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Risk of Severe COVID-19 Infection in Patients With Inflammatory Rheumatic Diseases

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ABSTRACT. ***Objective.*** To describe the cohort of patients with inflammatory rheumatic diseases (IRD) hospitalized due to SARS-CoV-2 infection in the Ramón y Cajal Hospital, and to determine the increased risk of severe coronavirus disease 2019 (COVID-19) in patients with no IRD.

Methods. This is a retrospective single-center observational study of patients with IRD actively monitored in the Department of Rheumatology who were hospitalized due to COVID-19.

Results. Forty-one (1.8%) out of 2315 patients admitted due to severe SARS-CoV-2 pneumonia suffered from an IRD. The admission OR for patients with IRD was 1.91 against the general population, and it was considerably higher in patients with Sjögren syndrome, vasculitis, and systemic lupus erythematosus. Twenty-seven patients were receiving treatment for IRD with corticosteroids, 23 with conventional DMARDs, 12 with biologics (7 rituximab [RTX], 4 anti–tumor necrosis factor [anti-TNF], and 1 abatacept), and 1 with Janus kinase inhibitors. Ten deaths were registered among patients with IRD. A higher hospitalization rate and a higher number of deaths were observed in patients treated with RTX (OR 12.9) but not in patients treated with anti-TNF (OR 0.9).

Conclusion. Patients with IRD, especially autoimmune diseases and patients treated with RTX, may be at higher risk of severe pneumonia due to SARS-CoV-2 compared to the general population. More studies are needed to analyze this association further in order to help manage these patients during the pandemic.

Key Indexing Terms: autoimmune diseases, biologic therapy, infection, rheumatic diseases, tumor necrosis factor inhibitor

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China, in December 2019, and then spread worldwide. The World Health Organization declared it a pandemic in March 2020, and updated data show more than 96,877,000 infected people and 2,098,000 deaths worldwide at the time of writing.[1]

Madrid is a high SARS-CoV-2 infection rate area, with official data showing more than 489,000 infected people; of these, 84,326 have been admitted due to severe disease and 13,566 died in hospitals.[2] A nationwide seroprevalence study in Spain showed that 11.3% of the Madrid population was seropositive for SARS-CoV-2 infection in May 2020.[3]

Patients with coronavirus disease 2019 (COVID-19) commonly present with fever, myalgia, dyspnea, dry cough, anosmia, and ageusia. Data suggest that elderly people develop further complications and have a higher mortality rate.[4]

Patients with inflammatory rheumatic diseases (IRDs) are at higher risk of general infection due to the presence of comorbidities, underlying disease activity, and use of targeted immune-modulating therapies. Immunosuppressive targeted therapies (ITTs; biologics and Janus kinase [JAK] inhibitors) have been associated with higher immunosuppression and an increase in bacterial and viral infections.[5,6,7] It is unknown whether patients diagnosed with IRD are at risk of suffering a severe course of COVID-19.

Some drugs used in patients with IRD are being investigated for COVID-19 treatment, such as hydroxychloroquine (HCQ), tocilizumab, anakinra, or baricitinib. It is believed that these

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The authors have no conflicts of interest.

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drugs may reduce the virus penetration into cells or control the massive cytokine storm related to respiratory distress.

The aims of our study were to (1) describe our cohort of patients with IRD hospitalized due to coronavirus infection, and (2) analyze the hospitalization risk compared to non-IRD patients, as well as the association with the type of rheumatic disease and immunosuppressive therapy.

METHODS

The Ramón y Cajal Hospital treats 492,745 adult patients (> 16 yrs) in the northeast of Madrid.[8] Of these, 4592 have been previously diagnosed with an IRD and 883 are receiving treatment with biologic or JAK inhibitor therapies. Patients are registered and actively monitored by the hospital's Department of Rheumatology. They are all adult patients diagnosed with rheumatoid arthritis (RA), spondyloarthritis (SpA), psoriatic arthritis (PsA), systemic lupus erythematosus (SLE), Sjögren syndrome (SS), vasculitis, myopathy, polymyalgia rheumatica (PMR), and 12 other IRDs.

The baseline characteristics and most important comorbidities in the 4592 patients with IRD were compared with those of the patients without IRD. Control group information was extracted from the last Spanish national health survey[9] of 2017 among the local population.

