate-severe COVID-19 disease in IRD.

Methods: An observational longitudinal study was conducted during the epidemic peak in Madrid (1 March to 15 April 2020). All patients attended at the rheumatology outpatient clinic of a tertiary hospital in Madrid with a medical diagnosis of IRD were included. Main outcome: hospital admission related to COVID-19. Independent variable: ts/bDMARDs. Covariates: sociodemographic, comorbidities, type of IRD diagnosis, glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). Incidence rate (IR) of hospital admission related to COVID-19 was expressed per 1000 patient-months. Cox multiple regression analysis was run to examine the influence of ts/bDMARDs and other covariates on IR of hospital admission related to COVID-19.

Results: A total of 3951 IRD patients were included (5896 patient-months). Methotrexate was the csDMARD most used. Eight hundred and two patients were on ts/bDMARDs, mainly anti-TNF agents, and Rtx. Hospital admissions related to COVID-19 occurred in 54 patients (1.36%) with an IR of 9.15 (95% confidence interval: 7–11.9). In the multivariate analysis, older, male, comorbidities, and specific systemic autoimmune conditions (Sjögren, polychondritis, Raynaud, and mixed connective tissue disease) had more risk of hospital admissions. Exposition to ts/bDMARDs did not achieve statistical significance. Use of glucocorticoids, NSAIDs, and csDMARDs dropped from the final model.

Conclusion: This study provides additional evidence in IRD patients regarding susceptibility to moderate–severe infection related to COVID-19.

Keywords: autoimmune diseases, COVID-19, disease-modifying antirheumatic drugs, rheumatic diseases

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Introduction

New severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a myriad of clinical signs and symptoms with analytic typical features. As a whole, all characteristics are called Coronavirus disease (COVID-19),[1] and it has affected millions of lives worldwide.

A majority of COVID-19 patients present no symptoms or mild symptomatology. Other,

smaller, subgroups show progression to a moderate disease. A further subgroup apparently develops a syndrome with auto-inflammatory features with critical/fatal outcomes.[2,3] In this sense, it seems that COVID-19 disease is having a particular incidence and severity in patients with advanced age and comorbidities, mainly diabetes, hypertension, ischemic heart disease, and previous respiratory diseases.[4,5]

Serious infection is a well-recognized cause of morbidity and mortality across a number of inflammatory rheumatic diseases (IRDs). In this pandemic, it is essential for rheumatologists and for patients themselves to know the relationship between COVID-19 and IRD. In this context, several guidances for the management of these patients based on expert opinion have been performed,[6–8] as there is scarce epidemiological research on the potential risk of IRD and/or disease-modifying antirheumatic drugs (DMARDs) on COVID-19 disease and its severity. A few experiences from Italy and Spain have been recently published, showing that patients with chronic inflammatory arthritis treated with biologic or synthetic DMARDs do not seem to be at increased risk of infection or respiratory complications from SARS-CoV-2 compared with the general population.[9–12] These preliminary findings, if corroborated, could be very relevant and helpful for the clinical management of IRD patients.

The purpose of this study was to estimate the incidence rate of moderate–severe COVID-19 disease, during the pandemic peak, globally and stratified by age, sex, type of diagnosis and therapy used in IRD patients from our health area. Then, we assessed the role of exposition to targeted synthetic or biologic DMARDs (ts/bDMARDs) in the development of moderate–severe COVID-19 disease, taking into account all other relevant parameters, such as age, sex, comorbidity, conventional synthetic DMARDs (csDMARDs), corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and type of rheumatic diagnosis.

Methods

Setting, design, and patients

The setting is a tertiary hospital of the Public Health System of the Community of Madrid, the Hospital Clínico San Carlos (HCSC), covering a catchment area of 400,000 people.

