UNIVERSIDAD COMPLUTENSE DE MADRID
FACULTAD DE MEDICINA

TESIS DOCTORAL

Enfermedades Reumáticas y Musculoesqueléticas en el Contexto del SARS-CoV-2

Rheumatic and Musculoskeletal Diseases in the Context of SARS-CoV-2

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

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Directores

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Benjamín Fernández Gutiérrez

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PhD Thesis

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List Of Abbreviations

Abbreviation	Meaning
ACE2	Angiotensin-converting enzyme 2
ACPA	Anti-Citrullinated Peptide Antibody
ACR	American College of Rheumatology
anti-TNF	Anti- Tumor Necrosis Factor Alfa
ARD	Autoimmune Rheumatic Diseases
ARDS	Acute Respiratory Distress Syndrome
AT1	Alveolar Type 1
AT2	Alveolar Type 2
BCDT	B Cell-Depleting Therapy
bDMARDs	Biological DMARDs
C19-GRA	COVID-19 Global Rheumatology Alliance
ccCoVs	Common Cold Coronaviruses
CFR	Case-Fatality Rate
CI	confidence interval
CIA	Chronic Inflammatory Arthritis
CMR	Cause specific mortality rate
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CRP	C Reactive Protein
CRS	Cytokine Release Syndrome
csDMARDs	Conventional Synthetic DMARDs
CTD	Connective Tissue Diseases
CYC	Cyclophosphamide
DAMPs	Damage-Associated Molecular Patterns
DAS	Disease Activity Score
DIC	Disseminated Intravascular Coagulation
DMARDs	Disease Modifying Anti- Rheumatic Drugs
dsRNA)	Double-stranded RNA
ESR	Erythrocyte sedimentation rate
EULAR	European Alliance of Associations for Rheumatology
GC	Glucocorticoids
GCA	Giant Cell Arteritis
HCQ	Hydroxychloroquine

HCSC	Hospital Clínico San Carlos
HIS	Hospital information system
HR	Hazard ratio
HRQoL	Health-Related Quality of Life
ICD	International Classification of Diseases
ICU	Intensive Care Unit
IFEMA	Institucion Ferial de Madrid
IL	Interleukin
IL-17	Interleukin-17
IL-6	Interleukin-6
ILD	Interstitial Lung Disease
IQR	Interquartile Ranges
IRDs	Inflammatory Rheumatic Diseases
JAKi	Januskinase Inhibitors
JCR	The Journal Citation Reports
JIF	Journal Impact Factor
MCTD	Mixed Connective Tissue Disease
MERS	Middle East respiratory sickness
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
non-ARD	Non-Autoimmune Rheumatic Diseases
NSAID	Non-Steroidal Anti-Inflammatory Drug
PAMPs	Pathogen-Associated Molecular Patterns
PCR	Polymerase chain reaction
PM	Polymyoitis
PRRs	Pattern recognition receptors
PsA	Psoriatic Arthritis
RA	Rheumatoid Arthritis
RCI	Rosser Classification Index
BCDT	Rituximab is a B cell-depleting therapy
RMD	Rheumatic and Musculoskeletal Diseases
SARS	Severe Acute Respiratory Syndrome
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
SIG	SARS-CoV-2 Interagency Group
SLE	Systemic Lupus Erythematosus
SpA	Spondylarthritis
SS	Sjögren's Syndrome
SSc	Systemic Sclerosis

TLRs	Toll-Like Receptors
TMPRSS2	Transmembrane serine protease at the S2′ site
tsDMARDs	Targeted Synthetic Disease-Modifying Anti-Rheumatic Drugs
WHO	World Health Organization

Resumen

A fines de 2019, se identificó un nuevo coronavirus como la causa de un grupo de casos de neumonía en Wuhan, una ciudad en la provincia China de Hubei. Se propagó rápidamente, lo que resultó en una epidemia en toda China, seguida de un número creciente de casos en otros países del mundo. En febrero de 2020, la Organización Mundial de la Salud designó la enfermedad, COVID-19, que significa enfermedad por coronavirus 2019. Es causada por un virus llamado SARS-CoV-2. El espectro clínico de la infección incluye desde infección asintomática hasta enfermedad grave y mortal. Si bien la mayoría de los pacientes con COVID-19 tienen un resultado favorable e infecciones sintomáticas leves, algunos desarrollan neumonía grave que finalmente conduce al síndrome de dificultad respiratoria aguda (SDRA) junto con otras manifestaciones orgánicas.

Al comienzo de la pandemia de COVID-19, existía la preocupación sobre si las personas con enfermedades reumáticas y musculoesqueléticas (RMD, por sus siglas en inglés) podrían experimentar un COVID-19 más grave o con peores resultados que la población general. La alteración inmunológica como resultado directo de la enfermedad reumática o un efecto indirecto del tratamiento potencialmente podría contribuir a los peores resultados de COVID-19 en estos pacientes.

El objetivo de esta tesis fue obtener información sobre la evolución clínica de pacientes con RMD en el contexto del SARS-CoV-2 en una consulta externa de reumatología de un hospital terciario de Madrid, España. Esta investigación se llevó a cabo en un entorno clínico de la vida real durante el brote de COVID-19, utilizando análisis descriptivo y estadística inferencial con métodos y procedimientos para obtener conclusiones útiles, con base en la información proporcionada por este grupo especial de pacientes. En esta investigación se realizaron técnicas de supervivencia, pruebas de estimación puntual (o intervalos de confianza), pruebas paramétricas, análisis no paramétricos, de correlación y de regresión logística bivariable y multivariable, análisis de varianza, entre otras.

Esta tesis presenta como resultados tres artículos originales publicados; La investigación describe las características sociodemográficas, clínicas y de tratamiento de una cohorte longitudinal y dinámica de pacientes con RMD que presentaron infección por SARS-CoV-2 durante los primeros meses del pico pandémico. En esta investigación, se analizaron los posibles factores de riesgo asociados con el ingreso hospitalario, los malos resultados, la mortalidad relacionada con el COVID-19 en pacientes con RMD.

La población de estudio varió según los diferentes escenarios temporales del periodo de estudio. Se incluyeron un total de 405 pacientes con RMD e infección por SARS-CoV-2 (642,5

pacientes-mes). Las RMD más comunes fueron las enfermedades reumáticas no autoinmunes (no-ARD) en 243 pacientes, seguidas de la artritis inflamatoria crónica (AIC) en el grupo de ARD (26 %), incluidos 65 pacientes con artritis reumatoide (AR). Del total, el 69% eran mujeres con una edad media de 59,37 años. Se informó la presencia de cualquier tipo de comorbilidad relacionada con la gravedad del COVID-19 (presencia de al menos uno de los siguientes: diabetes mellitus, enfermedad cardíaca, enfermedad vascular isquémica, hepatopatía e insuficiencia renal, tromboembolismo pulmonar y enfermedad pulmonar) en el 26% de los pacientes, resultando mayor en enfermedades del tejido conectivo (ETC).

Se requirió ingreso hospitalario relacionado con COVID-19 en 146 pacientes. Este porcentaje fue principalmente a expensas de las ETC. La edad media de ingreso fue de 69,7 años. En comparación con los pacientes ambulatorios, los factores que se asociaron de forma independiente con el ingreso hospitalario en el análisis multivariante fueron la edad avanzada, el sexo masculino, ciertas comorbilidades y algunas enfermedades autoinmunes sistémicas como el síndrome de Sjögren, policondritis recidivante y enfermedad mixta del tejido conectivo (EMTC).

Durante el período de estudio se registraron 44 (10,86%) muertes y la tasa de mortalidad por causa específica (CMR) fue de 6,8% pacientes-mes. La CMR resultó mayor en el sexo masculino, pacientes de mayor edad, en aquellos con comorbilidad basal relacionada con la gravedad del COVID-19 y con mayores niveles de discapacidad. Al evaluar un tipo específico de RMD, fue mayor, especialmente en pacientes con AR, vasculitis, polimialgia reumática y EMTC. Después de ajustar por factores de confusión, el riesgo de mortalidad en ARD en comparación con no-ARD no alcanzó significación estadística, ni ETC versus CIA, ni ETC versus no-ARD. La mayor edad y la comorbilidad relacionada con la gravedad del COVID-19 implicaron un mayor riesgo de mortalidad, sin embargo, la hipertensión arterial se eliminó del modelo. La CMR fue más alta en los pacientes diagnosticados en marzo en comparación con los diagnosticados en abril o mayo.

En cuanto a los tratamientos crónicos de las RMD, en la ETC la exposición a glucocorticoides fue más frecuente en comparación con otros grupos de RMD. El metotrexato fue el fármaco antirreumático modificador de la enfermedad convencional clásico más utilizado (FAMEcs). Entre los FAME biológicos y sintéticos dirigidos, los fármacos anti-TNF fueron los más utilizados. Los glucocorticoides tuvieron una CMR más alta, mientras que el uso de b/tDMARD tuvo una CMR más baja, ambos en comparación con la no exposición. Con respecto a los FAMEcs, los pacientes que tomaban estos fármacos no diferían en su CMR respecto de los que no. Sin embargo, en el análisis multivariante no se encontraron hallazgos estadísticamente significativos para la exposición a los diferentes FAMEs, ni para el ingreso hospitalario o para el riesgo de mortalidad. El uso de glucocorticoides y AINE se eliminó del modelo final.

La tesis incluye una discusión estructurada de las diferentes preguntas de investigación planteadas en esta problemática, comparando y contrastando nuestros resultados con estudios relevantes realizados durante la pandemia de COVID-19.

Finalmente, las conclusiones resumen las principales ideas y aportes de este trabajo. En pacientes con RMD y COVID-19, estos resultados sugieren que la edad avanzada y tener una enfermedad autoinmune sistémica aumentaron el riesgo de ingreso hospitalario. El riesgo de mortalidad es mayor en varones, pacientes mayores y en condiciones comórbidas específicas, y resulta similar entre las ETC, AIC y las no ARD. Los FAMEs no se asociaron con un riesgo de ingreso hospitalario o mortalidad. Los artículos desarrollados en esta tesis aportaron evidencia crucial en el manejo de pacientes con RMD en un momento de crisis sanitaria causado por el brote de COVID-19.

Palabras clave: Enfermedades Reumáticas y Musculoesqueléticas, COVID-19, datos de vida-real, epidemiología, fármaco antirreumático modificador de la enfermedad, hospitalización, mortalidad.

Summary

At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. It rapidly spread, resulting in an epidemic throughout China, followed by an increasing number of cases in other countries throughout the world. In February 2020, the World Health Organization designated the disease COVID-19, which stands for coronavirus disease 2019. It is caused by a virus called SARS-CoV-2. The clinical spectrum of SARS-COV-2 infection includes asymptomatic infection and serious and fatal disease. While most of patients with COVID-19 have a favorable outcome and mild symptomatic infections, some develop severe pneumonia that eventually leads to acute respiratory distress syndrome (ARDS) along with other organ manifestations.

At the beginning of the COVID-19 pandemic, concern existed regarding whether individuals with Rheumatic and Musculoskeletal Diseases (RMD) potentially experience more severe COVID-19 disease and poorer outcomes than the general population. Immunological alteration as a direct result of rheumatic disease or an indirect effect of treatment has the potential to contribute to poor COVID-19 outcomes.

The aim of this thesis was to obtain information about the clinical course of patients with RMD in the context of SARS-CoV-2 in an outpatient rheumatology clinic of a tertiary hospital in Madrid, Spain. This investigation was carried out in a real-life clinical setting during the COVID-19 outbreak, using descriptive analysis and inferential statistics with methods and procedures to obtain useful conclusions for deductive reasoning, based on the information given by this special group of patients. Survival techniques, point estimate tests (or confidence intervals), parametric tests, and non-parametric, correlation and bivariable and multivariable logistic regression analyses, and analysis of variance, among others, techniques were performed in this investigation.

This thesis presents three original published articles as results; The investigation describes the sociodemographic, clinical, and treatment characteristics of a dynamic longitudinal cohort of patients with RMD who had SARS-CoV-2 infection during the first months of the pandemic peak. In this research, potential risk factors associated with hospital admission, poor outcomes and mortality related to COVID-19 were analyzed in patients with RMD.

The study population varied according to the different time scenarios of the study period. A total of 405 patients with RMD and SARS-CoV-2 infection were included (642.5 patients-month). The most common RMD were non-autoimmune rheumatic diseases (non-ARD) in 243 patients, followed by chronic inflammatory arthritis (CIA) in the ARD group (26%), including

65 patients with rheumatoid arthritis. Of the total, 69% were women with a mean age of 59.37 years. The presence of any type of comorbidity related to COVID-19 severity (the presence of at least one of the following: diabetes mellitus, heart disease, ischemic vascular disease, chronic liver disease and renal failure, pulmonary embolism, and lung disease) was reported in 26% of the patients and results higher in connective tissue diseases (CTD).

Hospital admission related to COVID-19 was required in 146 patients. This percentage was primarily at the expense of CTD. The mean age at admission was 69.7 years. Compared to outpatients, factors independently associated with hospital admission in the multivariate analysis were older age, male, certain comorbidities, and specific systemic autoimmune diseases (Sjögren syndrome, relapsing polychondritis, and mixed connective tissue disease (MCTD)).

During the study period, 44 (10.86%) deaths were recorded and the cause-specific mortality rate (CMR) was 6.8% patients-month. The CMR resulted higher in male sex, older patients, in those with baseline comorbidity related to COVID-19 severity, and with higher levels of disability. When assessing a specific type of RMD, it was higher especially in patients with RA, vasculitis, polymyalgia rheumatic, and MCTD. After adjusting for confounders, the mortality risk in ARD compared to non-ARD did not achieve statistical significance, neither CTD versus CIA nor CTD versus non-ARD. Older age and comorbidity related to COVID-19 severity implied a higher risk of mortality, nevertheless, having hypertension dropped from the model. Interestingly, CMR was higher in those patients diagnosed in March compared to those diagnosed in April or May.

Concerning RMD chronic treatments, in CTD, exposure to glucocorticoids was more frequent compared to other RMD groups. Methotrexate was the most commonly used classical conventional disease-modifying antirheumatic drug (csDMARDs) followed by antimalarials. Among biological and target synthetic DMARDs, anti-TNF drugs were the most widely used. Glucocorticoids had higher CMR, whereas the use of b/tsDMARDs had lower CMR, both compared to non-exposure. Regarding csDMARDs, patients taking these drugs did not differ in their CMR from those without them. However, in the multivariate analysis, no statistically significant findings for exposure to different DMARDs were found nor for hospital admission or mortality risk. The use of glucocorticoids and NSAIDs dropped from the final model.

The thesis includes a structured discussion of the different research questions raised in this investigation, comparing and contrasting our results with relevant research conducted throughout the COVID-19 pandemic.

Finally, the conclusions summarize the main ideas and contributions of this work. In patients with RMD and COVID-19, these results suggest that older age and having a systemic autoimmune condition increased the risk of hospital admission. The mortality risk is higher in males, older patients, and in specific comorbid conditions, and similar between CTD, CIA, and non-ARD. DMARDs were not associated with a risk for hospital admission or mortality. The articles developed in this thesis provided crucial evidence in the management of patients with RMD at a time of health crisis caused by the COVID-19 outbreak.

Keywords: Rheumatic and Musculoskeletal Diseases, COVID-19, real-world data, epidemiology, disease-modifying antirheumatic drug, hospital admission, mortality.

CHAPTER 1

1 Introduction

1.1 Background and Relevance of Research

In December 2019, a new respiratory infection caused by a member of the coronoviridae family called severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) was reported in Wuhan, China (1). The infection spread rapidly and became a worldwide pandemic. The virus-related illness is called novel coronavirus disease 2019 (COVID-19). Cases are still in constant evolution globally with 757,264,511 confirmed cases of COVID-19, including 6,850,594 deaths, reported to the World Health Organization (WHO) as of 21 February 2023 (2).

The spectrum of COVID-19 in adults ranges from asymptomatic infection to mild respiratory tract symptoms to severe pneumonia with acute respiratory distress syndrome (ARDS), multiorgan dysfunction, and death. The understanding of the spectrum of disease as well as optimal management strategies continues to evolve, particularly with the emergence of SARS-CoV-2 variants (3,4).

There has been much research on the correlation between various diseases and COVID-19. Risk factors associated with higher mortality due to COVID-19 that have already been identified include age over 70, obesity, cardiovascular disease, diabetes mellitus, chronic kidney failure under dialysis, cancer under treatment, cirrhosis, and chronic respiratory disease (4,5). In this pandemic context, it is important to clarify the association between COVID-19 and a group of potentially fragile patients, those with rheumatic and musculoskeletal diseases (RMD).

According to the European Alliance of Associations for Rheumatology (EULAR), RMD are a diverse group of diseases that commonly affect the joints, but can also affect muscles, other tissues, and internal organs. There are more than 200 different RMD. They are usually caused by problems of the immune system, inflammation, infections, or gradual deterioration of joints, muscles, and bones. Many of these diseases are long-term and worsen over time. They are typically painful and Iimit function. In severe cases, RMD can result in significant disability, having a major impact on both quality of life and life expectancy (6).

Autoimmune rheumatic diseases affect 3-5% of the global population (7), and are a group of diseases characterized by chronic systemic inflammatory diseases involving the musculoskeletal system due to abnormal immune response to autoantigens (8) and examples of such diseases include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren's

syndrome (SS), systemic sclerosis (SSc), polymyositis (PM), and systemic vasculitis. Compared with the general population, patients with RMD are still facing a greater risk of viral and bacterial infection as well as complications as a result of underlying disease, associated comorbidities, and the use of potentially immunosuppressive treatments (9–11).

Globally, the health system has been focusing for the past three years on COVID-19. At the beginning of the COVID-19 pandemic, concern existed regarding whether individuals with rheumatic diseases potentially experience more severe COVID-19 disease and poorer outcomes than the general population. Immunological alteration as a direct result of rheumatic disease or an indirect effect of treatment has the potential to contribute to poor COVID-19 outcomes (12,13).

Although the risk of infection and the clinical outcomes of COVID-19 in patients with RMD have been discussed in previous studies, before our investigation there was still a gap of knowledge on this topic (14,15). Besides, during the first waves of the pandemic, the incidence of COVID-19 and serious clinical outcomes in patients with RMD was high, with differential risks in most regions, considering it essential and priority to obtain data about these specific groups of patients in Madrid, one of the cities importantly struggled by COVID19 outbreak.

1.2 Problem Statement

Whether people with RMD belong to a vulnerable, higher-risk population for SARS-CoV-2 infection and have poorer outcomes was feasible nevertheless this matter was still unclear. Scientific evidence in the clinical management of patients with RMD at a time of health crisis caused by the covid-19 outbreak was mandatory. This investigation provides a view of the impact of COVID-19 with relevance to people with RMD in a third-level hospital in Madrid-Spain, in a real-life clinical practice setting. There is a description of their characteristics, their incidence and the risks of severe SARS-CoV-2 infection, (including hospitalization and mortality), in those patients with RMD.