All registries of adult patients confirmed to have SARS-CoV-2 infection and hospitalized between March 1 and April 30, 2020, in the Ramón y Cajal Hospital were included for analysis. In the majority of cases, the criterion for hospitalization was the presence of viral pneumonia with respiratory failure (PO_2 < 60 mmHg). Other major criteria included the presence of thrombosis, dehydration, severe diarrhea, or rhabdomyolysis. More than 1250 inpatient beds were allocated by our hospital during the pandemic. However, approximately 2% of patients with hospitalization criteria were referred to medicalized hotels. Following our management protocol, only patients who were considered not to have a critical condition or an IRD were referred from our hospital. All inpatients were managed according to a treatment protocol designed by the local Department of Infectious Diseases. The hospitalization risk was calculated using the number of admissions due to SARS-CoV-2 infection among patients with IRD (4592) and non-IRD individuals (488,153).

The study was approved by the local ethics board (number 136-20). Written informed consent to participate and publish the results was obtained from all patients.

RESULTS

Comparison of baseline characteristics between patients in the general population (Madrid registries of Spanish national health survey[9]) and patients with IRD in our hospital showed no differences in sex (female 52.5% vs 53.02%; $P = 0.28$), percentages of arterial hypertension (18.73% vs 17.33%; $P = 0.08$), diabetes mellitus (7.39% vs 8.14%; $P = 0.16$), and heart disease (5.32% vs 6.24%; $P = 0.05$). There were differences in the mean age (52.9 vs 57.1 yrs; $P < 0.001$), in the percentage of smokers (22.16% vs 15.08%; $P < 0.001$), and in patients with chronic pulmonary diseases (chronic obstructive pulmonary disease [COPD], asthma, and interstitial lung disease; 9.94% vs 16.21%; $P < 0.001$; data not shown).

During the study period, 2315 patients were admitted due to severe SARS-CoV-2 infection, and 41 (1.8%) of them were individuals with IRD. The baseline characteristics of these 41 patients are shown in Table 1. All of them had both pneumonia and respiratory failure. Nasopharyngeal swab SARS-CoV-2 PCR was tested in all patients and the result was positive in 35 out of 41 cases. In the 6 PCR-negative patients, COVID-19 diagnosis was established based on bilateral pneumonia and severe lymphopenia. A high percentage of hospitalized patients with IRD presented comorbidities such as previous lung disease (14 patients) and cancer (5 cases, 2 of whom had been diagnosed with cancer in the last year). Twenty-three out of 41 patients suffered from inflammatory arthropathies (RA, SpA, and PsA) and 18 from a systemic autoimmune disease (SLE, SS, vasculitis, myositis, and PMR). Six patients had an active IRD (high clinical activity, newly diagnosed, or recently started biologic therapy).

Regarding treatment, > 65% were taking corticosteroids daily. The average dose was 5.2 mg/day of prednisone or the equivalent, and no patient was taking > 10 mg/day. Twenty-three patients were undergoing treatment with conventional synthetic disease-modifying antirheumatic drugs (14 received methotrexate [MTX], 4 HCQ, 2 sulfasalazine, 1 leflunomide, 1 azathioprine, and 1 mycophenolate mofetil), 12 (29%) with biologic therapies, and 1 with JAK inhibitors.

Out of the 41 hospitalized patients, 10 died (3 patients diagnosed with RA and pulmonary disease, 1 patient with RA and lung cancer, 2 with PMR of advanced age, 2 with active SLE, and 2 with vasculitis). Three of the 13 patients under ITT died, all of them receiving treatment with rituximab (RTX).

The hospitalization rates and ORs of admission in patients with IRD compared to the reference population are shown in Table 2. Patients with IRD presented a higher hospitalization rate. Further, OR was higher in patients with systemic autoimmune diseases, mainly SS, vasculitis, and SLE. RA and PMR also presented a significant increased risk of severe COVID-19 but SpA and PsA did not.

Table 3 shows an analysis of ORs in relation to the ITTs used for the patients with IRD. Seven out of 72 patients undergoing treatment with RTX were admitted (2 patients with vasculitis, 2 with SS, 2 with RA, and 1 with SLE) with a significantly higher risk of hospitalization. Conversely, no increase in the hospitalization rate due to severe pneumonia was found among the 603 patients receiving anti–tumor necrosis factor (anti-TNF) drug treatment.

DISCUSSION

The general increase in infections among patients with IRD can be attributed to comorbidities, disease immune activity, and immunodepression.[10] Biologic therapies lead to a change in the clinical course and prognosis of IRD, but at the cost of an increased risk of opportunistic infections or reactivation of latent ones.[5,6,7]

In our study we have analyzed the hospitalization rate due to COVID-19 in a broad population. Despite minimal differences related to the geographical location, our admission rate was similar to other tertiary hospitals in Madrid. Our results show a significantly higher risk of severe pneumonia and hospitalization among patients diagnosed with IRD compared to the reference population. These results contrast with the ones found in initial studies in which data were obtained through surveys,[11] among the pediatric population,[12] or in studies that did not include patients with SLE or other autoimmune diseases.[13]

Table 1. Demographics, baseline characteristics, and outcomes of patients with IRD admitted to hospital due to severe SARS-CoV-2 infection.