We performed a retrospective observational study during the epidemic peak in Madrid (from 1 March 2020 to 15 April 2020). The study population comprised all patients attended at the rheumatology outpatient clinic of HCSC and followed-up through regular visits every 3–6 months based on type of exposed drugs, diagnosis and severity, from 1 March 2019 until 1 March 2020. Their data were recorded in the health clinical record of our service (HCR Penelope). From these, we included all patients >16 years old with medical diagnosis (according to ICD-10) of inflammatory rheumatic disease including: (a) chronic inflammatory arthritis: rheumatoid arthritis (RA), psoriatic arthritis (PSA), spondyloarthritis (SPA), uveitis, inflammatory bowel disease, juvenile idiopathic arthritis, and inflammatory polyarthritis; (b) systemic autoimmune conditions: Sjögren's syndrome, systemic sclerosis, mixed connective tissue disease (MCTD); systemic lupus erythematosus (SLE), polymyalgia rheumatica (PMR), vasculitis, Behcet's syndrome, sarcoidosis, polychondritis, autoinflammatory syndrome, antiphospholipid syndrome, inflammatory myopathies, and primary Raynaud phenomenon.

The study was approved by the HCSC institutional ethics committee (approval number 20/268-E_BS).

Variables

The primary outcome was the development of moderate–severe COVID-19 disease defined as hospital admission related to COVID-19 during the study period. This definition was based on medical diagnosis ± polymerase chain reaction (PCR) positive diagnostic test. The independent variable was exposure to ts/bDMARDs including: (a) anti-TNF alfa (infliximab, adalimumab, etanercept, certolizumab, golimumab); (b) other biologics: anti-IL6 [tocilizumab (Tozi), sarilumab]; rituximab (Rtx); abatacept (Abata); belimumab (Beli); anti-IL17/23 (ustekinumab, ixekizumab, secukinumab); (c) Jakinibs (JAKi; tofacitinib, baricitinib).

As covariables we considered: (1) sociodemographic baseline characteristics including sex, age and IRD duration; (2) type of IRD, including chronic inflammatory arthritis and systemic autoimmune conditions; (3) baseline comorbidity, described in Table 1; (4) other chronic treatment for IRD: (a) glucocorticoids, (b) NSAIDs, (c) csDMARDs, including: leflunomide (Lef); methotrexate (Mtx); azathioprine or mycophenolate

Table 1. Baseline demographic and clinical characteristics among IRD patients.

Variable	All IRD patients N = 3951
Women, *n* (%)	2857 (72.3)
Age, mean (SD), years	61.8 (16.6)
Disease evolution time, mean (SD), years	10.80 (8.38)
Smoking habit, active*	170 (4.3)
Diagnosis, *n* (%)	
Rheumatoid arthritis	1486 (37.7)
Inflammatory polyarthritis	170 (4.3)
Axial spondyloarthritis	491 (12.4)
Psoriatic arthritis	289 (7.3)
Polymyalgia rheumatica	377 (9.5)
Systemic lupus erythematosus	248 (6.3)
Mixed connective tissue disease	158 (4.0)
Systemic sclerosis	80 (2.0)
Sjögren's syndrome	146 (3.7)
Vasculitis	115 (2.9)
Behcet disease	43 (1.1)
Polychondritis	16 (0.6)
Polymyositis	35 (0.89)
Raynaud	92 (2.3)
Uveitis	100 (2.5)
Others**	104 (2.6)
Comorbidities, *n* (%)	
Hypertension	860 (21.8)
Dyslipidemia	707 (17.9)
Depression	250 (6.3)
Diabetes mellitus	323 (8.2)
Heart disease***	296 (7.5)
Ischemic vascular disease****	181 (4.6)
Chronic liver disease	127 (3.2)
Chronic kidney disease	57 (1.5)
Lung disease (ILD/COPD)	312 (7.9)
History or presence of cancer	235 (5.9)
Venous thrombosis/lung embolism	54 (1.4)
Thyroid disease	430 (10.9)
NSAIDs use, *n* (%)	860 (21.7)
Glucocorticoid use, *n* (%)	1804 (45.6)
Colchicine use, *n* (%)	56 (1.4)
csDMARDs, *n* (%):	
Mtx–Lef–Aza	1961 (49.6)
Cpa	27 (0.68)
Ssz	317 (8.0)
Am	666 (16.8)
ts/bDMARDs, *n* (%)	
Anti-TNF	521 (13.2)
Ifx	52 (1.3)
Ada	188 (4.7)
Etn	117 (2.9)
Certo	103 (2.6)
Goli	61 (1.5)
Non-anti-TNF	246 (6.2)
Abata	27 (0.68)
Tozi	42 (1.06)
Rtx	122 (3.1)
Sari, Secu, Ixe, Uste	49 (1.2)
Beli	6 (0.15)
JAKi, *n* (%)	35 (0.89)
Bari	27 (0.68)
Tofa	8 (0.2)