1.3 Thesis Scope

This thesis focuses on the impact of the Covid-19 pandemic on individuals with RMD under follow-up in a tertiary hospital. For this investigation, we have included Autoimmune Rheumatic Diseases (ARD) and Non-Autoimmune Rheumatic Diseases (non-ARD). According to the International Classification of Diseases (ICD), a wide variety of diseases and medical conditions are included in the scope. The articles of this investigation explored the risks of SARS-CoV-2 infection, the factors associated with hospitalization, poor outcomes, mortality, and the management of COVID-19 in patients with RMD, abording the role of the type of the

rheumatic disease and its different immunosuppressives treatments. The geographical scope of this study is set in Madrid. More precisely, in an important healthcare area of the community, the one corresponding to the Hospital Clínico San Carlos (HCSC).

1.4 Thesis Organization

The format of this thesis follows the generic structure of a research document by the Doctoral School of the Complutense University of Madrid.

The guiding thread of this thesis stems from the concern and scientific questions during the health emergency generated by the COVID-19 pandemic in a special group of patients, such as individuals with RMD. From this starting point, the epidemiological situation by the moment the outbreak and medical research intersect to answer some of those questions collaboratively. Considerable efforts have been made to bring the real-life emergency scenario and the research closer together and make the document easy to read and understand.

Chapter 1 provided the necessary background information and introduced the reader to the topic, problem statement, research questions, and scope. Then, a comprehensive state of the art and literature review about COVID-19 elaborates on the virology, epidemiology, transmission, pathogenesis, and clinical manifestations, and introduces COVID-19 aspects in patients with RMD as the main foundation of this investigation.

Chapter 2 subsequently to the literature review, as researchers, we were allowed to create a broad understanding of the subject matter and develop the research questions and the gap finding logically and inductively.

Chapter 3 constitutes the materials and methods chapter. It starts by describing the study design, the setting, inclusion criteria, subjects, the data sources, the main and secondary variables, and the statistical analysis techniques used to answer the different research questions in the following chapters. Ethical considerations are also mentioned in this chapter.

Chapter 4 presents the three published original articles as results; the text and the tables exposed are an exact reproduction of the original research, each with its own references. This chapter addresses the information about the clinical course of patients with RMD in the context of SARS-CoV-2 in a rheumatology outpatient clinic of a tertiary hospital in Madrid, describing the sociodemographic, clinical and treatment characteristics of a cohort of patients with RMD who have presented COVID-19 during the three months of the first pandemic peak. Information about the risk of hospital admission and mortality in patients with RMD in the context of COVID-19 is exposed in this results chapter.

Chapter 5 shows a structured discussion of the different research questions raised in this investigation, comparing and contrasting our results with relevant research conducted throughout the COVID-19 pandemic.

Chapter 6 includes the conclusions, a summary of the main ideas, findings, and contributions of this thesis, provides an overview of future directions of research, and mentions the potential challenges to be addressed in the management of patients with RMD in the context of the COVID-19 pandemic.

Figure 1 illustrates the structure of this thesis. The design of the figure indicates the organic and logical development of the thesis's subjects. Following the literature review, a section for methodology, and the findings, with three original articles, a discussion, and a conclusion complete this work.

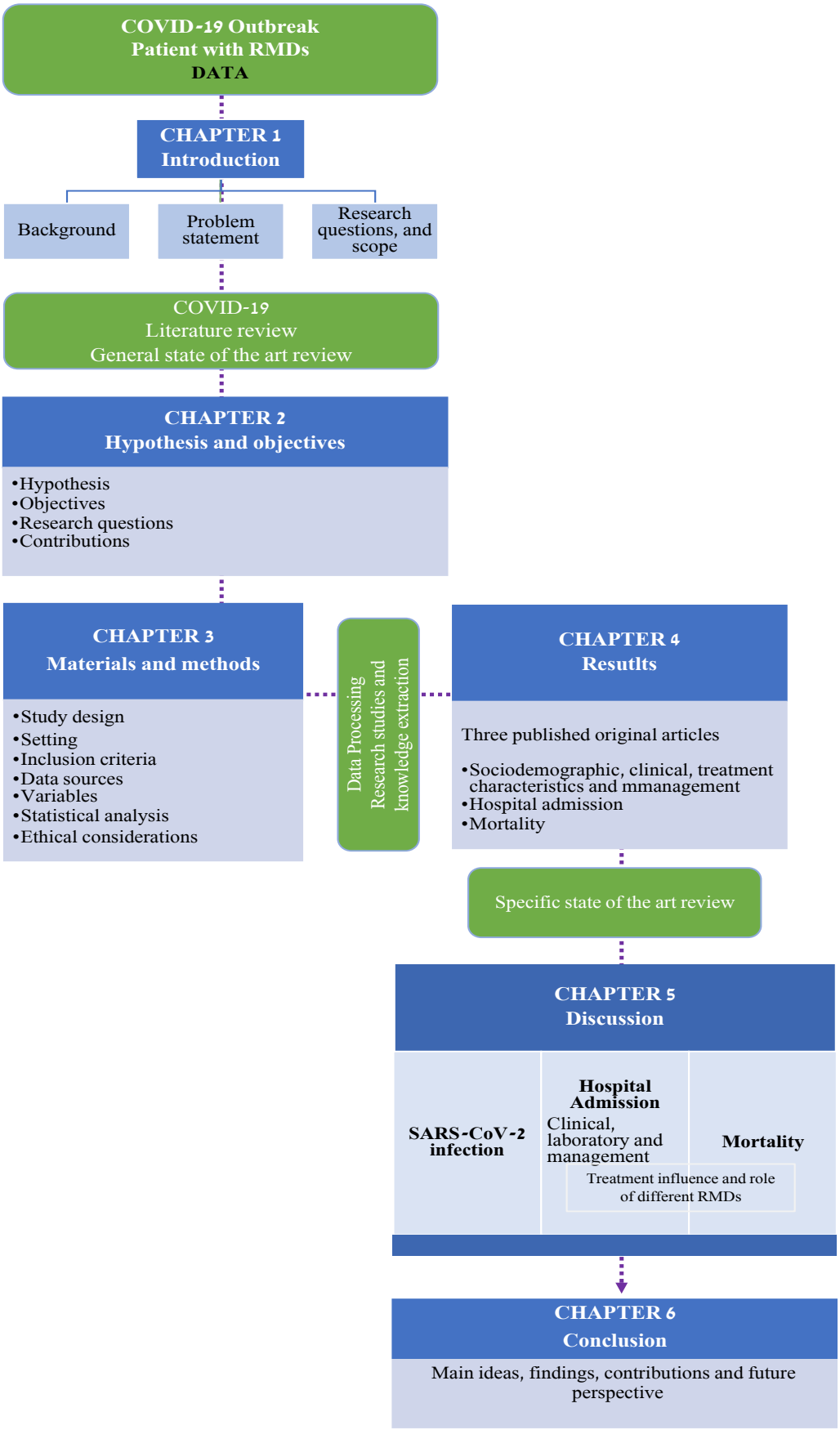


Figure 1. Structure of the Thesis

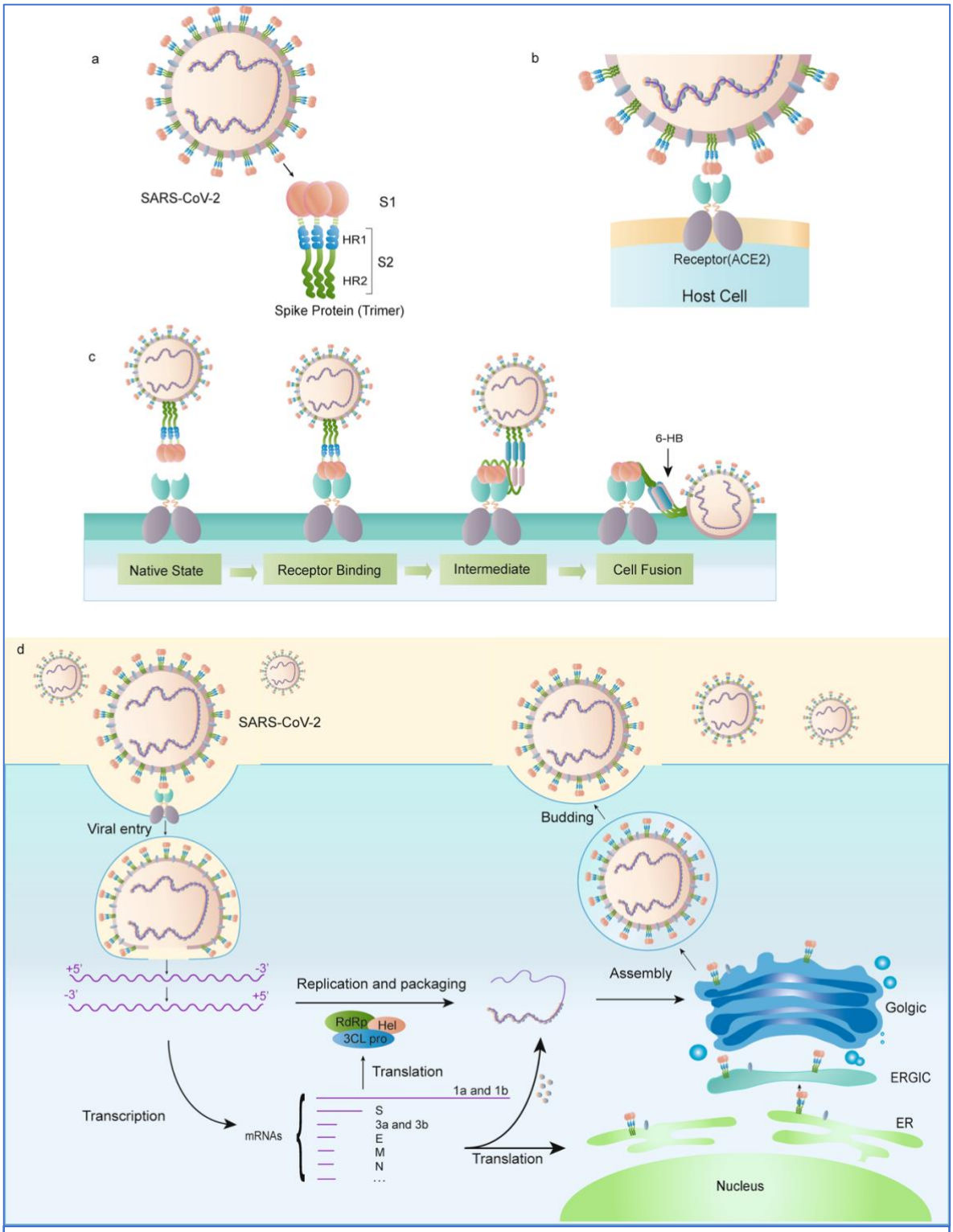
1.5 Review of the State of the Art

1.5.1 COVID-19: Virology

- **Coronavirus virology**

Coronavirus are enveloped positive-stranded RNA viruses. The coronavirus that causes COVID-19 is a betacoronavirus in the same subgenus as the severe acute respiratory syndrome (SARS) virus (as well as other bat coronaviruses), but in a different clade, according to full-genome sequencing and phylogenic analysis. SARS-CoV-2 has been proposed as the official name for this virus by the International Committee on Taxonomy of Viruses' Coronavirus Study Group (16). Another betacoronavirus known as the Middle East respiratory sickness (MERS) virus appears to be more distantly related (17,18). The COVID-19 virus shares the most RNA sequence similarities with two bat coronaviruses, making bats the primary source, however, it is unknown whether the virus is transmitted directly from bats or by another route (such as through an intermediary host) (19).

The host receptor for SARS-CoV-2 cell entry is the same as for SARS-CoV, the angiotensin-converting enzyme 2 (ACE2) (1). Through the receptor-binding domain of its spike protein, SARS-CoV-2 associates with ACE2 (Figure 2). For SARS-CoV-2 cell entrance, the cellular serine protease, transmembrane serine protease at the S2′ site (TMPRSS2) also seems to be crucial (20).



a The schematic structure of the S protein. **b** The S protein binds to the receptor ACE2. **c** The binding and virus–cell fusion process mediated by the S protein. **d** The life cycle of SARS-CoV-2 in host cells.

Figure 2. Schematic of the SARS-CoV-2 S protein. (21)

- **Virus variants of concern**

SARS-CoV-2 changes over time, just like other viruses. Most of SARS-CoV-2 genomic mutations have no effect on viral function. Due to their rapid emergence within populations and evidence for transmission or clinical implications, these are therefore regarded as variants of concern. The WHO has also assigned labels for noteworthy variants based on the Greek alphabet. Each variant has some designations based on the nomenclature used by various evolutionary classification schemes (Table 1) (22).

The Pango lineage system is hierarchical—like a family tree. Lineages are evolutionarily descendants of a "parent" lineage. A lineage may be described as a "sublineage" when it is being discussed in relation to its parent lineage. Lineages are named using an alphabetical prefix (such as B or BA) and numerical suffix (such as ".1" or ".1.1.5"). When a new lineage is defined, the Pango system assigns an additional number to the name of its parent lineage (e.g., BA.2.75 is a sublineage of BA.2). As the virus continues to change, the Pango lineage names can become very long. Lineages with longer names may be given alphabetic aliases and numbering continues (e.g., "BA" stands for "B.1.1.529," thus BA.2 is the same as B.1.1.529.2) (22,23).

The U.S. Department of Health and Human Services established a SARS-CoV-2 Interagency Group (SIG). The SIG regularly meets to assess SARS-CoV-2 variations present in the US and to offer suggestions about variant classification. A team of experts evaluates the national and regional variation proportion data that is currently available. Additionally, they evaluate how these changes can impact disease transmission and severity, therapies, diagnostics, and vaccinations. Variants may be reclassified as more information becomes available. The SIG uses four types of classifications: Variant of interest, variant of concern, variant of high consequence and variants being monitored (22).

Early in the pandemic, a D614G alteration (glycine for aspartic acid) was discovered in a study that tracked amino acid changes in the spike protein of SARS-CoV-2 that was included in a sizable sequence database (24). When compared to viruses with the D614 polymorphism, those with the G614 polymorphism exhibit larger quantities of infectious virus in the respiratory tract, improved binding to ACE-2, and better replication and transmissibility in animal and in vitro tests (25,26). The G614 mutation does not seem to affect anti-spike antibody binding (27) or to be linked to an increased risk of hospitalization (24). It is now present in most circulating SARS-CoV-2 lineages, including the variants of concern listed below.

Omicron (B.1.1.529) and its sublineages. First discovered in Botswana, the Omicron variant was then quickly discovered in South Africa in November 2021. (Table 1). It was quickly discovered in numerous other countries where it was also connected with sharp increases in

reported illnesses. In South Africa, it was linked to an increase in local infections, and it was also linked to an increase in regional infections (28–30). Subsequently, Omicron sublineages with increasingly greater replication advantages emerged, replacing the previous predominant sublineage. The original Omicron variant was sublineage BA.1. Sublineage BA.2 became the prevalent variant worldwide, although in some countries it has been supplanted by BA.2.12.1, BA.4, and BA.5; the latter two are increasing in many other locations and are expected to become the dominant variants. Except for BA.4 and BA.5, which have identical spike proteins, each sublineage differs from the others by the number of spike protein mutations (31).

Some Omicron sublineages have an advantage over the Delta variation in terms of replication and evade infection- and vaccine-induced humoral immunity to a higher extent. Additionally, compared to other variants, they seem to be linked to less severe disease.

- Replication advantage. Local increases in SARS-CoV-2 infections have been linked to the establishment of each dominant Omicron sublineage (BA.1, BA.2, BA.4, and BA.5), suggesting that these sublines have a replication advantage over the prior prevailing variant or sublineage. Based on an analysis of the shifting predominance of Omicron sublineages in that nation, it was estimated that BA.4 and BA.5 had a replication advantage over BA.2 that was equal to the advantage that BA.2 had over BA.1 when they were initially discovered in South Africa (31). According to an investigation from the United Kingdom, where both sublineages have been rising in prevalence, BA.5 has a bigger estimated replication advantage than BA.4 (32). In comparison to Delta, Omicron (particularly the BA.1 sublineage) has also been linked to a higher rate of secondary attacks (in one study, 25 versus 19 percent) (33). There is a dearth of information on secondary attack rates for other Omicron sublineages. The immunological escape by Omicron sublineages may be connected in part to the replication advantage. Uncertainty exists on whether Omicron sublineages are inherently more transmissible than the variants that precede them.

- Immune evasion. Omicron variants are linked to an increased risk of reinfection in people who have already been exposed to another strain and may evade humoral protection. The ratio of reinfection (repeat positive test at least 90 days after an earlier positive test) to primary infection was higher at the start of the case surge associated with the Omicron BA.1 variant compared to the surges associated with the Beta and Delta variants (0.25 versus 0.12 and 0.09) in a study evaluating national surveillance data from South Africa (34). Similar results were obtained from a case-control study conducted in Qatar, wherein a history of past infection was linked to a 56 percent reduced probability of infection with Omicron BA.1 but an 85 to 90 percent lower risk of infection with the Alpha, Delta, or Beta variants (35). Findings from numerous

laboratories that demonstrate that sera from people with prior infection or prior vaccination did not neutralize Omicron as well as other variants also support these observations. In some cases, neutralizing activity against Omicron was undetectable in convalescent as well as post-vaccination sera (36–38). Similar to Omicron BA.1, sublineages BA.2.12.1, BA.4, and BA.5 are not as well recognized by antibodies elicited by BA.1 or BA.2 infection or vaccination (39–41). As a result, people who have already contracted an infection during the Omicron era are likely susceptible to reinfection with other Omicron sublineages. It is covered elsewhere how Omicron affects vaccine-induced immunity.

- Severity of disease. According to observational data, Omicron infections are less likely to cause serious illness or death than earlier forms (42–49) [36–43]. In a study from a South African hospital at the epicenter of the initial Omicron surge, the rates of hospital deaths (1 versus 4.5 percent), rates of intensive care unit admission (4 versus 21 percent), and length of stay (4 versus 8.8 days) were lower among the 466 COVID-19 patients hospitalized during the Omicron BA.1 surge compared with the 3976 patients hospitalized with COVID-19 during earlier surges; Additionally, the average age was lower (39 vs. 50 years) during the Omicron BA.1 boom (46). When age, sex, vaccination history, and prior infections were taken into account, an analysis from England indicated that the risk of hospital admission or mortality with Omicron was almost one-third that with Delta [40]. Although there is a lack of information on Omicron sublineages BA.4 and BA.5, preliminary data suggests that the risk of severe disease is similar to that of earlier Omicron sublineages (32,50,51).