	Hospitalized, n = 41	Hospitalized and Surviving, n = 31	Hospitalized and Deceased, n = 10	*P**
Age, yrs, median (range)	72 (36–87)	72 (36–84)	76 (61–87)	0.06
Female	25 (61)	20 (64)	5 (50)	0.41
Hospital stay, days, median	9	9	9	0.88
Deaths	10 (24)	0 (0)	10 (100)	
Comorbidities				
Hypertension	23 (56)	17 (54)	6 (60)	0.77
Lung disease[a]	14 (34)	8 (25)	6 (60)	**0.04**
Diabetes	9 (22)	6 (19)	3 (30)	0.47
Cardiovascular disease	7 (17)	4 (13)	3 (30)	0.21
Malignant tumor	5 (12)	3 (10)	2 (20)	0.38
Other comorbidities	9 (22)	5 (16)	4 (40)	0.11
None	6 (15)	6 (19)	0	0.13
Rheumatic disease				
RA	16 (39)	12 (39)	4 (40)	0.94
SpA	3 (7)	3 (10)	0	0.30
PsA	4 (10)	4 (13)	0	0.23
SLE	4 (10)	2 (6)	2 (20)	0.20
Sjögren syndrome	4 (10)	4 (13)	0	0.23
Vasculitis	3 (7)	1 (3)	2 (20)	0.07
Inflammatory myopathy	1 (2)	1 (3)	0	0.56
PMR	6 (15)	4 (13)	2 (20)	0.58
Active IRD[b]	6 (15)	3 (10)	3 (30)	0.11
Disease duration, yrs, median	15	12	18	0.45
IRD treatment				
No DMARDs	10 (24)	6 (19)	4 (40)	0.18
Conventional synthetic DMARDs[c]	23 (56)	19 (61)	4 (40)	0.23
Biologic DMARDs	12 (29)	9 (29)	3 (30)	0.95
Anti-TNF	4 (10)	4 (13)	0	0.23
RTX	7 (17)	4 (13)	3 (30)	0.21
ABA	1 (2)	1 (3)	0	0.56
JAK inhibitors	1 (2)	1 (3)	0	0.56
GC use	27 (66)	18 (58)	9 (90)	0.06
GC dose, mg, mean	5.2	5.4	4.6	0.54

Values are expressed as n (%) unless otherwise indicated. Values in bold are statistically significant. [a] Lung disease included interstitial lung disease, chronic obstructive pulmonary disease, asthma, or smoking. [b] Active rheumatic disease included high clinical activity, or newly diagnosed or recently started biologics treatment. [c] Conventional synthetic DMARDs included methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, azathioprine, and mycophenolate mofetil. * Comparisons were between surviving and deceased patients. ABA: abatacept; DMARD: disease-modifying antirheumatic drug; GC: glucocorticoid; IRD: inflammatory rheumatic disease; JAK: Janus kinase; PMR: polymyalgia rheumatica; PsA: psoriatic arthritis; RA: rheumatoid arthritis; RTX: rituximab; SLE: systemic lupus erythematosus; SpA: spondyloarthritis; TNF: tumor necrosis factor.

Several higher-quality studies have subsequently been carried out. In a multicenter study in Spain, which included more than 26,000 patients with IRD, it was shown that these patients had an increased prevalence of hospital PCR+ (1.32-times higher) compared to the general population.[14] In a multicenter matched cohort study, from the same group of authors, the prevalence of severe COVID-19 (death, intensive care unit admission, or need for ventilation) was determined. The authors found that having a connective tissue disease was independently associated with severe COVID-19.[15] Another study conducted in Madrid also found that having a systemic autoimmune condition increased the risk of hospital admission.[16] Recently, a worldwide register of COVID-19 patients diagnosed with IRD was created, and its updated database has more than 2500 registries of patients, 36.4% of them hospitalized and 7.2% dead.[17] This register contains the largest amount of reported patients with IRD, to our knowledge. However, it is not possible to perform an estimation of the risk of severe illness among patients with IRD without a control group.

Different results have been communicated in patient case series of other chronic diseases with immunosuppressive treatments and COVID-19. A greater progression and higher mortality rate were reported in patients with kidney transplants,[18] although not in hepatic transplants in children[19] or adults,[20] or in intestinal inflammatory diseases.[21]

It has been reported that patients with SLE and those with other autoimmune diseases can be at higher risk of general infection than those with RA.[10] In this sense, our study has found a higher severe COVID-19 rate among patients with systemic autoimmune diseases. It has been suggested that patients with SLE can develop hypomethylation and an overexpression of

Table 2. COVID-19 hospital admission rate and ORs in patients with inflammatory rheumatic diseases.