*Smoking habit, active: more than one unit daily at least during the previous month.
**Inflammatory bowel disease, antiphospholipid syndrome, juvenile idiopathic arthritis, autoinflammatory syndromes, sarcoidosis.
***Heart disease: arrhythmias, valvulopathies, cardiomyopathies, heart failure.
****Ischemic vascular disease, stroke, cardiovascular and peripheral vascular disease.
Abata, abatacept; Ada, adalimumab; Am, antimalarial; anti-TNF, tumor necrosis factor-alpha inhibitor; Aza, azathioprine or mycophenolate mophetilo; Bari, baricitinib; Beli, belimumab; Certo, certolizumab; COPD, chronic obstructive pulmonary disease; Cpa, cyclosporine; csDMARD, conventional synthetic disease-modifying antirheumatic drug; Etn, etanercept; Goli, golimumab; Ifx, infliximab; ILD, interstitial lung disease; IRD, inflammatory rheumatic disease; Ixe, ixekizumab; JAKi, JAK inhibitor; Lef, leflunomide; Mtx, methotrexate; NSAID, non-steroidal anti-inflammatory drug; Rtx, rituximab; Sari, sarilumab; SD, standard deviation; Secu, secukinumab; Tofa, tofacitinib; Ssz, sulfasalazine; Tozi, tocilizumab; ts/bDMARD, target synthetic/biologic disease-modifying antirheumatic drug; Uste, ustekinumab.

mophetilo (Aza), cyclophosphamide; cyclosporine (Cpa); (d) other csDMARDs, including: antimalarial (Am: chloroquine/hydroxychloroquine); sulfasalazine (Ssz); and colchicine.

To consider patients who were exposed to drugs, treatment had to start at least one month before the beginning of the study, had to continue during the study period until the end of study or medical admission for Am, glucocorticoids, Ssz, and NSAIDs. Regarding Mtx, Lef, Aza, Cpa and ts/bDMARDs, treatment had to start at least 1 month before the beginning of the study, had to continue to at least 21 March 2020, end of study (15 April 2020) or hospital admission. In the case of Rtx, the last infusion had to be at least in January 2020.

Data sources

Patient sociodemographic, clinical, and therapeutic data were obtained from the HCR Penelope through face to face or telephonic visits of rheumatologists. SARS-CoV-2 PCR diagnostic tests information was obtained from the microbiology service of HCSC ($n = 5577$ patients with PCR test performed in the study period). Central Services of the hospital provided us with all the HCSC admissions ($n = 1146$ in the study period). All information from IRD patients was merged.

Statistical analysis

Patients' characteristics were described as mean and standard deviation for continuous variables, while proportions are shown for categorical variables.

Survival techniques were used to estimate the incidence rate (IR) of hospital admissions related to COVID-19. IR is given per 1000 person-months with a 95% confidence interval. All included patients were followed up from 1 March 2020 to the date of the patient's hospital admission or end of study (15 April 2020).

The incidence rate ratio of hospital admissions related to COVID-19 among IRD patients and the population from our health area older than 16 years was assessed.

Cox bivariate analyses were done to evaluate statistical differences between hospital admission risks and all variables. Then, Cox multivariate regression model (adjusted by age, sex, type of diagnosis, and comorbidities) was run to examine the possible influence of ts/bDMARDs in hospital admissions regardless of other factors. In the model we also included glucocorticoids, csDMARDs, and all other variables with a $p < 0.2$ from the bivariate analysis. Results were expressed as hazard ratio (HR) and confidence interval. Proportional hazard assumption was tested by scaled Schoenfeld residuals. All analyses were performed in Statav.13 statistical software (Stata Corp., College Station, TX, USA). A two-tailed p value under 0.05 was considered to indicate statistical significance.