However, even though the individual risk for developing a severe illness with Omicron is lower than it was with earlier variants, the high number of associated cases can still lead to a cumulative excess of COVID-19-related hospitalizations and fatalities when compared to other variants (52,53).

The decreased risk for serious illness may be due to the partial immunity provided by an earlier infection or immunization. However, animal studies that reveal milder clinical symptoms (such as reduced weight loss) and lower viral levels in lung tissue with Omicron compared to other variations provide additional evidence that Omicron infection may be inherently less severe (54,55).

Alpha (B.1.1.7 lineage). Before the advent of the Delta version (**Table 1**), this variant was originally discovered in the United Kingdom in late 2020 and subsequently become the dominant variant worldwide (56). In comparison to previously circulating strains, Alpha was

roughly 50–75% more transmissible (56–58). However, not all studies (58) found an association between the Alpha variation and more severe illness.

Beta (B.1.351 lineage) In South Africa in late 2020, this variety, also known as 20H/501Y.V2, was found and predominated (Table 1) (59). Despite being subsequently discovered in several nations, including the United States, it failed to establish itself as the dominant form worldwide. Immune evasion was the main issue with Beta variants: post-vaccination and convalescent plasma were less effective at neutralizing viral constructions with Beta spike protein than those with wild-type spike protein (60–63).

Gamma (P.1 lineage). This variant, also known as 20J/501Y.V3, was first identified in Japan in December 2020 and was prevalent in Brazil (Table 1). Despite being subsequently discovered in several nations, including the United States, it failed to establish itself as a globally dominant variant. Several mutations in the variant raised concern about increased transmissibility and an impact on immunity (64).

Delta (B.1.617.2 lineage). This lineage was discovered for the first time in India in December 2020 and has since been the most prevalent variant worldwide until emergence of the Omicron variant (Table 1). The Delta variant was more contagious than the Alpha variant (65), and it was linked to a higher risk of serious illness and hospitalization (66–68). Numerous studies suggest that vaccine effectiveness is slightly attenuated against symptomatic infection with Delta but remains high against severe disease and hospitalization.

Table 1. SARS-CoV-2 Variants of Concern (69–72)

WHO Label	Pango Lineage	Current Status	Date of Designation
Alpha	B.1.1.7 and Q lineages	VBM	VOC: December 29, 2020 VBM: September 21, 2021
Beta	B.1.351 and descendent lineages	VBM	VOC: December 29, 2020 VBM: September 21, 2021
Gamma	P.1 and descendent lineages	VBM	VOC: December 29, 2020 VBM: September 21, 2021
Delta	B.1.617.2 and descendant lineages	VBM	VOC: June 15, 2021 VBM: April 14, 2022
Epsilon	B.1.427 and B.1.429	VBM	VOC: March 19, 2021 VOI: February 26, 2021 VOI: June 29, 2021 VBM: September 21, 202
Eta	B.1.525	VBM	VOI: February 26, 2021 VBM: September 21, 2021

Iota	B.1.526	VBM	VOI: February 26, 2021 VBM: September 21, 2021
Kappa	B.1.617.1	VBM	VOI: May 7, 2021 VBM: September 21, 2021
N/A	B.1.617.3	VBM	VOI: May 7, 2021 VBM: September 21, 2021
Omicron	B.1.1.529 and descendant lineages	VOC	VOC: November 26, 2021
Zeta	P.2	VBM	VOI: February 26, 2021 VBM: September 21, 2021
Mu	B.1.621, B.1.621.1	VBM	VBM: September 21, 2021
VOI: Variant of interest; VOC: Variant of concern; VBM: Variants being monitored			

1.5.2 COVID-19: Epidemiology

- **Distribution by region and number of cases**

Since the beginning of 2019, cases have been documented on every continent, starting in the Chinese city of Wuhan in Hubei Province. Over 500 million COVID-19 verified cases have been recorded worldwide.

The reported case counts underestimate the overall burden of COVID-19, as only a portion of acute infections are diagnosed and reported. After adjusting for possible false positives or negatives, seropositivity results from seroprevalence surveys in the United States and Europe have suggested that the rate of prior exposure to SARS-CoV-2, as indicated by seropositivity, exceeds the incidence of reported cases by at least ten times (73–75). One study estimated that by November 2021, more than 3 billion people, or 44% of the world's population, would have contracted SARS-CoV-2 at least once (76). This study used multiple data sources, including databases on case counts, COVID-19-related deaths, and seroprevalence. Approximately one-third of the total cases were estimated to have occurred in South Asia (including India).

1.5.3 Transmission

- **Route of person-to-person transmission**

The main method of transmission for SARS-CoV-2 is direct person-to-person respiratory contact (77). Virus released in the respiratory secretions when an infected person coughs, sneezes, or talks can infect another person if it is inhaled or comes into contact with the mucous membranes. It is believed to spread primarily through close contact (i.e., within six feet or two

meters) via respiratory particles. Although contaminated surfaces are not thought to be a major route of transmission, the infection may also occur if an individual touches their eyes, nose, or mouth after having their hands contaminated by these secretions or after touching contaminated surfaces.

The extent to which this form of transmission has contributed to the pandemic is unknown (78–80). SARS-CoV-2 can also be transferred over longer distances by airborne route (through inhalation of particles that remain in the air over time and distance). The possibility of longer distance airborne transmission in enclosed, inadequately ventilated settings has been highlighted by sporadic reports of SARS-CoV-2 outbreaks (such as in a restaurant or on a bus) (81–83). The viability of airborne transmission has also been supported by experimental research (84,85). Although attempts to find viable virus in air and surface specimens in healthcare settings have only sporadically been successful (86–90), other studies have found viral RNA in ventilation systems and in air samples of hospital rooms of COVID-19 patients, including patients with mild infection (91–95). However, the SARS-overall CoV-2's transmission and secondary attack rates imply that long-distance airborne transmission is not the main method of transmission (80). Additionally, despite the lack of airborne precautions in a few reports of healthcare workers exposed to patients with undiagnosed infections while using only contact and droplet precautions, no secondary infections were found (96,97).

SARS-CoV-2 has been found in non-respiratory specimens like stool, blood, ocular secretions, and semen (98–103), but the role of these sites in transmission is uncertain. The possibility of virus aerosolization from sewage drainage has been raised by sporadic reports of clusters in a residential building and in a crowded urban area with poor sanitation (104). However, transmission via the fecal-oral route did not seem to be a significant factor in the spread of infection, according to a joint WHO-China report(105).

Some studies that tested for SARS-CoV-2 have also reported finding it in blood (106–109) Although respiratory viruses typically do not spread through the bloodborne route, transfusion-transmitted infection has not been reported for SARS-CoV-2 or for the associated Middle East respiratory syndrome coronavirus (MERS-CoV) or SARS-CoV. Additionally, there is no evidence that SARS-CoV-2 can spread through contact with non-mucous membrane sites.

- **Virus shedding and infectious period**

The risk of SARS-CoV-2 transmission increases before the onset of symptoms and is highest in the early stages of the illness; it then gradually decreases. After 10 days of illness, there is a low likelihood of transmission, especially in otherwise immunocompetent patients with mild infection.

- The first 7 to 10 days after infection, when viral RNA levels in upper respiratory specimens are at their maximum and the infectious virus is most likely to be detectable, they are when infected people are most likely to spread the disease (110–117). Data analysing the length of transmission risk corroborates this. One modelling study, in which 77 transmission pairs in China experienced a mean serial delay between the onset of symptoms of 5.8 days, predicted that infectiousness peaked two days before and one day after symptom start and reduced within seven days (115). In a different study that evaluated over 2500 close contacts of 100 COVID-19 patients in Taiwan, all 22 secondary cases had their first exposure to the index case within six days of the onset of symptoms; no infections were noted in the 850 contacts whose exposure occurred after this time frame (118). The majority of these statistics were collected in the initial year of the pandemic. The peak of viral RNA and the highest chance of infectious virus shedding may occur slightly later, around three to six days following the onset of symptoms, according to later studies on the Omicron variety. However, the median time infectious Omicron virus was found in nasal specimens after diagnosis was three to five days, and infectious virus was infrequently found more than 10 days after the onset of symptoms, indicating that transmission beyond this point with Omicron is still unlikely (119,120).
- The duration of viral RNA shedding is variable and may increase with age and the severity of the illness (107,117,121–127). According to this statement, extended viral RNA detection does not suggest prolonged infectiousness. A study of 28 studies found that the median time it took to find viral RNA in respiratory specimens after symptoms started to appear was 18 days (128). In some people, viral RNA was found in the respiratory system months after the original infection. There appears to be a viral RNA threshold below which infectiousness is unlikely, so the presence of detectable viral RNA does not necessarily indicate the presence of an infectious virus. For instance, when the viral RNA level was less than 106 copies/mL, infectious virus could not be found in respiratory specimens in a study of nine individuals with mild COVID-19 (117). Rarely have patients with non-severe infections who have recovered from their symptoms, had infectious viruses isolated from upper respiratory specimens more than 10 days after the illness began (117,129–133).

- **Risk of transmission depends on exposure type**

The risk of transmission from an individual with SARS-CoV-2 infection varies by the type and duration of exposure, use of preventive measures, and possibly individual factors (such as the amount of virus in respiratory secretions) all affect the risk of transmission from a person infected with SARS-CoV-2 (134). Numerous people do not spread SARS-CoV-2 to others, and

epidemiologic data indicate that the majority of secondary infections are caused by a small number of index cases (135–137).

The risk of transmission following contact with a person who has COVID-19 rises with proximity and time spent together, peaking during extended indoor contact. Therefore, the following contexts have been described for the majority of secondary infections:

- Among household contacts (138–141). The overall secondary household attack rate was 18.9% (95% CI 16.2-22) in a systematic review of 87 studies published through June 2021 that included more than 1.2 million household contacts of people with SARS-CoV-2 infection in 30 countries, despite the fact that there was significant heterogeneity among the studies (141). However, when more transmissible varieties emerged throughout time, the attack rate increased. The secondary household attack rate during circulation of various variants was 36 percent (95% CI 33-39) for the Alpha variant in a later systematic review of 58 studies published from June 2021 to March 2022, 29.7 percent (95% CI 23-37) for Delta, and 43 percent (95% CI 35-50) for Omicron. The index case's or household contacts' vaccination status during Omicron prevalence was not linked to a statistically significant difference in the secondary attack rate (142). Other factors, such as isolation from other family members, that might affect household transmission rates, however, were not taken into account. The highest rates of secondary infection occur in relationships between spouses or close friends within households (138). However, kids and teenagers can also act as index cases for secondary infections in the home (143–145).
- When personal protective equipment wasn't worn in healthcare facilities (including hospitals (146) and long-term care facilities (147)).
- In other collective contexts where people are living or working in close proximity to one another (eg, homeless shelters, detention facilities, college dormitories, and food processing facilities (148–151)).

Although household and congregate settings have the highest rates of transmission, frequently reported clusters of cases following social or professional gatherings also point to the danger of transmission through close, non-household social contact (152,153). Going to bars, restaurants, and other places where people congregate to drink or eat has also been linked to an increased risk of infection (154). This is probably because it is challenging to wear a mask and maintain distance in these places.

The main causes of the pandemic are believed to be superspreading episodes, in which vast clusters of infections can be linked to a single index case (134,137,155). They have primarily been described after extended group exposure in a cramped, usually indoor setting.

The varied risk of transmission from different people may be attributed to the variable viral loads in respiratory secretions. Only 32% of index patients were found to have transmission in an observational study that included 753 of their close contacts and 282 COVID-19 patients who had undergone respiratory tract viral RNA quantification as part of a trial (156). Higher respiratory tract RNA levels (taken at a median of four days after symptom onset) were independently associated with higher secondary attack rates.

Traveling with someone who has COVID-19 is likewise a high-risk exposure because it typically involves close contact for a long time (157–160). During a 10-hour flight, one study found that a business class cabin with the index case had a 62 percent attack rate; nearly all of the infected people (11 of 12) had been seated within six feet (two meters) of the index case (160). An analysis from China looked at the risk among passengers exposed to people within three rows who were later found to have COVID-19 (161). The study found 2334 primary cases and 234 secondary cases, for an overall attack rate 0.32 percent. The risk of secondary infection was higher (3.5%) for those seated next to the index patient and higher in the same row than for those in front or behind them. As the distance travelled increased, so did the risk.

Although data are scarce, it appears that the risk of transmission is significantly lower outside than indoors (162). Nevertheless, close contact with an individual with COVID-19 remains a risk outdoors.

It is unknown and probably very low if there is a chance of transmission from more indirect contact (such as passing an infected person on the street or handling objects that have previously been handled by an infected person). However, a large number of COVID-19 patients do not claim to have had a very close interaction with COVID-19 in the weeks before diagnosis (163).

- **Asymptomatic or presymptomatic transmission**

It has been well proven that SARS-CoV-2 can spread from people who are infected but have no symptoms, including those who subsequently develop symptoms and are therefore labelled presymptomatic (164–169) . A study of a SARS-CoV-2 outbreak in a long-term care facility provides evidence for the biological foundation for this; infectious virus was grown from upper respiratory tract specimens from presymptomatic and asymptomatic patients as early as six days before the onset of characteristic symptoms (170). Asymptomatic patients' upper respiratory tract viral RNA levels and persistence are comparable to those of symptomatic patients (171).

Asymptomatic people tend to pose a lower transmission risk than those who are symptomatic (139,172–174). A study of 628 COVID-19 cases and 3790 close contacts conducted in Singapore found, for instance, that the probability of secondary infection was 3.85 times higher among contacts of symptomatic individuals than among contacts of asymptomatic individuals (175).

Nevertheless, asymptomatic or presymptomatic individuals are less likely to isolate themselves from other people, and the extent to which transmission from such individuals contributes to the pandemic is uncertain. A study estimated that 59 percent of transmission could be attributed to individuals without symptoms: 35 percent from presymptomatic individuals and 24 percent from those who remained asymptomatic (176).

- **Environmental contamination**

Virus present on contaminated surfaces may be another source of infection if susceptible individuals touch these surfaces and then transfer infectious virus to mucous membranes in the mouth, eyes, or nose. Although contaminated surfaces are not a major source of transmission, the frequency and relative importance of this type of transmission are uncertain. In environments with high viral contamination (such as in an infected individual's household or in health care settings), it may be more likely to be a source of infection.

Environmental surfaces in hospital rooms and patients' homes that have COVID-19 have been extensively contaminated with SARS-CoV-2 RNA, according to reports (92,177,178). In a study from Singapore, before routine cleaning, viral RNA was found on almost all surfaces tested (handles, light switches, bed and handrails, interior doors and windows, toilet bowl, sink basin) in the airborne infection isolation room of a patient with mild COVID-19 symptoms. Following routine cleaning, no viral RNA was found on comparable surfaces in the rooms of two other symptomatic patients. It should be noted that the presence of viral RNA does not always imply the presence of an infectious virus (117) .

SARS-surface CoV-2's persistence is unknown (179–181), however, other coronaviruses have been investigated and have been shown to be able to live on inanimate surfaces for up to six to nine days without disinfection. A specimen containing SARS-CoV (a virus closely similar to SARS-CoV-2) demonstrated detectable infectivity at six days, but not at nine days, in a study testing the survivability of viruses dried on a plastic surface at ambient temperature (179). However, a number of coronaviruses connected to SARS-CoV-2 were rendered inactive in less than a minute by a variety of disinfectants, including ethanol at concentrations between 62 and 71 percent (181). In experimental settings, it has also been demonstrated that simulated sunlight inactivates SARS-CoV-2 during 15 to 20 minutes, with higher levels of ultraviolet-B light

associated with more rapid inactivation (182). According to information on other coronaviruses, the ambient temperature, relative humidity, and initial inoculum size are likely to have an impact on how long a virus remains on a surface (183).

- **Risk of animal contact**

SARS-CoV-2 infection is thought to have originally been transmitted to humans from an animal host, but the ongoing risk of transmission through animal contact is uncertain. There is no proof that domesticated animals or other animals are a major source of infection in humans.

Infection with SARS-CoV-2 has been documented in both natural and laboratory settings in animals. Rare cases of animals getting infected with SARS-CoV-2 after having close contact with a person who had COVID-19 include asymptomatic infections in dogs and symptomatic infections in cats (184,185). Additionally, domestic cats that have been experimentally infected but are asymptomatic may pass on SARS-CoV-2 to other cats in their cage (186). Species differences in infection risk may exist.

1.5.4 Immune responses after infection

After infection, protective SARS-CoV-2-specific antibodies and cell-mediated reactions are induced. According to the evidence, some of these reactions can be seen for at least a year after infection.

- **Humoral immunity**

After SARS-CoV-2 infection, the majority of patients develop detectable serum antibodies to the receptor-binding domain of the viral spike protein and associated neutralizing activity (117,187). However, the severity of the immune response may be correlated with the severity of the disease, and patients with mild infection may not develop detectable neutralising antibodies (188). Even though studies have shown that neutralising activity can be detected for up to 12 months, when neutralising antibodies are produced, they typically decline several months after infection (189–193). In one study of 121 convalescent plasma, donors with initial spike-binding titers $\geq$1:80, titers declined slightly over five months but remained $\geq$1:80 in the vast majority, and neutralizing titers correlated with the binding titers (194). Additionally, spike- and receptor-binding domain memory B cells as well as spike protein-specific plasma cells have been discovered in other studies, and these results raise the possibility of a long-term memory humoral response (192,193,195,196).

The ability to neutralise an infection has been linked to protection from recurrent infections (197). A lower risk of SARS-CoV-2 reinfection is also linked to detectable binding antibodies, which often correlate with neutralising activity (198–201).

- **Cell-mediated immunity**

Studies have also found SARS-CoV-2-specific CD4 and CD8 T cell responses in persons who had received COVID-19 vaccination as well as in patients who had recovered from COVID-19, which suggests the possibility of a long-lasting T cell immune response (193,195,202,203).

- **Uncertain impact of immunity to other coronaviruses**

If prior infection with common cold coronaviruses (ccCoVs) has any protective effect against SARS-CoV-2 infection, it is most likely minimal. Numerous investigations have looked at cellular and/or humoral immune responses that are cross-reactive to ccCoVs and SARS-CoV-2 in an effort to ascertain whether these reactions have an impact on the clinical incidence or severity of COVID-19. The results are inconsistent and challenging to understand. During COVID-19, immunity from prior ccCoVs infections has been shown in some studies to have a positive effect (204,205), while in others it has had no effect (206) or even a negative effect (207).

- **Risk of reinfection**

The risk of reinfection in the immediate aftermath of the initial infection was low prior to the emergence of the Omicron variant. Infection risk in the six to nine months after a prior infection was reduced by at least 80% to 85% (208–211). The risk of reinfection over that time period was calculated by several other studies to be less than 1% (212–216). Although it is uncertain, the risk of reinfection with specific Omicron sublineages following prior infection with a different Omicron sublineage is likely higher than earlier reinfection estimates given evidence of immune evasion (217).