	All Patients[a], n	Hospitalized Patients, n	Hospitalization Rate, %	OR*	95% CI*
Total population	492,745	2315	0.47		
Non-IRD patients	488,153	2274	0.47	1.00	
IRD patients	4592	41	0.89	1.91	**1.41–2.61**
RA	1708	16	0.94	2.01	**1.23–3.28**
SpA	862	3	0.35	0.74	0.24–2.31
PsA	515	4	0.78	1.66	0.63–4.43
SLE	254	4	1.57	3.38	**1.28–8.95**
Sjögren syndrome	175	4	2.29	4.90	**1.86–12.94**
Vasculitis	165	3	1.82	3.90	**1.27–11.99**
Inflammatory myopathy	88	1	1.14	2.43	0.35–17.13
PMR	474	6	1.27	2.71	**1.23–6.02**
Others	351	0	0	0	

Values in bold are statistically significant. [a] Hospitalized and nonhospitalized patients. * Comparisons were between each disease group and no inflammatory rheumatic disease patients. COVID-19: coronavirus disease 2019; IRD: inflammatory rheumatic disease; PMR: polymyalgia rheumatica; PsA: psoriatic arthritis; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SpA: spondyloarthritis.

Table 3. Biologics and JAK inhibitors in patients with IRD, including rates and ORs of hospitalization in relation to undergoing treatment.

	All Patients[a], n	Hospitalized Patients, n	Hospitalization Rate, %	OR*	95% CI*
IRD patients without biologics/JAK inhibitors	3709	28	0.75	1	
Anti-TNF	603	4	0.66	0.88	0.31–2.50
RTX	72	7	9.72	12.88	5.82–28.51
ABA	40	1	2.50	3.31	0.46–23.75
JAK inhibitors	18	1	5.55	7.36	1.06–51.22
Others	150	0	0	0	

[a] Hospitalized and nonhospitalized patients, diagnosed with IRD and monitored by the Department of Rheumatology. * Comparisons were between each treatment group and IRD patients without biologic/JAK inhibitor treatment. ABA: abatacept; IRD: inflammatory rheumatic disease; JAK: Janus kinase; RTX: rituximab; TNF: tumor necrosis factor.

angiotensin-converting enzyme 2 that could facilitate the viral entrance inside the cell.[22]

With regard to the treatments used for patients with IRD, a systematic review has not found evidence supporting that low doses of MTX, anti-TNF, or JAK inhibitors result in higher risk of infection within the COVID-19 context.[23] Following the same line, our study's results indicate that anti-TNF drugs confer no additional risk of severe infection compared to IRD patients without ITT. Conversely, we have found that patients undergoing treatment with RTX have a markedly higher rate of hospitalization and death due to COVID-19. RTX is a chimeric monoclonal antibody anti-CD20 that reduces mature B cells, but it can also have an indirect effect on T lymphocytes, inducing a reduction of CD4 and CD8 cells.[24] Concerning RA, the decreased count of CD4 cells has been associated with a clinical response to RTX.[25] The B and CD4 lymphocyte decrease induced by RTX, associated with severe lymphopenia and a deregulation between innate and adaptive immunity due to SARS-CoV-2, would predispose to a worse prognosis regarding COVID-19. From a broad series of patients in Wuhan, [26] lymphopenia was correlated with the severity course of COVID-19.

Our study has 2 relevant limitations that must be considered before interpreting our results. It is a retrospective, single-center study. For that reason, results can be affected by the features of the local population (sex, age, socioeconomic status, and academic level) or treatment behavior of our hospital. On the other hand, part of the increase in the risk of severe disease could be attributed to some base characteristics of our cohort absent in non-IRD patients. In particular, older age and frequency of lung disease and COPD were identified in our IRD cohort compared with data obtained from the general population. Although general population data was obtained through a global health survey in Madrid in 2017,[9] differences detected in comorbidities could explain part of the results obtained. Our results need to be confirmed in multicenter registries, and those should be considered for treatment recommendations in patients with IRD during the COVID-19 pandemic.

With these limitations, we conclude that patients with IRD may be at higher risk of hospitalization for COVID-19 as compared to the reference population. This risk seems to be particularly high for those with systemic autoimmune diseases such as SLE, SS, and vasculitis, as well as patients undergoing treatment with RTX. Conversely, treatment with anti-TNF was not associated with a higher rate of severe SARS-CoV-2 illness.

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