Results

3951 IRD patients were included, with a total follow up of 5896 patients-months. As we shown in Table 1, mostly were women in their sixties. The main diagnosis was RA, followed by SPA, PMR, PSA and SLE. Regarding comorbidities, hypertension, dyslipidemia, thyroid disease and diabetes mellitus were the most prevalent. Concerning csDMARDs, Mtx was the most used ($n = 1461$), followed by Am, Lef ($n = 333$), Ssz, and Aza ($n = 245$). Six patients were using cyclophosphamide. 32% of the patients did not use csDMARDs, 47% were on monotherapy and the remaining 21% used at least two concomitant csDMARDs (mainly Mtx+Am; Mtx+Ssz and Mtx+Lef). Concerning ts/bDMARD ($n = 802$), 12.5% of them were on monotherapy and the remaining 87.5% combined with csDMARDs. The most frequent were anti-TNF agents, followed by Rtx.

Hospital admissions related to COVID-19 occurred in 54 patients (1.36%) during the follow-up. 76% were positive to PCR test, 5% were negative and in the remaining 19% the PCR test was not performed.

IR of hospital admission related to COVID-19

The IR was estimated as 9.15 (7–11.9) per 1000 patient-months. As expected, IR had been increasing throughout the study: when we analyzed in fortnightly cuts, the IR from 1 March to 15 March was 1.01 per 1000; for 15 March to 30 March it was 6.3 per 1000; and for 1 April to 15 April it was 6.6 per 1000 patients. In fact, IR in the period of 15 March to 15 April was higher, estimated as 13 per 1000 patients.

For IRD, the cumulative incidence of hospital admissions related to COVID-19 during the study

period was 15 per 1000 patients, whereas the cumulative incidence for hospitalized patients related to COVID-19 ($n=1059$) in our health area ($n>16$ years: 325.900)[13] was lower, being estimated as 3.2 per 1000 persons [IR: 4.6 (3.4–6.1); $p=0.000$].

As shown in Table 2 the crude IR could vary depending on different variables. It was higher for men than for women and for those older compared with younger. It seemed lower for those included in the chronic inflammatory arthritis group compared with those from the systemic autoimmune conditions, with

Table 2. Incidence rate of hospital admissions related to COVID-19 in IRD patients.

Variable	Patient-months	Events	IR per 1000 patient-months	95% CI
Global	5896	54	9.15	7.0–11.9
Sex				
Men	1628	22	13.5	8.9–20.5
Women	4268	32	7.5	5.3–10.6
Age, years				
<50	1473	6	4.07	1.8–9.1
51–60	1199	12	10.0	5.7–17.6
61–75	1736	13	7.5	3.3–12.8
>75	1488	23	15.4	10.2–23.2
Diagnosis:				
SLE	374	2	5.3	1.3–21.5
RA	2219	18	8.1	5.1–12.8
IA	253	2	7.9	1.9–31.5
PSA	432	3	6.9	2.2–21.5
SPA	731	7	9.5	4.5–20.0
PMR	562	6	10.7	4.8–23.7
SSc	119	1	8.3	1.2–59.3
MCTD	234	4	17.1	6.4–45.6
Sjo	216	4	18.5	6.9–49.2
Vasculitis	171	2	11.7	2.9–46.7
Raynaud	136	3	21.9	7.1–78.0
Polychondritis	23	1	43.3	6.1–307
Behcet	64	0	–	–
Polymyositis	52	1	19.2	2.7–136.2
Uveitis	150	0	–	–
Others*	156	0	–	–
NSAIDs				
Yes	1286	8	6.2	3.1–12.4
No	4610	46	9.9	7.5–13.3

(Continued)

Table 2. (Continued)

Variable	Patient-months	Events	IR per 1000 patient-months	95% CI
Glucocorticoids				
Yes	2087	32	11.9	8.4–16.8
No	3209	22	6.8	4.5–10.4
csDMARDs:				
Mtx–Lef–Aza				
Yes	2927	28	9.5	6.6–13.8
No	2969	26	8.8	5.9–12.8
Ssz				
Yes	472.7	4	8.5	3.2–22.5
No	5427.3	50	9.2	6.9–12.2
Am				
Yes	993.8	9	9.0	4.7–17.0
No	4903.2	45	9.2	6.8–12.3
ts/bDMARDs				
None	4967	46	9.8	7.3–13.1
Anti-TNF	781	2	2.6	0.6–10.2
Other biologics	368	5	13.6	5.6–32.7
Rtx	181	4	22.1	8.3–58.8
Abata	41	0	–	–
Tozi, Sari, Secu, Uste, Ixe	136	1	7.3	1.0–52
Beli	9	0	–	–
JAKi	51.4	1	19.4	2.7–138