An observational study from Denmark looked at the likelihood that someone who had undergone polymerase chain reaction (PCR) testing during the first COVID-19 surge (February to June 2020) would test positive during the second COVID-19 surge (September to December 2020) in an effort to assess the risk of reinfection (208). The estimated "protective effect" of prior infection was estimated to be around 80%. Of the 11,068 people who had a positive PCR test during the first surge, 72 tested positive during the second surge (0.65 percent), compared with 16,819 of 514,271 people (3.27 percent) who had tested negative during the first surge. In both surges, a higher rate of testing positive was related to age over 65.

These findings support recent observational studies' findings that those with detectable anti-SARS-CoV-2 antibodies have a decreased rate of PCR positivity for the virus (218–220). Lower anti-spike IgG titers and lower rates of detectable neutralising activity have been linked to reinfection in those who were seropositive at baseline (199) .

According to several research, reinfections are less severe than original infections. For instance, in a study from Qatar, there were no incidences of critical illness or fatalities among the 1304 individuals with reinfection group, and the odds of severe disease were 0.12 compared to individuals with an initial infection who were age-, sex-, and infection date-matched (221). (Compared with 28 and 7, respectively, in the initial infection group). However, both deadly and reinfections that were more severe than the first infection have been documented (222,223). Simply having a positive SARS-CoV-2 viral test after recovery does not rule out reinfection; however, sequencing that reveals a different strain at the time of presumed reinfection is required to distinguish it from persistent or irregular viral RNA shedding after an initial infection.

1.5.5 SARS-CoV-2 pathogenesis

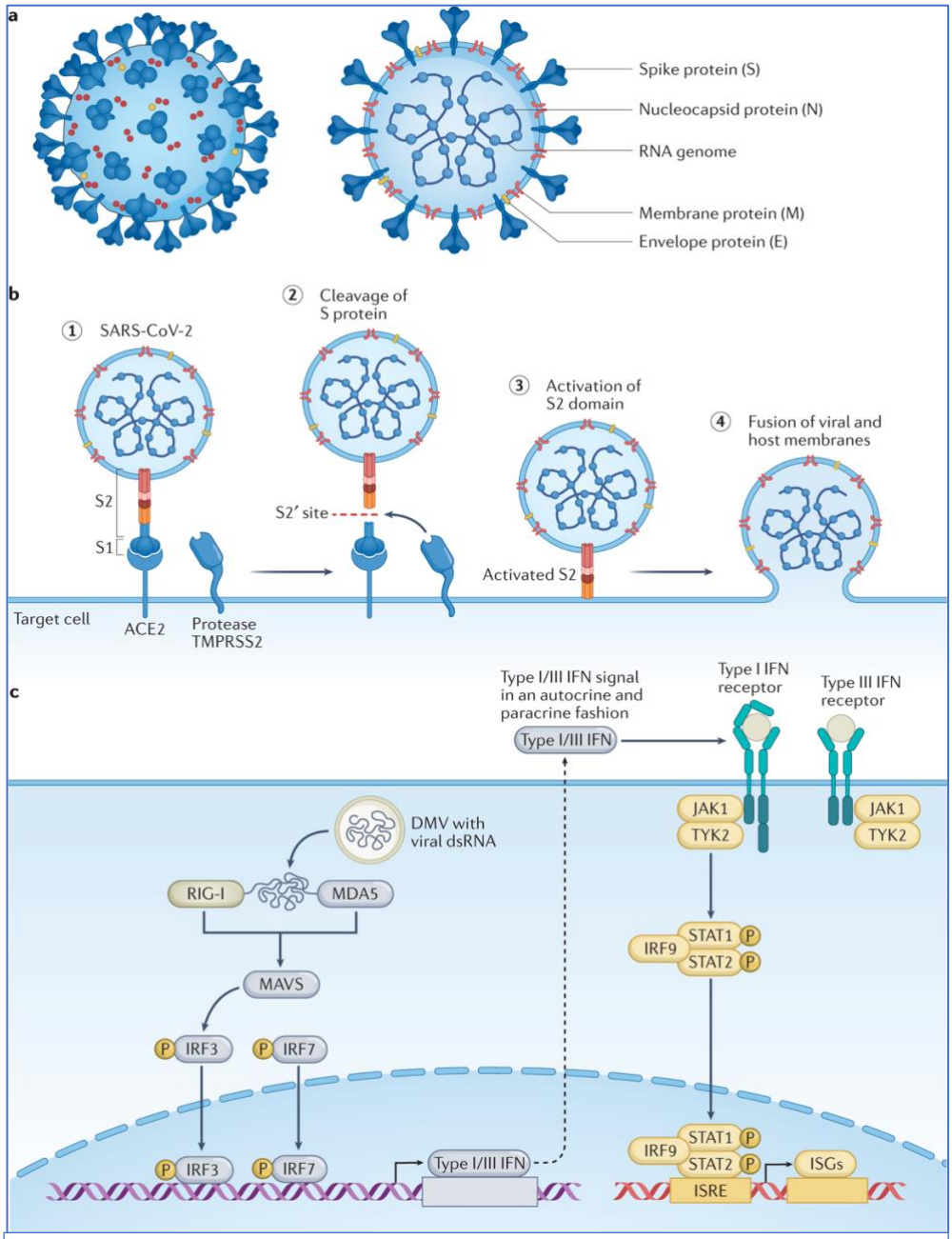
Coronaviruses (family Coronaviridae) are common pathogens of humans and animals. Four coronaviruses are endemic in humans (human coronavirus NL63 (HCoV-NL63), HCoV-229E, HCoV-OC43 and HCoV-HKU1) and typically infect the upper respiratory tract, causing common-cold symptoms. In the past two decades, three zoonotic coronaviruses (severe acute respiratory syndrome coronavirus (SARS-CoV), MERS-CoV and SARS-CoV-2 have infected humans, after spilling over from animal reservoirs (224–227). SARS-CoV originated in China and caused an epidemic in 2003, whereas MERS-CoV is currently causing intermittent outbreaks in the Middle East. SARS-CoV-2, was first detected in Wuhan, China, in late 2019 in a cluster of patients with pneumonia, it quickly spread, resulting in an epidemic throughout China, followed by a pandemic. In February 2020, the WHO designated the disease COVID-19, which stands for coronavirus disease 2019 (18). These three viruses can replicate in the lower respiratory tract and may cause potentially fatal ARDS. Both SARS-CoV and MERS-CoV are zoonotic pathogens that crossed the species barriers to infect humans. The via of viral interspecies transmission is a crucial scientific question to be addressed.

SARS-CoV-2, shares 79% sequence analogy with SARS-CoV, belongs to the genus Sarbecovirus (228). This virus encodes a set of structural proteins (membrane protein, nucleocapsid protein, envelope protein and spike glycoprotein), non-structural proteins (most of them compose the viral replication and transcription complex) and accessory proteins. The structural proteins — together with a lipid bilayer derived from the host — form an enveloped

virion (or virus particle) that delivers viral genomic RNA into the cell (Figure 3a). These spike proteins give the virus a crown-like appearance under an electron microscope, coining the name "coronavirus." The principal function of these proteins is host receptor binding, determining host tropism and transmission capacity (229).The accessory proteins are disposable for replication, however often have immunoevasive activities (230–232).

The main important of coronavirus tropism is the spike glycoprotein, which forms trimers on the surface of virions (233) . The spike protein consists of two subunits: the S1 subunit, which binds to the host entry receptor ACE2 (1) , and the S2 subunit, which mediates membrane fusion (Figure 3b). These two subunits are separated by the S1–S2 site, which contains a furin cleavage motif and is cleaved in the virus-producing cell. After binding to ACE2 on the target cell, the spike protein is cleaved by the TMPRSS2 (234–236). This cleavage activates the S2 subunit trimers to fuse viral and host lipid bilayers, releasing the viral ribonucleoprotein complex into the cell. Another entry route that may be used by the virus is the endosome, in which cathepsins can cleave the spike protein, but this route is not efficiently used in primary epithelial cells (235,237–239). Other co-receptors (for example, neuropilin 1) and proteases (for example, cathepsin L, TMPRSS11D and TMPRSS13) have been also proposed to be involved in SARS-CoV-2 entry (240–242), however their contribution to SARS-CoV-2 pathogenesis remains unclear (235).

The first cells targeted by SARS-CoV-2 during natural infection in humans are likely to be multiciliated cells in the nasopharynx or trachea, or sustentacular cells in the nasal olfactory mucosa (243–245). After entry, the positive-sense SARS-CoV-2 genome directly begins the production of viral proteins, including the replicase proteins that form replication factories from endoplasmic reticulum membranes (246,247). These replication factories contain double-membrane vesicles in which transcription occurs, shielding the double-stranded RNA (dsRNA) transcription intermediates from detection by cytoplasmic pattern recognition receptors (PRRs) (Figure 3c). The main cytoplasmic PRR able of detecting SARS-CoV-2 is considered MDA5 (248,249), which recognizes long dsRNAs and initiates a signaling cascade to promote the transcription of type I and type III interferons. Interferons and chemokines are also produced by bystander epithelial cells and local immune cells (neutrophils and macrophages) in response to the detection of SARS-CoV-2 using endosomal Toll-like receptors (TLRs) or paracrine effects of locally produced interferons (250–252). Interferons signals in an autocrine and paracrine fashion to induce an antiviral cellular state through the production of interferon-stimulated genes, which may have direct or indirect (attraction of immune cells) antiviral functions.



a | The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virion consists of the following structural proteins: spike protein (S), nucleocapsid protein (N), membrane protein (M) and envelope protein (E). b | The S protein attaches to the receptor angiotensin-converting enzyme 2 (ACE2) on the host cell using the S1 domain (stage 1). This allows TMPRSS2 to cleave the S protein (stage 2), leading to activation of the S2 domain for fusion (stage 3). Activated S2 fuses viral and host lipid bilayers, leading to deposition of the viral positive-sense, single-stranded RNA genome into the host cell (stage 4). c | Viral replication creates double-stranded RNA (dsRNA) replication intermediates that can activate cytoplasmic innate immune sensing pathways through activation of MDA5 or RIG-I, initiating a signalling cascade though MAVS that eventually leads to the production of type I and type III interferons (IFNs). These interferons act in a paracrine and autocrine fashion via the plasma membrane receptors and a JAK–STAT1/2 signalling cascade and lead to the production of interferon-stimulated genes (ISGs) that have direct and indirect antiviral functions. DMV, double-membrane vesicle; ISRE, interferon-sensitive response element.

Figure 3. Molecular and cellular pathogenesis of SARS-CoV-2 (253)

The cytokine production also stimulates the development of adaptive B cell and T cell responses that help clear the virus. If the virus is not cleared by innate or adaptive responses, it can spread to the lower respiratory tract by inhalation of virus particles from the upper respiratory tract or by gradual dissemination along the tracheobronchial tree. Alternatively, the initial site of infection can be the lower respiratory tract. This may lead to the infection of the alveoli, causing inflammation and affecting gas exchange. In the alveoli, SARS-CoV-2 has been shown to mainly infect alveolar type 2 (AT2) cells both in vivo and in vitro (244,254–258). Whereas alveolar type 1 (AT1) cells cover most of the alveolar surface and mediate gas exchange, AT2 cells secrete pulmonary surfactants necessary for lubricating the lung, which reduces surface tension in the alveoli during respiration. Additionally, AT2 cells are the progenitor cells of AT1 cells in the adult human lung (259).

The COVID-19 pandemic continues to cause an immense global health crisis, with more than 3.5 million deaths. The overall case fatality rate of COVID-19 is estimated around 1%, and around 3–20% of people with COVID-19 require hospitalization, of which a considerable number (~10–30%) require intensive care, conditioning a great strain on health systems (260–264).

1.5.6 COVID-19 clinical findings

SARS-CoV-2 is transmitted through respiratory aerosols and droplets, and the median incubation period is 4–5 days before symptom onset (265–267). Although in some cases the infection is asymptomatic, the novel disease, termed COVID-19, is marked by symptoms reminiscent of other respiratory infections: dry cough, fever, myalgia, or fatigue are commonly observed, whereas sputum production, headache, hemoptysis, and diarrhea are less prevalent (268,269). While the majority of patients with COVID-19 have a favorable outcome (270,271), some develop severe pneumonia eventually leading to ARDS along with other organ manifestations (272).

Severe illness usually begins approximately seven days after symptom onset. The most frequent symptom of severe disease is dyspnoea, as a result of hypoxaemia (273,274). Soon after the onset of dyspnoea and hypoxaemia, progressive respiratory failure develops in patients with severe COVID-19. These patients may presents ARDS, which is characterized as severe hypoxaemia and bilateral radiographic opacities (275–277). ARDS is a form of lung injury that is characterized by inflammation, pulmonary vascular leakage, and consequently a loss of aerated lung tissue. Patients with COVID-19 with hypoxic respiratory failure have evidence of systemic hyperinflammation, including the release of pro-inflammatory cytokines, such as interleukin-1 (IL-1), IL-6, IL-8 and TNF, and elevated levels of inflammatory markers as D-dimer, ferritin and C-reactive protein (CRP) (278,279). Severe COVID-19 may also lead to

extrapulmonary disease, including gastrointestinal symptoms and acute cardiac, kidney and liver injury, rhabdomyolysis, coagulopathy and shock (280). Although SARS-CoV-2 RNA has been detected in several organs at low levels (281–284), it is largely unknown to what extent these manifestations are the result of direct infection. There is also evidence of the shedding of viral RNA in faeces and productive infection of gut enterocytes, which express higher levels of ACE2 than respiratory cells (285). In addition, sustentacular cells are a main target of SARS-CoV-2 in the nasal olfactory mucosa, which may be the cause of anosmia (245,286). Although increasing evidence suggests that severe COVID-19 is an inflammatory disease affecting many organs, the primary cause of COVID-19 is pulmonary viral replication.

COVID-19 appears to have at least two distinct disease phases: a phase characterized by the immune response against the virus with the objective of eliminating the pathogen. Some patients, even though they may have had only mild initial symptoms, subsequently develop a phase of severe "cytokine storm" (cytokine release syndrome, CRS) instead of the expected phase of re-convalescence leading to fatal autoinflammation of the lung and other organs (287). There are distinctive features of this disease, increased age, obesity, and male sex are well-established risk factors for the development of severe COVID-19 (269,288–291). Common co-morbidities include hypertension, heart failure, arrhythmia, diabetes, kidney failure, and chronic pulmonary disease (263). In addition, there are genetic predispositions to developing severe COVID-19, which can be highly informative in understanding SARS-CoV-2 pathophysiology. Genome-wide association studies have linked loci containing variants at DPP9 and FOXP4, which have been linked to pulmonary fibrosis (292–294) , as well as variants at the chemokine receptor genes CXCR6 and CCR9 (for which CCR1 and CCR2 are flanking genes) to severe COVID-19 (292,293,295). In addition, the genetic predisposition for severe COVID-19 concerns genes involved in TLR3-dependent and TLR7-dependent type I interferon induction and amplification (296,297) and in type I interferon detection (293). These findings support an important role for interferon signaling in combatting SARS-CoV-2. This is evidenced by studies that have found that neutralizing autoantibodies to interferon-α (IFNα) are associated with severe COVID-19 (298,299). These antibodies are present in ~4% of uninfected individuals older than 70 years and have been estimated to contribute to ~20% of COVID-19-related deaths (300).

The overall case-fatality rate (CFR) was 2.3%, which is lower than that during the earlier coronavirus outbreaks with SARS- CoV (9%) and MERS-CoV (36%) (301). Whereas the comorbidities and risk factors for worse outcomes of COVID-19 are comparable throughout international reports, mortality rates diverge largely from 0.06% in Singapore up to 18.3% in France. The causes for this discrepancy are multiple and may include disease factors and genetic susceptibility of the population, virus variants, but also differences in health care organization

(e.g., number of tests conducted, criteria for testing) and deceased outcome reporting due to or with COVID-19.

1.5.7 Risk of infections in patients with RMD

Patients with RMD are generally considered more susceptible to bacterial and certain viral infections such as the herpes zoster virus. The susceptibility to infections is multifactorial and is related to disease aspects such as disease activity, disease damage, comorbidities, and treatment. An analysis of the US CORONA registry, which included 16,242 patients with RA, shows that 0.6 point increment of the disease activity score (DAS), led to a 25% increase in hospital admissions and a 4% increase of outpatient infections rate ($p = 0.01$) (302). These data highlight the importance of maintaining strict disease control in patients with RMD to reduce infectious complications (303).

In the same aspect, a two -to four-fold increased risk of hospitalized infections was reported in patients with inflammatory polyarthritis ($n = 2108$) compared with that in the healthy population in a UK-based prospective cohort study. This higher risk was according to the degree of disease activity (304).

In a multicentric matched cohort study, composed of 456 rheumatic and non-rheumatic patients, with a mean age was 63 years and male sex 41% in both cohorts. Rheumatic diseases were chronic inflammatory arthritis (CIA) (60%) and connective tissue disease (CTD) (40%), concluded that in hospitalized patients with chronic inflammatory rheumatic diseases, having a CTD but not IA nor previous immunosuppressive therapies was associated with severe COVID-19 (305).

In SLE, a 6-fold increased susceptibility to infections was seen in an insurance database (306) and an incidence rate of 29.2 severe infections/1,000 patients per year was observed in the Spanish SLE-registry (307). Current and past use of hydroxychloroquine seemed to have a protective effect, whereas glucocorticoids (≥10 mg/d), rituximab, mycophenolate mofetil/mycophenolic acid, and lupus activity/severity were linked to a higher risk of severe infection.

Moreover, the comorbidities that often complicate the RMD course also increase the risk of infections (308). Diabetes mellitus, cardiovascular diseases, lung disease (Interstitial lung disease (ILD), chronic obstructive pulmonary disease (COPD)), and kidney failure are the comorbidities most frequently associated with an increased risk of infections in RA (309,310).

1.5.8 Infection susceptibility through immunosuppressive treatment in patients with RMD

According to a Cochrane review, the risk of infection in patients with CIA; including RA, psoriatic arthritis (PsA), and spondylarthritis (SpA)] is higher under therapy with TNF-blockers than with conventional disease modifying anti- rheumatic drugs (cDMARDs) only (311). A meta-analysis of other biological DMARDs (bDMARDs) used in RA indicated a 1.3-fold increased risk of serious infections in standard doses (312). Whereas, the risk of serious infections under anti-IL-17 therapy is comparable to that of TNF-blockers; anti- IL-12/23 therapy seems to carry a lower risk (313).

Due to their inhibition of interferon-alpha, Januskinase inhibitors (JAKi) increase the risk of viral infections, especially of herpes zoster (314). In contrast, the overall risk for severe infections of RA patients with JAKi is comparable to that of healthy controls according to a recent meta-análisis (315).