*Inflammatory bowel disease, antiphospholipid syndrome, juvenile idiopathic arthritis, autoinflammatory syndromes, sarcoidosis.
Abata, abatacept; Am, antimalarial; Anti-TNF, tumor necrosis factor-alpha inhibitor; Aza, azathioprine or mycophenolate mophetilo; Beli, belimumab; CI, confidence interval; Cpa, cyclosporine; csDMARD, conventional synthetic disease-modifying antirheumatic drug; IA, inflammatory polyarthritis; IR, incidence rate; IRD, inflammatory rheumatic disease; Ixe, ixekizumab; JAKi, JAK inhibitor; Lef, leflunomide; MCTD, mixed connective tissue disease; Mtx, methotrexate; NSAID, non-steroidal anti-inflammatory drug; PA, spondyloarthritis; PMR, polymyalgia rheumatica; PSA, psoriatic arthritis; RA, rheumatoid arthritis; Rtx, rituximab; Sari, sarilumab; Secu, secukinumab; Sjo, Sjögren's syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis, Ssz, sulfasalazine; Tozi, tocilizumab; ts/bDMARD, target synthetic/biologic disease-modifying antirheumatic drug; Uste, ustekinumab.

the exception of SLE. It was similar in patients with or without csDMARDs. No hospital admissions were found for patients with Cpa, colchicine, nor cyclophosphamide. Finally, concerning ts/bDMARDs, IR was higher in patients on Rtx and lower in patients using anti-TNF. No hospital admissions were found for patients with Abata, sarilumab, ustekinumab, ixekizumab, secukinumab nor Beli.

Bivariate analysis

As expected age, sex, and several comorbidities, but also the use of glucocorticoids, was statistically associated with hospital admission related to COVID-19 in IRD. NSAIDs and ts/bDMARDs did not achieve statistical significance, but had a trend (Table 3). When we analyzed separately other biologics, Rtx, compared with the rest, had a

Table 3. Hazard ratios of medical admission related to COVID-19 in IRD patients. Bivariate analysis.

Variable	HR	95% CI	*p*
Women	0.5	0.32–0.9	0.033
Age, years	1.02	1.01–1.04	0.002
Disease duration	1.002	0.97–1.03	0.8
Diagnosis (one category *versus* the rest)			
RA	0.83	0.5–1.4	0.5
IA	0.85	0.2–3.5	0.8
SLE	0.57	0.1–2.3	0.4
PSA	0.7	0.2–2.4	0.6
SPA	1.05	0.5–2.3	0.8
PMR	1.2	0.5–2.7	0.6
SSc	0.9	0.13–6.5	0.9
MCTD	1.9	0.7–5.4	0.2
Sjo	2.1	0.7–5.8	0.1
Vasculitis	1.3	0.3–5.2	0.7
Raynaud	2.5	0.8–7.9	0.1
Polychondritis	4.8	0.7–35	0.1
Behcet	–	–	–
Polymyositis	2.1	0.3–15.3	0.4
Uveitis	–	–	–
Others*	–	–	–
Smoking habit (Active *versus* none)	1.3	0.4–4.2	0.6
Comorbidities (yes)			
Hypertension	1.3	0.7–2.3	0.4
Dyslipidemia	0.7	0.3–1.5	0.3
Depression	0.3	0.04–2.0	0.2
Diabetes mellitus	2.6	1.3–5.1	0.007
Heart disease	1.3	0.5–3.2	0.6
Vascular disease	1.2	0.4–3.9	0.7
Liver disease	3.1	1.2–7.8	0.001
Renal disease	4.1	1.3–13.2	0.02
Lung disease (ILD/COPD)	2.6	1.3–5.3	0.005
Cancer	0.9	0.3–2.9	0.8
Venous thrombosis/lung embolism	4.3	1.3–13.9	0.01
Thyroid disease	0.8	0.3–2.1	0.7
NSAIDs	0.6	0.3–1.3	0.2
Glucocorticoids	1.7	1.01–2.9	0.04

(Continued)

Table 3. (Continued)

Variable	HR	95% CI	*p*
csDMARDs:	1.15	0.6–2.0	0.6
Mtx–Lef–Aza	1.09	0.6–1.9	0.7
Cpa	–	–	–
Ssz	0.92	0.3–2.5	0.8
Am	0.95	0.5–2.1	0.8
ts/bDMARDs	0.6	0.3–1.3	0.2
None	1	–	–
Anti-TNF	0.3	0.06–1.1	0.07
Other biologics	1.7	0.7–3.8	0.2
JAKi	2.2	0.3–15.5	0.4

*Inflammatory bowel disease, antiphospholipid syndrome, juvenile idiopathic arthritis, autoinflammatory syndromes, sarcoidosis.
Am, antimalarial; Anti-TNF, tumor necrosis factor-alpha inhibitor; Aza, azathioprine or mycophenolate mophetilo; CI, confidence interval; COPD, chronic obstructive pulmonary disease; Cpa, cyclosporine; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HR, hazard ratio; IA, inflammatory polyarthritis; ILD, interstitial lung disease; IRD, inflammatory rheumatic disease; JAKi, JAK inhibitor; Lef, leflunomide; MCTD, mixed connective tissue disease; Mtx, methotrexate; NSAID, non-steroidal anti-inflammatory drug; PMR, polymyalgia rheumatica; PSA, psoriatic arthritis; RA, rheumatoid arthritis; Sjo, Sjögren's syndrome; SLE, systemic lupus erythematosus; SPA, spondyloarthritis; SSc, systemic sclerosis, Ssz, sulfasalazine; ts/bDMARD, target synthetic/biologic disease-modifying antirheumatic drug.

Table 4. Role of ts/bDMARDs on risk of hospital admission related to COVID-19 in IRD patients. Adjusted by rheumatic diagnosis, age, sex, and comorbidity. Multivariate analysis.

Variable	HR	95% CI	*p*
Women	0.55	0.3–0.95	0.035
Age, >75 years	1.8	1.03–3.17	0.039
Diagnosis: systemic autoimmune conditions versus chronic inflammatory arthritis	1.23	0.7–2.15	0.4
Comorbidities (yes)	2.23	1.2–3.9	0.005
ts/bDMARDs			
None	1	–	–
Anti-TNF	0.32	0.07–1.36	0.123
Non anti-TNF	1.57	0.66–3.7	0.31

Systemic autoimmune conditions (polymyalgia rheumatica; systemic sclerosis, Sjögren's syndrome, mixed connective tissue disease, vasculitis, Raynaud, polymyositis, polychondritis; Behcet, sarcoidosis, antiphospholipid syndrome, systemic lupus erythematosus) *versus* chronic inflammatory arthritis (rheumatoid arthritis, inflammatory polyarthritis, juvenile idiopathic arthritis, psoriatic arthritis, spondyloarthritis, uveitis, inflammatory bowel disease). Comorbidities including the presence of at least one of the following: ischemic vascular disease, diabetes mellitus, venous thrombosis/lung embolism, chronic kidney disease, liver disease, lung disease (interstitial lung disease/chronic obstructive pulmonary disease). Non-anti-TNF: anti-IL6 (tocilizumab, sarilumab); rituximab; anti-IL17/23; anti-IL17+JAK inhibitors.
Anti-TNF, tumor necrosis factor-alpha inhibitor; CI, confidence interval; HR, hazard ratio; IRD, inflammatory rheumatic disease; ts/bDMARD, target synthetic/biologic disease-modifying anti rheumatic drug.

trend of more risk of hospital admission [HR: 2.2 (0.85–2.4), $p=0.1$]. Regarding type of diagnosis, some systemic autoimmune conditions had a trend of more risk of hospital admission except for SLE, which had lower risk ($p=0.4$). SLE *versus* chronic inflammatory arthritis did not reach statistical significance [HR: 0.68 (0.16–2.8), $p=0.59$]. However, other systemic autoimmune conditions (not SLE) *versus* chronic inflammatory arthritis achieved a trend of more risk [HR: 1.62 (0.94–2.8), $p=0.08$].