The use of glucocorticoids in both CIA (36) and CTD leads (306) to an increased rate of infection overall and viral infections in particular, especially for herpes zoster correlating with the actual GC dose, treatment duration, and the cumulative GC dose; however even doses considered relatively safe such as 5mg prednisone equivalent have been associated with an increased infections risk.

Among conventional synthetic DMARDs (csDMARDs), methotrexate has not been associated with an increased infection rate according to a study with over 27,000 RA patients (316). In contrast, mycophenolate mofetil, azathioprine, and cyclophosphamide were linked to a higher risk of infection, particularly in patients with CTD (317).

CHAPTER 2

2 Hypothesis And Objectives

Hereafter, the hypothesis, main objectives, research questions, main contributions, and their respective publications arising from this thesis are presented.

2.1 Hypothesis

As COVID-19 pandemic continued to spread rapidly during the first peak, many unresolved questions of how the SARS-CoV-2 would impact on patients with RMD needed to be clarified. The hypothesis established for this doctoral thesis was that those patients with RMD due to a direct result of rheumatic disease, or an indirect effect of treatment, could be a more vulnerable group of patients, with an increased risk of SARS- CoV-2 infection, severe COVID-19 outcomes and mortality.

2.2 Main objective

The main objective is to obtain information from real clinical practice about the clinical course of patients with RMD in the context of SARS-CoV-2 in a rheumatology outpatient clinic of a tertiary hospital of Madrid.

2.3 Specific objectives

The specific objectives, research questions, main contributions, and publications arising from this thesis are:

The specific objectives, research questions, main contributions, and publications arising from this thesis are:

Specific objective 1

- To recruit and describe the sociodemographic, clinical, and treatment characteristics of a longitudinal cohort of patients with RMD under follow-up in the rheumatology outpatient clinic who presented SARS-CoV-2 infection during the two months of the first pandemic peak.

- **Research Question 1:**

  Which are the main sociodemographic and clinical characteristics of patients with RMD who have presented SARS-CoV-2 infection in the rheumatology outpatient clinic?

- **Contribution 1:**

  Identification of a set of sociodemographic, clinical, and treatment characteristics in patients with RMD who presented SARS-CoV-2 infection. A descriptive analysis was performed, and development of illustrative tables with representative articles, with updated data in different publications according to the real-life conditions during the first months of the COVID-19 pandemic.

- **Publications 1:**

- Freites Nuñez DD, Leon L, Mucientes A, Rodriguez-Rodriguez L, Font Urgelles J, Madrid García A, Colomer JI, Jover JA, Fernandez-Gutierrez B, Abasolo L. Risk factors for hospital admissions related to COVID-19 in patients with autoimmune inflammatory rheumatic diseases. In: Annals of The Rheumatic Diseases, 2020 Nov; 79(11): 1393-1399. doi: 10.1136/annrheumdis-2020-217984. Epub 2020 Aug 7. PMID: 32769150; PMCID: PMC7415073. url: https://doi.org/10.1136/annrheumdis-2020-217984.
- Fernandez-Gutierrez B, Leon L, Madrid A, Rodriguez-Rodriguez L, Freites D, Font J, Mucientes A, Culebras E, Colome JI, Jover JA, Abasolo L. Hospital admissions in inflammatory rheumatic diseases during the peak of COVID-19 pandemic: incidence and role of disease-modifying agents. In: Therapeutic advances in musculoskeletal disease. 2021 Feb 4; 13: 1759720X20962692. doi: 10.1177/1759720X20962692. PMID: 33613703; PMCID: PMC7869066. url: https://doi.org/10.1177/1759720X20962692
- Nuñez DF, Leon L, Garcia AM, Arce JIC, Mucientes A, Gutierrez-Fernandez B, Rodriguez L, Cristóbal IPS, Álvarez P, Prada CM, Abasolo L. Mortality related to COVID-19 in patients with rheumatic and musculoskeletal diseases, first wave of the outbreak: a single-center study. In: Therapeutic advances in musculoskeletal disease. 2022 Apr 29; 14: 1759720X221090296. doi: 10.1177/1759720X221090296. PMID: 35510167; PMCID: PMC9058342. url: https://doi.org/10.1177/1759720X221090296

Specific objective 2	• To report the incidence rate of hospital admission related to COVID-19 in patients with RMD. To analyze the risk of hospital admission and to explore the potential risk factors associated with hospital admission related to COVID-19. To describe clinical and laboratory findings and treatment used in RMD patients hospitalized with COVID-19.

- **Research Question 2:**

- Which is the incidence rate of hospital admission related to COVID-19 in patients with RMD?
- Is there is a risk for hospital admission in patients with RMD in the context of COVID-19 and which are the potential risk factors associated?
- Is there is influence of the RMD treatment on hospital admission related to COVID-19?
- Which is the role of different RMD and hospital admission related to COVID-19?
- Which are the clinical symptoms, laboratory reports and treatment used in RMD patients hospitalized with COVID-19.

- **Contribution 2:**

COVID-19 hospital admission incidence rate was calculated. Identification of a group of demographic, clinical, and treatment predictors associated with risk for hospital admission in patients with RMD with COVID-19 using inferential statistics techniques, with special interest in the evaluation of the potential impact of various RMD and the immunomodulatory therapy that they may require. Identification of a set of clinical, laboratory and treatment features in RMD patients hospitalized with COVID-19.

- **Publications 2:**

- Freites Nuñez DD, Leon L, Mucientes A, Rodriguez-Rodriguez L, Font Urgelles J, Madrid García A, Colomer JI, Jover JA, Fernandez-Gutierrez B, Abasolo L. Risk factors for hospital admissions related to COVID-19 in patients with autoimmune inflammatory rheumatic diseases. In: Annals of The Rheumatic Diseases, 2020 Nov; 79(11): 1393-1399. doi: 10.1136/annrheumdis-2020-217984. Epub 2020 Aug 7. PMID: 32769150; PMCID: PMC7415073. url: https://doi.org/10.1136/annrheumdis-2020-217984.
- Fernandez-Gutierrez B, Leon L, Madrid A, Rodriguez-Rodriguez L, Freites D, Font J, Mucientes A, Culebras E, Colome JI, Jover JA, Abasolo L. Hospital admissions in inflammatory rheumatic diseases during the peak of COVID-19 pandemic: incidence and role of disease-modifying agents. In: Therapeutic advances in musculoskeletal disease. 2021 Feb 4; 13: 1759720X20962692. doi: 10.1177/1759720X20962692. PMID: 33613703; PMCID: PMC7869066. url: https://doi.org/10.1177/1759720X20962692.

Specific objective 3

- To report the COVID-19 specific mortality rate in patients with differents RMD, during the three months of the first pandemic peak and to analyze the role of specific types of ARD and other possible factors including month of COVID-19 diagnosis, in the risk of death related to COVID-19.

- **Research Question 3:**

- Which is the COVID-19 specific mortality rate in patients with RMD and which are the potential risk factors associated with mortality related to COVID-19?
- Is there is influence of the RMD treatment on mortality related to COVID-19?
- Which is the role of different RMD and death related to COVID-19?

- **Contribution 3:**

Case fatality rate was calculated. Identification of different clinical, demographic, and treatment predictors associated with a mortality risk in patients with RMD in the context of COVID-19 using inferential statistics techniques. The role that the different RMD, their specific immunomodulatory treatments, and period time (diagnosis month) have been analyzed.

- **Publications 3:**

- Nuñez DF, Leon L, Garcia AM, Arce JIC, Mucientes A, Gutierrez-Fernandez B, Rodriguez L, Cristóbal IPS, Álvarez P, Prada CM, Abasolo L. Mortality related to COVID-19 in patients with rheumatic and musculoskeletal diseases, first wave of the outbreak: a single-center study. In: Therapeutic advances in musculoskeletal disease. 2022 Apr 29;14:1759720X221090296. doi: 10.1177/1759720X221090296. PMID: 35510167; PMCID: PMC9058342. url: https://doi.org/10.1177/1759720X221090296

CHAPTER 3

3 Material and Methods

This chapter introduces the data sources and the methodology followed to extract, process, and acquire knowledge from the data. It also lays the foundation for answering the different research questions. The methodology of each of the publications is specified in the text of the corresponding article. In these sections, the common methodological characteristics of the research are presented.

3.1 Study Design

We performed a retrospective observational study during the first wave of the COVID-19 pandemic in Madrid, Spain. The inclusion period ranges from March 1st (when our health area had the first hospital admission related to COVID-19) to May 20th, 2020. The follow-up period comprised from their inclusion until the loss of follow-up of the patient, death or the end of the study (May 20th).

3.2 Setting

The study was conducted at the Rheumatology Department of the Hospital Clínico San Carlos (HCSC) in Madrid. The HCSC is a public reference tertiary hospital of the National Health System of Madrid, Spain, that covers an area of approximately 400,000 people and the Rheumatology Department provides care to this entire population. Patients are referred to the rheumatologist by primary care physicians and other medical specialists if required. The clinical activity is carried out fundamentally in the outpatient consultation, located at the hospital and in any of the two affiliated specialty centers (S.C. Avenida de Portugal and S.C. Modesto la Fuente).

3.3 Subjects

To assure all RMD potential patients, the study population comprised all patients being attended (first or follow-up visit) at the rheumatology outpatient clinic of HCSC from 1 March 2019 until 1 March 2020. We included these patients during the study period whose clinical data and management were recorded in our departmental electronic health record (EHR Penelope).

3.3.1 Inclusion criteria

In the present study, we selected patients with the following criteria: patients older than 16 years old with a medical diagnosis of RMD including ARD and non-ARD (according to ICD9 and ICD10)) and diagnosed with COVID-19 according to a medical diagnosis and/or confirmed with a positive SARS-CoV-2 CRP diagnostic test. Patients had to have made at least two visits to the Rheumatology Department during the inclusion period. All patients were included since the date of COVID-19 diagnosis until death or end of the study (May 20th).

3.3.2 Exclusion criteria

Only patients with impossibility to access their clinical information were excluded.

3.3.3 Ethical considerations

- **Ethics approval**

The study protocol was approved by the HCSC institutional ethics committee (approval number 20/268-E-BS). This study was conducted according to the principles of the Declaration of Helsinki and the principles of Good Clinical Practice.

- **Confidentiality**

The sociodemographic, clinical, and treatment data was obtained during the routing clinical practice and collected from the databases of the Rheumatology, and the Hospital Information System (HIS) of the HCSC. The data was treated confidentially at all times. The people who carry out the data analysis did not have access to the identifying data of the participants. All researchers of the project were responsible for not disseminating identifying data. In accordance with compliance with Law 15/1999 on the Protection of Personal Data and in order to guarantee the confidentiality of the data, the name and surname of the patient did not appear in the database, and instead it was assigned a patient code.

- **Informed consent**

According to the fact that this study involves a scientific interest, that a risk to the health of the participants is not expected, that the absolute confidentiality of the patients is guaranteed, and that obtaining informed consent document requires the adoption of disproportionate

measures, it has been considered that the absence of informed consent from the study participants can be justified.

3.3.4 Data sources

Sociodemographic, clinical, disability, laboratory information, and data treatment for RMD was obtained from our departmental EHR Penelope, which is used in all outpatient interactions between health professionals and patients. In each patient visit, information was collected both as free text (including clinical notes and comorbidities or medications prescribed by other physicians) and codified (including rheumatology diagnoses (using the ICD9/ICD10), prescribed drugs (using the Spanish Drug and Medical Device Agency codification system), disability (using the Rosser Classification Index: RCI (318)), and the patient´s follow-up plan.

Patients with RMD and COVID-19 were detected by different ways a) phone contact: warning calls to 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. The information was provided from March 1st to May 20th, 2020.

An exhaustive review of the clinical histories of admitted patients to identify COVID-19 cases and rule out patients admitted for other reasons was carried out. Once the COVID-19 cases were identified, clinical, laboratory, and treatment data during admission was collected until the end of admission (either discharge or death) in order to describe the progress of the disease.

- **Penelope departmental EHR**

The data sources described in this section store the data in raw format, which is to say, as they were introduced in the EHR, and consequently in the database by the physician at the time of consultation and without performing any cleaning or transformation operations.

The 2019 implementation of Penelope, a new EHR solution, expanded the patient's medical history with new data while incorporating previous EHR data. By integrating data from various sources, facilitating scalability, offering new functionalities, and creating a user-friendly environment, it was created to overcome the limitations of MediLog, the first departmental EHR used in the rheumatology department until the end of 2018. Penelope accelerated the codification of data in clinical practise.

- **Diagnoses**

A diagnosis code must be codified by a physician at each medical consultation. Diagnoses were codified using both ICD ninth (ICD-9) and tenth versions (ICD-10). There were reasons for using and maintaining different ICD versions in the same EHR system.

The first reason was due to legal requirements, the second was due to the fact that when completing the patient diagnosis information in the consultation, the physician chooses the ICD code description—not the actual code—from a list of potential diagnoses when filling out the patient's diagnosis details in the consultation. Therefore, if the description of an ICD-9 code is more suitable than any other description in later versions, the physician will select it and the disease will be codified with ICD-9. The ICD-9 and ICD-10 year versions were not provided. The level of codification used is up to two decimal points for ICD-9 and one decimal point for ICD-10. As a strategy, the coded diagnoses were grouped into two main categories, (a) ARD and b) non-ARD, as described below are the main variables of our investigation.

3.3.5 Variables

- **Main variables**

The main outcome in this study was:

- Hospital admission related to COVID-19 in patients with RMD.
- Mortality related to COVID-19 in patients with RMD.

The independent variable was:

- Type of RMD: (a) Autoimmune Rheumatic Diseases (ARD) and b) Non-Autoimmune Rheumatic Diseases (non-ARD).

  ARD included: (a1) chronic inflammatory arthritis (CIA) (RA, undifferentiated inflammatory polyarthritis, PsA, axial SpA or other SpA and uveitis); and (a2) CTD (polymyalgia rheumatica, mixed connective tissue disease (MCTD), SSc, SS, vasculitis, Raynaud phenomenon, PM, polychondritis, Behçet's disease, antiphospholipid syndrome, and SLE).

  Non-ARD included: (b1) Musculoskeletal mechanical diseases (back pain, neck pain, sciatica, peripheral neuropathy, disorders of muscles including

fibromyalgia, osteoarthritis, osteoporosis and other soft tissue disorders including internal knee pain); (b2) Inflammatory conditions (microcrystalline arthritis (gout and chondrocalcinosis arthritis), disorders of synovium and tendon). A classification of the RMD can be seen in Figure 4.

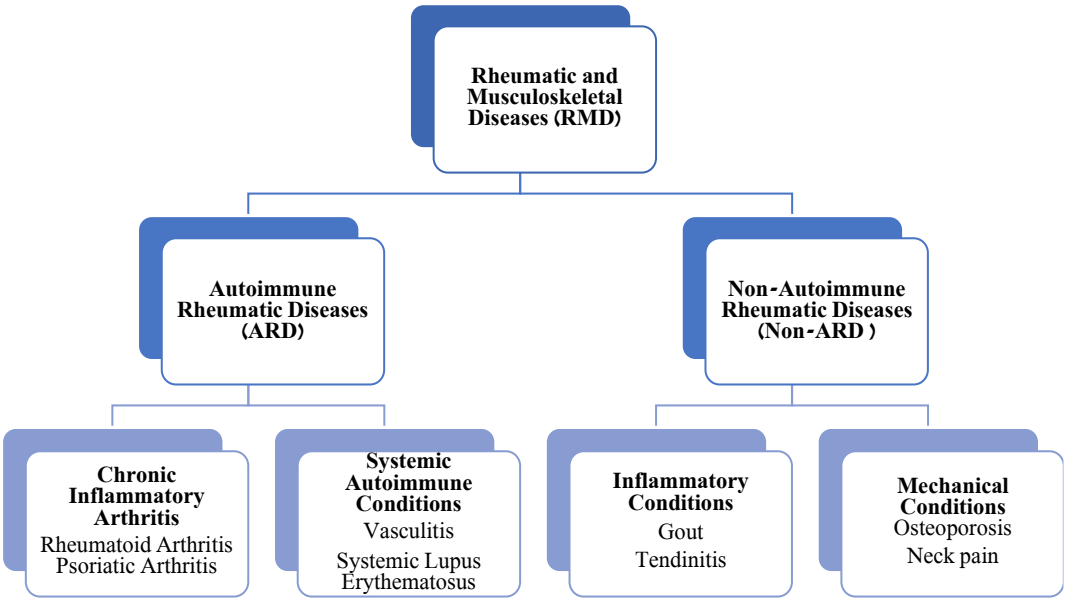


Figure 4. RMD classification with some examples per category

- Exposure to ts/bDMARDs including: Biologic DMARDs (bDMARDs): anti-tumour necrosis factor (TNF)-alpha drugs (infliximab, adalimumab, etanercept, certolizumab and golimumab); other biologics: anti-interleukin (IL)-6 (tocilizumab and sarilumab); rituximab; abatacept; belimumab; anti-IL-12/23 (ustekinumab); anti-IL-17 (ixekizumab and secukinumab) and Targeted synthetic DMARDs (tsDMARDs): Janus kinase (JAK) inhibitors (tofacitinib and baricitinib).

- **Co-variables**

The co-variables recorded at baseline were the following:

1) Sociodemographic characteristics including sex, age, and RMD duration.

2) Disability level (using a seven ordinal level scale from 1 as perfect health to 7 unable to get out of bed) from the RCI (318), Table S1. This Health-Related Quality of Life (HRQoL) measure, validated by the HCSC rheumatology service (319), comprises

two components, the level of disability and the level of distress, and is calculated in all consultations of patients in the outpatient clinic.

The disability level takes into account eight ordinal levels, from no disability to unconsciousness, and covers the daily life activities of individuals (such as mobility, self-care, and social relationships), **Table S2**.

The distress level differentiates between emotional and/or physical distress (pain) and has four distinct categories ranging from non-distress to a high level of distress, **Table S3**. Up to 29 RCI values arise when these two components are combined. The main advantage of RCI is its simplicity; in fact, a patient can be classified in less than 30 seconds, overcoming the time consumption drawback of other HRQoL measures and questionnaires.

3) Erythrocyte sedimentation rate (ESR) as a surrogate variable of disease activity (mean value, at least 3 months prior to COVID-19 infection).

4) Comorbid conditions: Including hypertension, dyslipidemia, depression, diabetes mellitus, smoking habit, chronic renal insufficiency, chronic liver disease, lung diseases (ILD and COPD), 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 history of cancer.