Multivariate analysis

In the final model, after adjusting by sex, age, comorbidities, and type of diagnosis, ts/bDMARDs did not achieve statistical significance compared with no use (Table 4). Regarding specific non-TNFs *versus* none, they did not reach statistical significance either [Rtx HR: 2 (0.71–5.6) $p=0.190$; JAKi HR: 2.6 (0.3–19.3) $p=0.3$; and Tozi HR: 2.2 (0.3–16.3) $p=0.4$].

Interestingly, glucocorticoids [HR: 1.48 (0.8–2.58); $p=0.17$], Am [HR: 1.22 (0.58–2.5); $p=0.5$], Ssz [HR: 1.28 (0.4–3.6); $p=0.6$], Mtx–Lef–Aza [HR: 1.25 (0.7–2.2); $p=0.4$], and NSAIDs [HR: 0.97 (0.4–2.1); $p=8$] dropped from the final model.

Concerning diagnosis, systemic autoimmune conditions *versus* chronic inflammatory arthritis did not achieve statistical significance. When we categorized this variable in specific diagnoses (we grouped RA–PSA as reference category based on syndromic similarity and incidence rates), the final model did not change but we found some interesting results: Sjögren [HR: 3.1 (1.01–9.1); $p = 0.04$], primary Raynaud phenomenon [HR: 3.8 (1.2–13.8); $p = 0.03$], and polychondritis [HR: 19.3 (1.3–70.7); $p = 0.03$] increased the risk of hospital admission related to COVID-19 compared with RA–PSA and independently of other factors. SLE [HR: 0.93 (0.2–4.0); $p = 0.8$] did not achieve statistical significance. MCTD [HR: 2.3 (0.8–6.9); $p = 0.1$] achieved a trend of more risk, and the HR in the rest of the diagnoses did not differ ($p > 0.2$).

When analyzing the final model using as variables specific comorbidities instead of the presence of comorbidities, lung disease [HR: 2.1 (1.05–4.2), $p = 0.03$], liver disease [HR: 3.5 (1.4–8.8), $p = 0.008$], and venous thrombosis/lung embolism [HR: 3.4 (1.1–10.9), $p = 0.04$] achieved statistical significance.

The proportionality of these regression models was tested with a p value = 0.7.

Discussion

This real-world longitudinal study of 1.5 months, has been performed during the period of maximum health emergency due to pandemic COVID-19 in Madrid, the main epicenter of the COVID-19 outbreak in Spain. The study includes a big sample size and a broad spectrum of IRDs treated with or without ts/bDMARDs, csDMARDs, and glucocorticoids. With all this information, we have been able to estimate the IR of hospital admissions related to COVID-19 in IRD, and also to evaluate the influence of ts/bDMARDs, csDMARDs, types of IRD, and other factors in the risk of hospital admissions related to COVID-19.

This pandemic has had a great impact, especially in Madrid, with more than 41,304 hospital admissions until the first week of May.[14] In this study we have been able to show the rise of this incidence from March to April.

In our study, the IR of hospital admissions related to COVID-19 in IRD patients was estimated at 9.15 per 1000 patient-months. When we compare the IR of hospital admissions related to COVID-19 among IRD patients and the reference population, it seems that IRDs have an increased risk. Age, sex, therapies, and disease specific factors contribute for sure. Other studies have compared the IR of IRD with their reference population without differences,[10–12,15] but they have compared PCR confirmed cases regardless of the severity. Otherwise, two of them[10,11] did not include patients with systemic autoimmune conditions. Moreover, the IR varies per region and time period.[10–12,15–17]

Regarding ts/bDMARDs, the crude IR of hospital admission related to COVID-19 found in our study was lower for those on anti-TNF and higher for those with non-TNF biologics. But in the multivariate analysis the slight statistical differences from the bivariate analysis dissapeared. Interestingly, only one hospital admission related to COVID-19 was found on tocilizumab, and none were found on Abata, anti IL-17/23 nor baricitinib. This may be promising, but we should also bear in mind that the numbers of patients on these drugs were not sufficient to draw specific conclusions. But, in agreement with other authors,[16–19] ts/bDMARDs, and mainly anti-TNF, do not seem to be associated with worse outcomes in IRD.