5) Stable treatments for RMD: all treatments were considered stable in terms of prescription and dose at least one month prior the diagnosis of COVID-19.

   a. Non-steroidal anti-inflammatory drugs (NSAIDs).
   b. Glucocorticoids (specifically it is being registered as the 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. bDMARDs including: (d1) anti-tumour necrosis factor (TNF)-alpha drugs (infliximab, adalimumab, etanercept, certolizumab and golimumab); (d2) other biologics: anti-interleukin (IL)-6 (tocilizumab and sarilumab); rituximab; abatacept; belimumab; anti-IL-12/23 (ustekinumab); anti-IL-17 (ixekizumab and secukinumab)

e. (tsDMARDs including (e1) Janus kinase (JAK) inhibitors (tofacitinib and baricitinib).

Co-variables at hospital admission:

1) Lag time from onset of symptoms to admission (days)

2) Clinical symptoms at admission: Presence of pneumonia, fever, cough.

3) Laboratory data at admission: Hemoglobin (g/dL), D-dimer (ng/mL), neutrophil count (×109/L), lymphocyte count (×109/L), CRP (mg/dL), LDH (U/L), platelet count (×109/L), creatinine (mg/dL), ferritin (ng/mL).

4) COVID-19-related treatments during admission: Azithromycin, other antibiotics, glucocorticoids, lopinavir/ritonavir, remdesivir, darunavir/cobicistat, tocilizumab; hydroxychloroquine.

5) Clinical complications during hospital admission: intensive care unit during hospital admission.

6) Length of stay (days)

Discharge reason: Improvement, home isolation, other care center (medicalized hotel/IFEMA hospital), death, end of study (no discharge).

3.3.6 Statistical analysis

- **Descriptive analysis**

a. A descriptive analysis of the sociodemographic, different characteristics of the study population and main outcomes were performed. Continuous variables were expressed as mean (and standard deviation (SD) or median values (and interquartile ranges (IQR)). Categorical variables were expressed as frequencies and percentages. Continuous variables were compared using a two-sample t-test and ANOVA for continuous normally distributed variables or Mann-Whitney U test for continuous non-normally distributed variables, the adjustment of the normality of the continuous variables was confirmed with the Kolmogorov-Smirnov test. Discrete variables were compared using Pearson's chi-squared test ($\chi 2$ test) or Fisher's Exact Test.

b. Case fatality rate estimation.

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.

c. Incidence rate of hospital admission and the mortality rate related to COVID-19.

The exposure time comprises the period from the COVID-19 diagnosis date in pa The exposure time comprises the period from the COVID-19 diagnosis date in patients with RMD to the occurrence of any of the following cut-off points: loss to follow-up, development of the main variable, or the end of the study. Survival techniques were applied to estimate the incidence rate (IR) of hospital admission related to COVID-19 and to estimate the cause-specific mortality rate related to COVID-19 (CMR), rates were expressed per 1,000 patients-month with a 95% confidence interval [CI]. Survival over time was evaluated using Kaplan-Meier curves.

- **Analysis of associated factors**

Regression analysis were conducted to determine the risk factors for hospital admission and death related to COVID-19. Univariable logistic regression analyses were performed to assess differences between main outcomes and covariates. Multivariable logistic regression models (adjusted for age, sex and comorbidity) were performed to examine the influence of independent variables in the main outcome regardless of other factors.

They were run in a stepwise manner to examine the possible effect of sociodemographic, clinical and therapeutic factors on hospital admissions and death related to COVID-19. The models also included all other variables with a p< 0.2 from the simple regression analysis. The models used were as follows:

a. Logistic regression models were run to examine associations of sociodemographic, clinical and therapeutic factors on hospital admissions related to COVID-19. The results were expressed as the OR with its respective 95% CI.

b. Cox regression analysis were conducted to examine the possible influence of sociodemographic, clinical and therapeutic factors in the development of hospital admissions and death regardless of other factors. The results were expressed as the HR with its respective 95% 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 <0.05 was considered to indicate statistical significance. Data was anonymized.

CHAPTER 4

4 Results

The COVID-19 outbreak had triggered a global health crisis, with serious negative effects produced worldwide. During this period, there have been a lot of studies on RMD combined with COVID-19. Over the past year, researchers have been actively working on the impact of COVID-19 on patients with RMD, and this topic is still on going with a constant update of evidence.

Since the confirmation of the first patient infected with SARS-CoV-2 in Spain in January 2020, Madrid was one of the cities most struggled by the COVID-19 outbreak. The purpose of this study is to review and summarize these experiences in a rheumatology outpatient clinic of a tertiary hospital (HCSC) during the first wave of the COVID-19 pandemic in Madrid, Spain.

The results are presented in article format together with a summary:

- **Article 1.**
  "Risk factors for hospital admissions related to COVID-19 in patients with autoimmune inflammatory rheumatic diseases." Annals of the rheumatic diseases, vol. 79,11 (2020): 1393-1399. For the original version of the published article, see **Supplementary Material Article 1.**

- **Article 2.**
  "Hospital admissions in inflammatory rheumatic diseases during the peak of COVID-19 pandemic: incidence and role of disease-modifying agents." Therapeutic advances in musculoskeletal disease, vol. 13 1759720X20962692. 4 Feb. 2021. For the original version of the published article, see **Supplementary Material Article 2.**

- **Article 3.**
  "Mortality related to COVID-19 in patients with rheumatic and musculoskeletal diseases, first wave of the outbreak: a single-center study." Therapeutic advances in musculoskeletal disease, vol. 14 1759720X221090296. 29 Apr. 2022. For the original version of the published article, see **Supplementary Material Article 3.**

The following **Table 2**, shows the Journal's performance of the main articles (manifested in this chapter) and the two correspondence responses (as supplementary material) published. The table reports the journal name, the Journal Impact Factor (JIF) (a journal-level metric calculated from data indexed in the Web of Science Core Collection), the rank by JIF in the rheumatology category, and citations in Scopus. The Journal Citation Reports dataset was obtained according to the year of publication. The Digital Object Identifier (DOI) and publication information of each of the articles is also included.

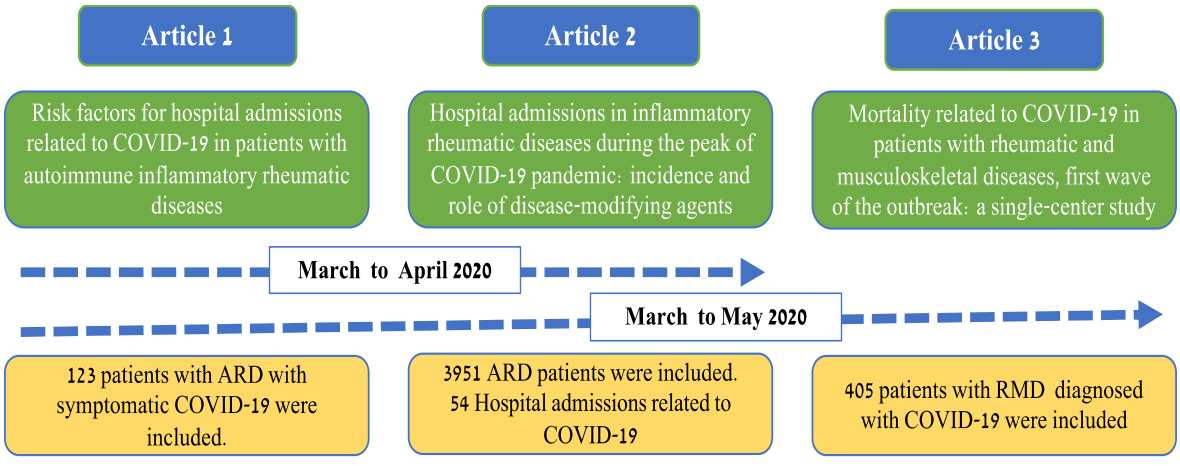
Table 2. Summary information of the articles included in the thesis

Article	Journal	JIF	Rank by JIF	Citations in Scopus	DOI	Publication history
Risk factors for hospital admissions related to COVID-19 in patients with autoimmune inflammatory rheumatic diseases	Annals of the Rheumatic Diseases (ARD)	19.103	2/34	112	10.1136/annrheumdis-2020-217984	Received May 14, 2020 Revised July 23, 2020 Accepted July 25, 2020 First published August 7, 2020. Online issue publication October 12, 2020
Hospital admissions in inflammatory rheumatic diseases during the peak of COVID-19 pandemic: incidence and role of disease-modifying agents	Therapeutic Advances in Musculoskeletal Disease	5.346	8/34	15	10.1177/1759720X20962692	Manuscript received: July 3, 2020 Manuscript accepted: September 1, 2020 Issue published: January-December 2021 Published online: February 4, 2021
Mortality related to COVID-19 in patients with rheumatic and musculoskeletal diseases, first wave of the outbreak: a single-center study	Therapeutic Advances in Musculoskeletal Disease	3.625	21/34	2	10.1177/1759720X221090296	Manuscript received: December 17, 2021 Issue published: January-December 2022 Manuscript accepted: March 10, 2022 Published online: April 29, 2022
Response to: 'Correspondence on 'Risk factors for hospital admissions related to COVID-19 in	Annals of the Rheumatic Diseases (ARD)	28.003	3/34	1	10.1136/annrheumdis-2020-219230	Received October 13, 2020 Accepted October 15, 2020 First published October 30, 2020. Online issue publication January 03, 2023

patients with autoimmune inflammatory rheumatic diseases'' by Schulze-Koops et al						
Response to: 'Correspondence on 'Risk factors for hospital admissions related to COVID-19 in patients with autoimmune inflammatory rheumatic diseases'' by Aydin et al	Annals of the Rheumatic Diseases (ARD)	28.003	3/34	0	10.1136/annrheumdis-2020-219580	Received December 9, 2020. Accepted December 10, 2020. First published December 18, 2020. Online issue publication February 10, 2023

JIF. Journal Impact Factor; JCR, Journal Citation Reports; DOI, Digital Object Identifier.

The following **Figure 5**, squamates the study period time and the patients included in the different articles published.



ARD, autoimmune rheumatic disease; COVID-19 Coronavirus Disease 2019; RMD, rheumatic musculoskeletal diseases.

Figure 5. Study period and patients of the articles included in the thesis

4.1 ARTICLE 1.

Risk Factors For Hospital Admissions Related To COVID-19 In Patients With Autoimmune Inflammatory Rheumatic Diseases

ABSTRACT

Objectives To describe patients with autoimmune inflammatory rheumatic diseases (AIRD) who had COVID-19 disease; to compare patients who required hospital admission with those who did not and assess risk factors for hospital admission related to COVID-19.

Methods An observational longitudinal study was conducted during the pandemic peak of severe acute respiratory syndrome coronavirus 2 (1 March 2020 to 24 April). All patients attended at the rheumatology outpatient clinic of a tertiary hospital in Madrid, Spain with a medical diagnosis of AIRD and with symptomatic COVID-19 were included. The main outcome was hospital admission related to COVID-19. The covariates were sociodemographic, clinical, and treatments. We ran a multivariable logistic regression model to assess risk factors for the hospital admission.

Results The study population included 123 patients with AIRD and COVID-19. Of these, 54 patients required hospital admission related to COVID-19. The mean age on admission was 69.7 (15.7) years, and the median time from onset of symptoms to hospital admission was 5 (3–10) days. The median length of stay was 9 (6–14) days. A total of 12 patients died (22%) during admission. Compared with outpatients, the factors independently associated with hospital admission were older age (OR: 1.08; p=0.00) and autoimmune systemic condition (vs chronic inflammatory arthritis) (OR: 3.55; p=0.01). No statistically significant findings for exposure to disease-modifying antirheumatic drugs were found in the final model.

Conclusion Our results suggest that age and having a systemic autoimmune condition increased the risk of hospital admission, whereas disease-modifying antirheumatic drugs were not associated with hospital admission.

Keywords: antirheumatic agents, communicable diseases, imported, epidemiology, outcome assessment, health care.

KEY MESSAGES

What is already known about this subject?

The epidemiological scenario is changing daily. There is little evidence for risk factors of poor outcome with COVID-19 specific to autoimmune inflammatory rheumatic diseases.

What does this study add?

Patients with an autoimmune systemic condition have a higher risk of hospital admission related to COVID-19 compared with those with chronic inflammatory arthritis.

Disease-modifying agents were not associated with a higher risk of hospital admission related to COVID-19.

How might this impact on clinical practice or future developments?

Our data show that, in a real-world setting, a high percentage of patients with autoimmune inflammatory rheumatic diseases and COVID-19 required hospital admission. The patients were mainly elderly, with comorbidities and a systemic autoimmune condition.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a myriad of clinical signs and symptoms, together with typical laboratory abnormalities, that manifest as the disease COVID-19.1

Since the confirmation of the first patient infected with SARS-CoV-2 in Spain in January 2020, the current COVID-19 outbreak has had a considerable impact, especially in the Madrid region, where the highest incidence of COVID-19 cases has been recorded, with more than 41 304 patients admitted to the hospital until the first week of May.2

The incidence and severity of COVID-19 disease seem to be higher in patients with risk factors, such as advanced age and associated comorbidities, mainly hypertension, diabetes, heart disease and previous respiratory diseases.3 It is not clear whether patients with rheumatic diseases are more susceptible to SARS-CoV-2 infection, or, when they are infected, whether they have more severe disease or a poorer outcome. Previous outbreaks caused by coronaviruses did not yield overwhelming evidence that patients with rheumatic diseases are at an increased risk,4 although some patients are candidates for a higher number of infections owing to their rheumatic disease (predominantly systemic) or the treatment they are receiving for rheumatic diseases.5 Preliminary experiences in patients with COVID-19 show that those with chronic arthritis treated with synthetic conventional or targeted synthetic/biologic disease-modifying antirheumatic drugs (DMARDs) do not seem to be at a greater risk of respiratory or life-threatening complications from SARS-CoV-2 than the general population.6 7

The epidemiological scenario is changing, and evidence on the risk factors of poor outcome with COVID-19 specific to inflammatory rheumatic disease is scarce. In addition, there are little data on how the hospital admissions of these patients with severe COVID-19 infection have evolved.8

The aim of our study was to describe patients with autoimmune inflammatory rheumatic diseases (AIRD) who had COVID-19 during the pandemic peak. We also explored possible risk

factors associated with hospital admission related to COVID-19 disease in patients with AIRD from a tertiary hospital in Madrid, Spain.

METHODS

Setting, study design and patients

The study was performed in a public tertiary hospital, Hospital Clínico San Carlos (HCSC), in Madrid, Spain. The catchment area is home to almost 400 000 people.

We performed a prospective observational study from 1 March 2020 (when our health area had the first hospital admission related to COVID-19) to 24 April 2020. We preselected all patients attended at the rheumatology outpatient clinic of our centre during the study period whose data were recorded in the electronic clinical history of our department (HCR Penelope). The inclusion criteria were age >16 years, a medical diagnosis (according to International Classification of Diseases (ICD-10)) of inflammatory rheumatic disease and symptomatic COVID-19 disease assessed by medical diagnosis or confirmed with a positive SARS-CoV-2 PCR diagnostic test.

Patient data were obtained during routine clinical practice. The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice and was approved by the HCSC Ethics Committee (approval number 20/268-E-BS).

Variables

The primary outcome was admission to hospital with a medical diagnosis of COVID-19 and/or a positive PCR result between 1 March and 15 April compared with outpatients with symptomatic COVID-19 disease.

The covariables recorded were as follows: (1) sociodemographic baseline characteristics including sex, age and rheumatic disease duration. (2) Type of AIRD, including systemic autoimmune conditions (polymyalgia rheumatica, mixed connective tissue disease, systemic sclerosis, Sjogren's syndrome, vasculitis, Raynaud phenomenon, polymyositis, polychondritis, sarcoidosis, antiphospholipid syndrome, autoinflammatory syndromes and systemic lupus erythematosus) and chronic inflammatory arthritis (rheumatoid arthritis, inflammatory polyarthritis, juvenile idiopathic arthritis, psoriatic arthritis, axial spondyloarthritis, uveitis and inflammatory bowel disease). (3) Baseline comorbid conditions, including hypertension, dyslipidaemia, depression, diabetes mellitus, smoking habit, kidney disease, chronic liver disease, respiratory diseases (chronic obstructive pulmonary disease and interstitial lung disease), thyroid disease, heart disease (valve disease, arrythmias, cardiomyopathy, heart failure and pericarditis), ischaemic vascular disease (stroke, cardiovascular and peripheral vascular disease), venous thrombosis/lung embolism and cancer. (4) Treatment for inflammatory rheumatic disease: (a) glucocorticoids, (b) non-steroidal anti-inflammatory drugs (NSAIDs), (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 (ts/bDMARDs) including: (1) antitumour necrosis factor (TNF)-alpha drugs (infliximab, adalimumab, etanercept, certolizumab and golimumab); (2) other biologics: anti-interleukin (IL)-6 (tocilizumab and sarilumab); rituximab; abatacept; belimumab; anti-IL-12/23 (ustekinumab); anti-IL-17 (ixekizumab and secukinumab); (3) Janus kinase (JAK) inhibitors (tofacitinib and baricitinib).

Treatment had to start at least 1 month before the beginning of the study and continue during the study period until the end of the study or hospital admission for antimalarial therapy, glucocorticoids, sulfasalazine, NSAIDs or colchicine. Regarding csDMARDs and ts/bDMARDs, treatment had to start at least 1 month before the beginning of the study and continue until at least 21st March, the end of the study or hospital admission. In the case of rituximab, the last infusion had to be at least in January.

Data sources

Patient sociodemographic, clinical, laboratory and data on treatment of rheumatic disease were obtained through HCR Penelope.

Patients with COVID-19 were detected by warning calls to our rheumatologists or nurses or via routine telephone consultation. Other infected patients were detected through their sick leave forms for COVID-19. The results of SARS-CoV-2 PCR diagnostic assays were obtained from the microbiology/infectious service of HCSC. In addition, our Hospital Central Services registered all medical admissions to HCSC. This information was provided from 1 March to 15 April.

The researchers carried out an exhaustive review of the clinical histories of admitted patients to identify COVID-19 cases and rule out patients admitted for other reasons. Once the COVID-19 cases were identified, we collected clinical, laboratory and treatment data during admission until the end of admission (either discharge or death) in order to describe the progress of the disease. The review was performed until 24th April in order to include follow-up data from patients admitted to the hospital with COVID-19.

Statistical analysis

Patient characteristics are expressed as mean and SD or median and IQR for continuous variables; categorical variables are expressed as percentages. Statistical tests were performed to compare characteristics between patients admitted with COVID-19 and those without hospital admissions. Continuous variables were analysed using the Mann-Whitney test or t-test, and discrete variables were analysed using the $\chi 2$ or Fisher exact test. Univariable logistic regression analyses were performed to assess differences between hospital admissions related to COVID-19 risk and covariates. Multivariable logistic regression models (adjusted for age,

sex and comorbidity) were run in a stepwise manner to examine the possible effect of sociodemographic, clinical and therapeutic factors on hospital admissions related to COVID-19 The model also included csDMARDs and all other variables with a p<0.2 from the simple regression analysis. The results were expressed as the OR with its respective 95% CI.

All analyses were performed in Stata V.13 statistical software (Stata Corp). A two-tailed p value <0.05 was considered to indicate statistical significance.

RESULTS

A total of 123 patients with AIRD with symptomatic COVID-19 disease were included in the study (Table 3). The tests were performed as an exploratory measure of the association between a variable and the outcome.

Table 3. Baseline demographic and clinical characteristics of patients with AIRD and with COVID-19 (admitted vs no admitted at the hospital)

Variable	AIRD-COVID-19 patients (N=123)	AIRD–COVID non-admitted patients (N=69)	AIRD–COVID admitted patients (N=54)	P value
Women, n (%)	86 (69.92)	54 (78.26)	32 (59.26)	0.02
Age (years), mean (SD)	59.88 (14.90)	52.91 (9.58)	68.78 (15.79)	0.0001
Time since diagnosis (years), mean (SD)	10.65 (8.31)	10.37 (7.99)	11 (8.77)	0.8
PCR test, n (%)				0
Positive	58(47)	17(25)	41(76)	
Negative	3 (2)	0	3 (5)	
Not performed	62(51)	52(75)	10 (19)	
Smoking habit (active vs none)	4 (3.25)	1 (1.45)	3 (5.56)	0.31
Diagnosis (AIRD), n (%)				0.01
Rheumatoid arthritis	50 (40.65)	32 (46.38)	18 (33.33)	
Axial spondyloarthritis	18 (14.63)	11 (15.94)	7 (12.96)	
Polymyalgia rheumatica	6 (4.88)	0	6 (11.11)	
Psoriatic arthritis	6 (4.88)	3 (4.35)	3 (5.56)	
Systemic lupus	8 (6.50)	6 (8.70)	2 (3.70)	
erythematosus	6 (4.88)	2 (2.90)	4 (7.41)	
Mixed connective tissue	9 (7.32)	5 (7.25)	4 (7.41)	
disease	2 (1.63)	0	2 (3.70)	

Sjogren's syndrome	1 (0.81)	1 (1.45)	0	
Vasculitis	1 (0.81)	0	1 (1.85)	
Uveitis	8 (6.50)	6 (8.70)	2 (3.20)	
Systemic sclerosis	1 (0.81)	0	1 (1.85)	
Inflammatory	1 (0.81)	0	1 (1.85)	
polyarthritis	3 (2.44)	0	3 (5.56)	
Polychondritis	3 (2.44)	3 (4.35)	0	
Polymyositis				
Raynaud phenomenon				
Other*				
Comorbidities, n (%)				
Arterial Hypertension	40 (32.52)	14 (20.29)	26 (48.15)	0.002
Dyslipidemia	27 (21.95)	12 (17.35)	15 (27.38)	0.19
Depression	9 (7.32)	8 (11.59)	1 (1.85)	0.039
Diabetes mellitus	17 (13.82)	4 (5.80)	13 (24.07)	0.007
Heart disease	15 (12.20)	5 (7.25)	10 (18.52)	0.09
Vascular disease	8 (6.50)	2 (2.90)	6 (11.11)	0.13
Liver disease	7 (5.69)	3 (4.35)	4 (7.41)	0.69
Kidney disease	6 (4.88)	0	6 (11.11)	0.006
Lung disease (ILD/COPD)	19 (15.45)	6 (8.70)	13 (24.07)	0.02
Cancer	5 (4.07)	1 (1.45)	4 (7.41)	0.16
Venous thrombosis/lung embolism	3 (2.44)	0	3 (5.56)	0.08
Thyroid disease	17 (13.8)	12 (17.39)	5 (9.26)	0.29
NSAIDs, n (%)	30 (24.39)	22 (31.88)	8 (14.81)	0.03
Glucocorticoids, n (%)	61 (49.59)	29 (42.03)	32 (59.26)	0.07
csDMARDs, n (%)				
Methotrexate–leflunomide-azathioprine	68 (55.28)	40 (57.97)	28 (51.85)	0.49
Sulfasalazine	9 (7.32)	5 (7.25)	4 (7.41)	0.97
Antimalarials	27 (21.95)	18 (26.09)	9 (16.67)	0.21
b/tsDMARDs, n (%)	26 (21.14)	19 (27.54)	7 (12.96)	0.04
Anti-TNF-alpha agent	17 (13.82)	15 (21.74)	2 (3.70)	0.004
Other biologics	9 (7.32)	4 (5.80)	5 (9.26)	0.4
Abatacept	1 (0.81)	1 (1.45)	0	0.99
Tocilizumab	2 (1.63)	1 (1.45)	1 (1.85)	0.99
Belimumab	1 (0.81)	1 (1.45)	0	0
Rituximab	5 (4.07)	1 (1.45)	4 (7.41)	0.16
JAKi, n (%)	1 (0.89)	0	1 (2)	0.43

AIRD, autoimmune inflammatory rheumatic disease; Anti-TNF, tumor necrosis factor-alpha inhibitor; COPD, chronic obstructive pulmonary disease; csDMARD, conventional synthetic disease-modifying antirheumatic drug; ILD, interstitial lung disease; JAKi, JAK inhibitor; b/tsDMARDs, biologic/target synthetic disease-modifying antirheumatic drug.

*Others: inflammatory bowel disease, antiphospholipid syndrome, juvenile idiopathic arthritis, autoinflammatory syndromes and sarcoidosis.

† Heart disease: arrhythmias,valve disease, cardiomyopathy and heart failure. Ischaemic vascular disease: stroke, cardiovascular and peripheral vascular disease.

Most of the patients were women, with a mean age of 59.88 (14.9) years and a mean time since diagnosis of 10.65 (8.31) years. The main diagnosis was rheumatoid arthritis (40.65%), followed by axial spondyloarthritis (14.63%). Many patients had at least one baseline comorbid condition, the most prevalent being hypertension, dyslipidaemia and lung disease. Most patients were taking csDMARDs (71.54%). Half of the patients were taking glucocorticoids (49.59%), a quarter were taking NSAIDs (24.39%) and 21.14% were taking ts/bDMARDs, of which adalimumab was the most frequently prescribed (6.50%), followed by rituximab (4.07%). Only one patient was taking a JAK inhibitor. Interestingly, 14.63% of the patients taking ts/bDMARDs were taking the drug in combination with a csDMARD.

A total of 54 patients had to be admitted to the hospital because of COVID-19. Of these, 51 were evaluated in the HCSC Emergency Department (49 were admitted to HCSC and 2 were transferred to the Institucion Ferial de Madrid (IFEMA) support hospital owing to the lack of capacity in our hospital at that time). The remaining three patients were evaluated and admitted to other hospitals in the Autonomous Community of Madrid. **Table 4** presents data for the 51 patients admitted to HCSC.

Of the patients admitted to our hospital, 59.2% were women, with a mean age at admission of 69.7 (15.7) years and median lag time from the onset of symptoms to the admission of 5 (3–10) days. The median length of stay was 9 (6–14) days (**Table 4**).

Table 4. Hospital admissions related to COVID-19 among patients with AIRD

Variable	Value
Admissions, n	54
Lag time from onset of symptoms to admission (days), median (IQR)	5 (3–10)
Pneumonia at admission, n (%)	47 (87)
Systemic autoimmune conditions, n (%)	24 (44.4)
Laboratory data at admission, median (IQR)	
Haemoglobin (g/dL)	12.9 (12.4–13.8)
D-dimer (ng/mL)	727 (487–1091)
Neutrophil count (×109/L)	4500 (3500–5700)

Lymphocyte count (×109/L)	700 (500–1200)
CRP (mg/dL)	9.19 (2.9–14.6)
LDH (U/L)	618 (489–919)
Platelet count (×109/L)	199000 (158000–267000)
Creatinine (mg/dL)	0.86 (0.76–1.28)
Ferritin (ng/mL)	319 (151–885)
COVID-19-related treatments during admission*, n (%)	
Azithromycin	17 (34)
Other antibiotics	29 (58)
Glucocorticoids	26 (52)
Lopinavir/ritonavir	18 (6)
Remdesivir	0
Darunavir/cobicistat	4 (8)
Tocilizumab	3 (6)
Interferon	4 (8)
Hydroxychloroquine	43 (86)
Immunoglobulin	0
Admitted by intensive care unit during hospital admission	
No	52 (96.29)
Yes	2 (3.71)
Length of stay (days), median (IQR)	9 (6-14)
Discharge reason, n (%)	
Improvement, home isolation	29 (53.70)
Other care centre (medicalised hotel/IFEMA hospital)	8 (14.82)
Death	12 (22.22)
End of study (no discharge)	5 (9.26)

CPR, C Reactive Protein; LDH, Lactate dehydrogenase.
*Data for 50 patients (4 patients were treated in other support centers after referral or admission in other centers)

At admission, the median haemoglobin was 12.9 (12.4–13.8) g/dL and the median total lymphocyte count was 700 (500–1200) ng/mL. The median D-dimer value was 727 (487–1091) ng/mL. In 10% of patients, median interleukin (IL)-6 levels were 213 (43–383) pg/mL. Patients received various antibiotics (mainly azithromycin, levofloxacin and third-generation cephalosporins).

Most patients were treated with hydroxychloroquine during admission (86%). About half received glucocorticoids (52%). Eighteen were treated with lopinavir/ritonavir and 3 received the anti-IL-6R antibody tocilizumab (**Table 4**).

A total of 20 patients (44%) developed relevant complications during admission, the most frequent being myocarditis, thrombosis and kidney failure. Only two patients were admitted to

the intensive care unit during admission. The first was a patient in 50s with mixed connective tissue disease and associated comorbidities who developed acute respiratory insufficiency and bilateral pneumonia. The patient was treated with antibiotic therapy, lopinavir/ritonavir, hydroxychloroquine and β-interferon. Finally, the patient was extubated 40 days later and is recovering. The other was a young adult patient with systemic lupus erythematosus treated with methotrexate, rituximab, hydroxychloroquine and glucocorticoids, who, days after being diagnosed with COVID-19 (PCR+), developed an erythematous rash and generalised urticaria requiring hospitalisation in the intensive care unit owing to general clinical and laboratory worsening (elevated D-dimer values). The patient was treated with methylprednisolone, heparin and cephalosporin. A few days later, the patient's condition improved and he recovered completely at discharge.

Of the 49 patients admitted to HCSC, 5 were sent to another care centre (converted-hotel hospital/IFEMA support hospital) when their condition improved. A further 29 patients (53.7%) were discharged home to continue self-isolation after improvement. At the end of the study, five patients remained in hospital (9.26%). A total of 12 patients died (22%) during admission (6 men and 6 women), with a median age of 81 (76.5–87) years. Of the patients who died, 87% had relevant comorbidity (diabetes mellitus, pulmonary disease, ischaemic vascular disease, hypertension, venous thrombosis/lung embolism, lung disease and or liver disease). The main diagnoses were rheumatoid arthritis (6), followed by spondyloarthritis (2), polymyalgia rheumatica (2), vasculitis (1) and Sjogren's syndrome (1).

The results of the univariable analysis are shown in **Table 5**. Older age, systemic autoimmune conditions (vs chronic inflammatory arthritis) (OR: 2.65; 95% CI 1.22–5.7, p=0.014), hypertension, diabetes mellitus, lung disease, heart disease and glucocorticoids were associated with statistically significant greater risk of admission to the hospital. Female sex, NSAIDs, and anti-TNF drugs (vs non-use) were associated with a statistically significant lower risk. The differences reported for the remaining variables did not reach statistical significance.

Table 5. Odds Ratio of hospital admission related to COVID-19 in patients with AIRD (univariable analysis)

Variable	OR	95% CI	*p*
Gender, women	0.4	0.18–0.988	0.02
Age (years)	1.09	1.05–1.14	0
Diagnosis (AIRD: one category vs the rest) *			
Rheumatoid arthritis	0.57	0.27–1.20	0.14
Inflammatory polyarthritis	0.4	0.07–2.08	0.27
Systemic lupus erythematosus	0.4	0.07–2.08	0.27
Psoriatic arthritis	1.29	0.25–6.68	0.7

Spondyloarthritis	0.78	0.28–2.18	0.64
Mixed connective tissue disease	2.68	0.47–15.2	0.26
Sjogren syndrome	1.02	0.26–4.01	0.93
Disease duration	1.01	0.96–1.05	0.67
Smoking habit (active vs none)	3.99	0.40–39.58	0.23
Comorbidities (yes)			
Hypertension	3.64	1.65–8.06	0.001
Dyslipidemia	1.82	0.77–4.32	0.17
Depression	0.14	0.01–1.18	0.07
Diabetes mellitus	5.15	1.5–16.8	0.007
Heart disease	2.9	0.93–9.09	0.06
Vascular disease	4.18	0.81–21.64	0.09
Liver disease	1.76	0.37–8.22	0.47
Kidney disease	1	–	–
Lung disease (ILD/COPD)	3.32	1.17–9.45	0.02
Cancer	5.4	0.58–50.1	0.13
Venous thrombosis/lung embolism	1	–	–
Thyroid disease	0.48	0.15–1.47	0.2
NSAIDs	0.37	0.15 –0.91	0.03
Glucocorticoids	2.01	0.97–4.13	0.05
csDMARDSs			
Methotrexate–leflunomide–azathioprine	0.78	0.38–1.59	0.49
Sulfasalazine	1.02	0.26–4.01	0.97
Antimalarials	0.56	0.23–1.38	0.21
b/tsDMARDs	0.39	0.15–1.01	0.05
None	1	–	–
Anti-TNF agents	0.13	0.03–0.63	0.01
Other biologics	1.65	0.46–6.49	0.46
JAKi	1	–	–

AIRD, autoimmune inflammatory rheumatic disease; Anti-TNF, tumor necrosis factor-alpha inhibitor; csDMARD, Conventional synthetic disease-modifying antirheumatic drug; IL-6, interleukin-6; JAKi, JAK inhibitors; b/tsDMARDs, biologic/target synthetic disease-modifying antirheumatic drug; OR, odds ratio; CI, confidence interval.

Other biologics: anti-IL-6 (tocilizumab, sarilumab); rituximab; anti-IL-17/23; anti-IL-17.

*Other categories could not be represented: polymalgia rheumatica, systemic sclerosis, vasculitis, Raynaud phenomenon, polychondritis, Behçet disease,polymyositis, uveitis inflammatory bowel disease, antiphospholipid syndrome, juvenile idiopathic arthritis, autoinflammatory syndromes and sarcoidosis.

The multivariable analysis was adjusted for gender, age and comorbidities related to COVID-19. These comorbidities were diabetes mellitus, pulmonary disease, ischaemic vascular disease, hypertension, venous thrombosis/lung embolism, lung disease and/or liver disease (**Table 6**). Age and systemic autoimmune conditions had more probability of hospital

admissions, regardless of other factors. Differences in exposure to glucocorticoids were not statistically significant. The type of exposed DMARDs did not reach statistical significance in the multivariate model. In fact, long-term treatment with antimalarials (OR: 0.76; 95% CI 0.26–2.53; p=0.66), other csDMARDs (including methotrexate, leflunomide and azathioprine) (OR: 0.95; 95% CI 0.36–2.51; p=0.9) and NSAIDs (OR: 1.49; 95% CI 0.42–5.23; p=0.5) dropped from the final model. The variable ts/bDMARDs was also eliminated from the final model (anti-TNF vs none: OR: 0.29; 95% CI 0.05–1.66; p=0.16; and non-anti-TNF vs none: OR: 2.21; 95% CI 0.47–10.2; p=0.3).

Table 6. Multivariable analysis. Risk factors for hospital admission related to COVID-19 in patients with AIRD

Variable	OR	95% CI	*p*
Gender, women	0.45	0.15–1.29	0.14
Age (years)	1.08	1.04–1.13	0
AIRD (systemic autoimmune conditions vs chronic inflammatory arthritis)	3.55	1.30–9.67	0.01
COVID comorbidities (yes)	1.82	0.69–4.80	0.22
Glucocorticoids	1.97	0.77–5.01	0.15

AIRD, autoimmune inflammatory rheumatic disease; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease.
Systemic autoimmune conditions (polymyalgia rheumatica; mixed connective tissue disease, systemic sclerosis, Sjogren's syndrome, vasculitis, Raynaud, polymyositis polychondritis, sarcoidosis, antiphospholipid syndrome; autoinflammatory syndromes and systemic lupus erythematosus) vs chronic inflammatory arthritis (rheumatoid arthritis; inflammatory polyarthritis; juvenile idiopathic arthritis, psoriatic arthritis, axial spondyloarthritis, uveitis and inflammatory bowel disease). Comorbidities including the presence of at least one of the follows: hypertension, heart disease, vascular disease, diabetes mellitus, venous thrombosis/lung embolism, chronic kidney disease, liver disease and lung disease (ILD/COPD).

DISCUSSION

Our study aims to shed light on rheumatologists' concerns regarding their patients. We found that, in a real-world setting, 44% of patients with AIRD and COVID-19 required hospital admission. These were mainly elderly patients, with more comorbidities and systemic autoimmune conditions. Our data show that patients exposed to disease-modifying agents do not seem to be at higher risk of hospital admission related to COVID-19.

Of the 123 patients included in the study with COVID-19, 54 required hospital admission. Comparison of the characteristics of patients admitted to hospital because of COVID-19 and those who did not require hospital admission were as follows: admitted patients had a median age close to 70 years, that is, more than 15 years older than patients who were not admitted.

Moreover, those who were admitted more frequently had baseline comorbidities and systemic autoimmune conditions. As for therapy, admitted patients were less frequently exposed to antimalarial and anti-TNF-alpha agents.

The median lag time from onset of symptoms to admission was 5 days, and almost 90% of patients had pneumonia at admission. The baseline laboratory results for admitted patients in our study are consistent with those published elsewhere 9–12 and are characterised by lymphopenia and elevated acute-phase reactants. In fact, 75% of the patients had elevated D-dimers (normal, <500) and elevated IL-6 (normal, <7 pg/mL). Treatment during admission varied widely as the disease proved challenging for specialists, who prescribed various combinations of drugs based on little published evidence. In this sense, the anti-IL-6R antibody tocilizumab has proven to be beneficial in patients with COVID-19.12 Treatment may also be successful in the early stages of cytokine release syndrome, if it can effectively block the signal transduction pathway of IL-6; therefore, tocilizumab and sarilumab are likely to emerge as effective drugs for patients with moderate to severe COVID-19.13 14 In our study, almost 10% of the patients were treated with tocilizumab.

The patients who eventually died had a median age of >80 years. This finding is in line with data for the general population, where over 95% of deaths occurred in persons >60 years and more than 50% of all deaths were in people aged ≥80 years.7

The multivariable regression model showed that only age (increasing by 8% per year) and systemic autoimmune conditions continued to be risk factors for hospital admission related to COVID-19.