Another interesting finding of this study is that the crude IR of hospital admissions related to COVID-19 differs among rheumatologic diseases, being somewhat higher in the systemic autoinmune conditions. In the multivariate analysis, these differences remained statistically significant for Sjögren, polychondritis, and MCTD, but also for primary Raynaud phenomenon. Nevertheless, SLE had the same risk as RA–PSA without statistical significance. Other systemic autoimmune conditions did not reach statistical significance, but maybe the number of patients was not high enough to find those differences.

Regarding other therapies, the crude IRs seems to be similar in patients with and without csDMARDs, higher in those on corticoids, and lower in those using NSAIDs. Nevertheless, after the multivariate analysis none of them remained statistically significant. According to Favalli *et al.*,[17] it seems that Mtx, Lef or Aza do not increase the risk of hospital admission related to COVID-19. In the case of Am, several authors have published its beneficial effect for the acute treatment of moderate–severe infection related to COVID-19.[20,21] In agreement with other authors,[22,23] we

are not able to demonstrate the protective effect of the chronic use of Am on moderate–severe infection related to COVID-19. Regarding glucocorticoids, although the crude IR was higher, they dropped from the final model. Nevertheless, these results should be corroborated analyzing corticoids by doses.

Interestingly, we corroborated the role of age, male sex and comorbidities[2,3] in the susceptibility of moderate–severe COVID-19 disease development. Specifically liver disease, lung disease and venous thrombosis/lung embolism achieved statistical significance in the multivariate analysis. Ischemic vascular disease and diabetes mellitus were only a trend, and hypertension, cancer or dyslipidemia did not achieve statistical signification. We must not forget that data were recorded during routine consultations, with a heavy workload environment, making more likely the possibility of incomplete information, mainly related to comorbidity.

It is true that the PCR test should be required as a part of the main outcome definition. However, in all admissions included, almost 20% of them did not have the PCR performed due to a lack of available tests and/or extreme health care overload at that time. Nevertheless, all were reviewed, being clinically compatible and managed as COVID-19. But, if we exclude these cases, the real incidence of hospital admissions related to COVID-19 would be underestimated. Another limitation is that we could have lost hospital admissions that had gone to other hospitals. Two of them were rescued for analysis, and we think there will not be many more, considering the state of alarm and confinement decreed in Spain since 14 March. Another limitation we must not forget is that there may be patients that died/or experienced severe COVID-19 at home who did not go to the hospital and therefore were not recorded as hospital admitted patients; therefore the number of severe COVID-19 might be underestimated. As strengths, we include 3951 non-selected patients with a broad spectrum of IRDs, with not standardized immunosuppressive therapy reflecting clinical practice in our health area, being able to adjust for confounders.

To our knowledge, this is the largest study to date outlining the severity of COVID-19 in terms of hospital admissions in IRD. It seems that patients with IRD could have a higher susceptibility of moderate–severe COVID-19 disease development compared with the general population, maybe due to systemic autoimmune diseases rather than chronic inflammatory arthritis. Moreover, we have been able to analyze to a greater extent the safety surrounding the administration of disease-modifying treatments. It seems that predisposition to develop moderate–severe COVID-19 disease in IRD is due to the type of diagnosis, age, sex and comorbidities, rather than the treatments exposed, including ts/bDMARDs and csDMARDs.

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Author contributions

BF, LL, JAJ, LRR, and LA contributed to the conception and design of the study. DF, JF, AMG, AM, JIC, and LL were involved in data collection. LA, AMG, and JIC were involved in database management. LA and LL performed the data analysis and interpretation of data. All authors contributed to drafting and/or revising the manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethics and consent statement

The study was approved by the HCSC institutional ethics committee (approval number 20/268-E_BS). It was carried out in accordance with the protocol and with the standard work procedures that ensure compliance with the Declaration of Helsinki and Good Clinical Practice standards, regulated by (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on data protection (RGPD) that entered into force on 25 May 2018. Retrospective data have been obtained during routine clinical practice with the informed consent of the patients to be treated in a service that performs assistance and research tasks. Taking into account the health emergency that constitutes the pandemic, the critical situation of the patients, the absence of direct intervention on them and the effort to collect the consent of their relatives, the ethics committee considered justified the absence of obtaining informed consent. The exploitation of

the databases was carried out in accordance with the standards established by the Information Systems department of the HCSC.

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