As for the association between sex and risk of hospital admission, we did not find a higher risk of admission in women, despite the fact that rheumatic diseases are more prevalent in this group. The type of diagnosis seems to play an important role in the probability of hospital admission, and patients with systemic autoimmune conditions seem to have the highest risk compared with chronic inflammatory arthritis.

As it has been reported elsewhere, comorbidities play an important role in the risk of hospital admission.15 Clinical outcomes are poorer in patients with COVID-19 with a comorbid condition than in those without, and a greater number of comorbidities correlates with poorer clinical outcomes.16 Diabetes is a major comorbidity in COVID-19, and patient's history of diabetes is an independent risk factor for morbidity and mortality in this condition.17 18 Diabetes has been associated with admissions to the intensive care unit due to COVID-19 in recent series19 20 and has been shown to increase mortality.6 Therefore, we adjusted for comorbidity in the multivariable analysis.

Treatment with glucocorticoids lost its statistical significance in the multiple regression model. However, the dose was not reported in our data, and in the case of these agents, the risk

could be dose-dependent. In a recent publication from a European registry, the authors found that exposure to >10 mg/day was associated with a greater probability of hospitalisation.[21]

The exposure to DMARDs, regardless of whether they were biological or synthetic, does not seem to be associated with a higher hospital admission related to COVID-19. Although we have to consider the limited number of patients in our study, our results are in concordance with data reported elsewhere.[8 20]

Our results should be interpreted taking into account other limitations. First, patients were included from a single centre. Second of all patients with COVID-19 [19] who did not require admission, one-third contacted the rheumatology service to report the disease and the remainder were detected through the COVID-19 discharge reports sent to their primary care physician. Elderly persons and homemakers who did not contact us can be considered missing. Consequently, there may be some selection bias between those admitted and those not admitted, although this problem was addressed by adjusting for confounders in the multivariable analysis. Third, while it is acknowledged that clinical suspicion must be confirmed by PCR assay, almost 20% of patients admitted did not undergo PCR owing to the lack of tests or the extreme healthcare overload. Nevertheless, all cases included were clinically compatible and managed as COVID-19.

The key strength of our study is that it was performed in real-life conditions during then pandemic peak, with access to complete sociodemographic and clinical data from our rheumatology electronic clinical history, including thorough hospital admission data such as laboratory abnormalities and COVID-19 treatment data from the hospital computer services. Consequently, this has allowed us to analyse the risk of hospital admission related to COVID-19 adjusted for confounders, thus avoiding possible bias.

Although we are unable to modify the factors reported here, knowing them can help rheumatologists to treat and advise their patients during this new and challenging period. Results provided by our study are preliminary and should be corroborated with other real-life studies, but we consider our findings helpful to increase the knowledge in the management of patients with AIRD and COVID-19.

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4.2 ARTICLE 2.

Hospital Admissions In Inflammatory Rheumatic Diseases During The Peak Of COVID-19 Pandemic: Incidence And Role Of Disease-Modifying Agents

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.

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, and type of diagnosis and therapy used in IRD patients from our health area. Then, we assessed the role of exposition to target 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 >16years 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, sarilumab]; rituximab; abatacept; belimumab; anti-IL12/23 (ustekinumab), anti-IL17 (ixekizumab, secukinumab); (c) JAK inhibitor (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; methotrexate; azathioprine or mycophenolate mophetilo, cyclophosphamide; cyclosporine; (d) other csDMARDs, including: antimalarial (chloroquine/hydroxychloroquine); sulfasalazine; 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 antimalarial, glucocorticoids, sulfasalazine, and NSAIDs. Regarding methotrexate, leflunomide, azathioprine, cyclosporine and ts/bDMARDs, treatment had to start at least 1month 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 rituximab, 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 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 $p < 0.2$ 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 7**, 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, methotrexate was the most used (n = 1461), followed by antimalarials, leflunomide (n = 333), sulfasalazine, and azathioprine (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 methotrexate + antimalarials; methotrexate + sulfasalazine and methotrexate + eflunomide). 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 rituximab.

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.

Table 7. Baseline demographic and clinical characteristics among IRD patients

Variable	AII 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)
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 Syndrome	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 (%):	
Methotrexate –Leflunomide–Azathioprine	1961 (49.6)
Cyclosporine	27 (0.68)
Sulfasalazine	317 (8.0)
Antimalarals	666 (16.8)
b/tsDMARDs, n (%)	
Anti-TNF	521 (13.2)
Infliximab	52 (1.3)
Adalimumab	188 (4.7)
Etanercept	117 (2.9)
Golimumab	61 (1.5)
Non-anti-TNF	246 (6.2)
Abatacept	27 (0.68)
Tocilizumab	42 (1.06)
Rituximab	122 (3.2)
Sarilumab, Secukinumab, Ixekizumab, Ustekinumab	49 (1.2)
Belimumab	6 (0.15)
JAKi	
Baricitinib	27 (0.68)
Tofacitinib	8 (0.2)

Anti-TNF, tumor necrosis factor-alpha inhibitor; COPD, chronic obstructive pulmonary disease; csDMARD, conventional synthetic disease-modifying antirheumatic drug; ILD, interstitial lung disease; IRD, inflammatory rheumatic disease; JAKi, JAK inhibitor; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; b/tsDMARDs, biologic/target synthetic disease-modifying antirheumatic drug.

*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, valvopathies, cardiomyopathies, heart failure. ****Ischemic vascular disease, stroke, cardiovascular and peripheral vascular disease.

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 8**, 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, except for SLE. It was similar in patients with or without csDMARDs. No hospital admissions were found for patients with cyclosporine, colchicine, nor cyclophosphamide. Finally, concerning ts/bDMARDs, IR was higher in patients on rituximab and lower in patients using anti-TNF. No hospital admissions were found for patients with abatacept, sarilumab, ustekinumab, ixekizumab, secukinumab nor belimumab.

Table 8. 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				
Systemic lupus erythematosus	374	2	5.3	1.3–21.5
Rheumatoid arthritis	2219	18	8.1	5.1–12.8
Inflammatory polyarthritis	253	2	7.9	1.9–31.5
Psoriatic arthritis	432	3	6.9	2.2–21.5
Spondyloarthritis	731	7	9.5	4.5–20.0
Polymyalgia rheumatica	562	6	10.7	4.8–23.7
Systemic sclerosis	119	1	8.3	1.2–59.3
Mixed connective tissue disease	234	4	17.1	6.4–45.6
Sjögren's syndrome	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
Behçet's disease	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
Glucocorticoids				
Yes	2087	32	11.9	8.4–16.8
No	3209	22	6.8	4.5–10.4
csDMARDs, n (%):				
Methotrexate–Leflunomide-Azathioprine				
Yes	2927	28	9.5	6.6–13.8
No	2969	26	8.8	5.9–12.8
Sulfasalazine				
Yes	472.7	4	8.5	3.2–22.5
No	5427.3	50	9.2	6.9–12.2
Antimalarics				
Yes	993.8	9	9.0	4.7–17.0
No	4903.2	45	9.2	6.8–12.3
b/tsDMARDs				
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
Rituximab	181	4	22.1	8.3–58.8
Abatacept	41	0	–	–
Sarilumab, Secukinumab, Ixekizumab, Ustekinumab	136	1	7.3	1.0–52
Belimumab	9	0	–	–
JAKi	51.4	1	19.4	2.7–138

Anti-TNF, tumor necrosis factor-alpha inhibitor; csDMARD, conventional synthetic disease-modifying antirheumatic drug; IA, inflammatory polyarthritis; IR, incidence rate; IRD, inflammatory rheumatic disease; JAKi, JAK inhibitor; NSAID, non-steroidal anti-inflammatory drug; b/tsDMARDs, biologic/target synthetic disease-modifying antirheumatic drug.

*Inflammatory bowel disease, antiphospholipid syndrome, juvenile idiopathic arthritis, autoinflammatory syndromes, sarcoidosis.

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 9). When we analyzed separately other biologics, Rtx, compared with the rest, had a 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].

Table 9. Hazard ratios of medical admission related to COVID-19 in IRD patients. Bivariate analysis

Variable	HR	95% CI	*p*
Women, n (%)	0.5	0.32–0.9	0.033
Age, mean (SD), years	1.02	1.01–1.04	0.002
Disease evolution time	1.002	0.97–1.03	0.8
Diagnosis (one category versus the rest)			
Rheumatoid arthritis	0.83	0.5–1.4	0.5
Inflammatory polyarthritis	0.85	0.2–3.5	0.8
Systemic lupus erythematosus	0.57	0.1–2.3	0.4
Psoriatic arthritis	0.7	0.2–2.4	0.6
Spondyloarthritis	1.05	0.5–2.3	0.8
Polymyalgia rheumatica	1.2	0.5–2.7	0.6
Systemic sclerosis	0.9	0.13–6.5	0.9
Mixed connective tissue disease	1.9	0.7–5.4	0.2
Sjögren's syndrome	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
Behçet's disease	-	.-	-
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
csDMARDs:	1.15	0.6–2.0	0.6
Methotrexate –Leflunomide–Azathioprine	1.09	0.6–1.9	0.7
Cyclosporine	–	–	–
Sulfasalazine	0.92	0.3–2.5	0.8
Antimalarics	0.95	0.5–2.1	0.8
b/tsDMARDs	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.

Anti-TNF, tumor necrosis factor-alpha inhibitor; CI, confidence interval; COPD, chronic obstructive pulmonary disease; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HR, hazard ratio; IA, inflammatory polyarthritis; ILD, interstitial lung disease; IRD, inflammatory rheumatic disease; JAKi, JAK inhibitor; NSAID, non-steroidal anti-inflammatory drug; b/tsDMARDs, biologic/target synthetic disease-modifying antirheumatic drug.

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 10**). Regarding specific non-TNFs versus none, they did not reach statistical significance either [R HR: 2 (0.71–5.6) p = 0.190; JAKi HR: 2.6 (0.3–19.3) p = 0.3; and Tocilizumab 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], Sulfasalazine [HR: 1.28 (0.4–3.6); p = 0.6], Methotrexate–Leflunomide–Azathioprine [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's syndrome [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.

Table 10. 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
b/tsDMARDs			
None	1	–	–
Anti-TNF	0.32	0.07–1.36	0.123
Non-anti-TNF	1.57	0.66–3.7	0.31

Anti-TNF, tumor necrosis factor-alpha inhibitor; CI, confidence interval; HR, hazard ratio; IRD, inflammatory rheumatic disease; b/tsDMARDs, biologic/target synthetic disease-modifying antirheumatic drug.
Systemic autoimmune conditions (polymyalgia rheumatica; systemic sclerosis, Sjögren's syndrome, mixed connective tissue disease, vasculitis, Raynaud, polymyositis, polychondritis; Behcet disease, 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-IL12/23; anti-IL17+JAK inhibitors.

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 disappeared. Interestingly, only one hospital admission related to COVID-19 was found on tocilizumab, and none were found on abatacept, anti IL-12/23 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 autoimmune 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 methotrexate, leflunomide or azathioprine do not increase the risk of hospital admission related to COVID-19. In the case of antimalarials, 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 antimalarials 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 analyse 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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4.3 ARTICLE 3.

Mortality Related To COVID-19 In Patients With Rheumatic And Musculoskeletal Diseases, First Wave Of The Outbreak: A Single-Center Study

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 (RMD) and COVID-19 and to analyze the role of the different RMD in their mortality risk.

Methods: An observational longitudinal study was conducted during the first pandemic wave in our center. Patients with the diagnosis of RMD and COVID-19 were included. Main outcome is the death related to COVID-19. Independent variable – type of RMD: 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 RMD 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.

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

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 RMD 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.

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

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 (RMD), 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 RMD hospitalized with COVID-19, certain features might determine critical or fatal disease.[4,9]

Thus, individuals with RMD 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 RMD 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 RMD, 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 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 RMD 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 RMD. 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 RMD – (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 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 RMD on survival. The model also included DMARDs and all other variables with $p < 0.2$ 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 RMD 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 RA patients (Table 1).

Table 11. Type of diagnoses by RMD groups

		Diagnosis	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)

RMD, rheumatic and musculoskeletal diseases; ARD, autoimmune rheumatic diseases; CIA, chronic inflammatory arthritis; CTD, connective tissue diseases.

Table 12 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 RMD 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 12**) 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 RMD chronic treatments, in CTD, the use of NSAIDs was less frequent, whereas exposure to glucocorticoids was more frequent compared to other RMD 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.

Table 12. Baseline demographic and clinical characteristics of patients with RMD and COVID-19

Variable	COVID-19 patients (N = 405)	ARD CIA (N = 107)	ARD CTD (N = 55)	Non-ARD (N = 243)	p
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)	44 (41.12)	31 (56.36)	110 (45.27)	0.43
Not performed	201 (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
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;

[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).

JAKi, JAK inhibitor; PCR, polymerase chain reaction; RMD, 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 ≥3.

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 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 RMD, the CMR was estimated in 68.48 cases per 1000 patients-month (95% CI: 50.96–92.01). **Figure 6** 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.

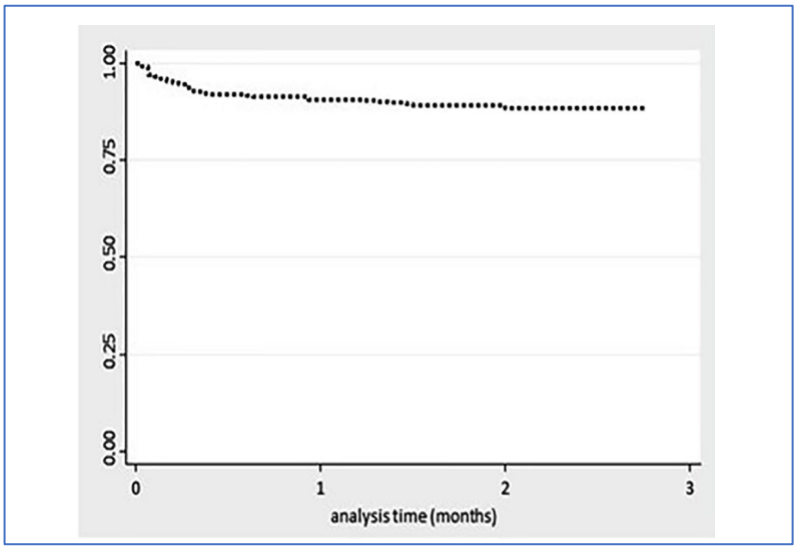

Figure 6. Cumulative incidence of deaths related to COVID-19 over time in patients with RMD during the study period. Kaplan–Meier survival estimate curve

Table 13 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 RMD 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 with 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 methotrexate, and antimalarials, the CMR was estimated in 43.6 [18.1–104.7], and in 82.05 [34.1–197.14], respectively.

Table 13. COVID-19-specific mortality rate analysis per 1000 patients-month in patients with RMD and COVID-19

Variable	*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
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, *n* (%)				
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	–
JAK1	1	0.007	-	-

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; RMD, 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).

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

In the bivariate analysis (Table 14), 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.

Table 14. Risk factors of death related to COVID-19 in patients with RMD: 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
RMD			
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; RMD, 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).

Multivariate regression model is shown in **Table 15**. 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 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.

Table 15. Role of RMD and other risk factors of death related to COVID-19 in patients with RMD: 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
RMD			
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; RMD, 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).

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 RMD 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 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 RMD, 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 RMD 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 RMD 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 RMD 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.

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CHAPTER 5

5 Discussion

The articles presented aim to shed light on rheumatologists' concerns regarding their patients. These real-world longitudinal studies conducted during the whole first wave of the COVID-19 pandemic in Madrid, the epicenter of the outbreak in Spain and performed in a period of maximum health emergency of the country, included a big sample size and a broad spectrum of RMD with different types of treatments, giving us a general picture of the situation in a variety of patients with RMD infected by SARS-CoV-2.

5.1 SARS-CoV-2 infection in patients with RMD

Abording the infection risk of patients with RMD, especially those with ARD, this group of individuals are generally considered more prone to bacterial and certain viral infections such as the herpes zoster virus. The risk of infection is multifactorial and influenced by therapy, disease activity, disease damage, and comorbidities, among other factors. In a US registry of more than 16,000 patients with RA, every 0.6-point rise in the DAS, resulted in a 25% increase in hospital admissions and a 4% increase in outpatient infections (320). An insurance database revealed that SLE patients had a 6-fold higher susceptibility to infections and an incidence rate of 29.2 severe infections/1,000 patients per year in the Spanish SLE-registry (307). While glucocorticoids (10 mg/d), rituximab, mycophenolate mofetil/mycophenolic acid, and lupus activity/severity were associated with a higher chance of severe infection, current and past hydroxychloroquine appeared to have a protective effect (RR 0.49, p = 0.0000).

There is a gap of knowledge about RMD patients who were exposed to coronaviruses like SARS and MERS in previous epidemics. Additionally, because of the small geographic scope and the small number of patients impacted, no special containment measures regarding the diagnosis and treatment of patients with RMD were announced, and there were no issues with the supply of DMARDs (321,322)

In the thesis (**articles 1, 2, and 3**), the demographic and disease characteristics of individuals with RMD diagnosed with COVID-19 are comparable to the ones reported by the COVID 19 Global Rheumatology Alliance registry (C19-GRA) (323). Adjusting to the pandemic progression (data collection) in this investigation, the (**article 3**) describes in a more complete way the characteristics of patients with RMD who presented SARS-CoV-2 infection. From the

total, almost 70% were women with a mean age of 59 years, without differences between diagnosis groups (ARD and non-ARD patients). Focus on the ARD, the main diagnosis was RA, followed by spondyloarthritis (**articles 1, 2, and 3**). Around thirty percent of the patients presented comorbidities, being the highest in those with CTD and the most frequent were the traditional cardiovascular risk factors.

In previous meta-analysis (324,325), the relative risk of developing SARS–CoV-2 infection was 52% higher in patients with RMD compared to the general population, and similar to our study, a systematic review and meta-analysis, focused on RMD as a combined group, which limits our ability to extrapolate our findings to any individual patient with an RMD. This group was composed of patients with different diseases that have different organ manifestations, severity, and treatments.

5.2 Hospital admission related to COVID-19 in patients with RMD

This pandemic has had a great impact, especially in Madrid, with more than 41,304 hospital admissions until the first week of May14. In our real-world setting study (**article 1**), 44% of patients with AIRD and COVID-19 required hospital admission, similar to the C19-GRA registry, with more than 20,000 records from people in 81 different countries, that reported that 277 people (46%), out of the first 600 records (up to April 2020), were hospitalized (326–328).

Regarding incidence, in our study (**article 2**), the IR of hospital admissions related to COVID-19 in IRD patients was estimated at 9.15 per 1000 patient-months, comparing this IR of hospital admissions related to COVID-19 with the reference population, it seemed that IRDs have an increased risk. Some of the large population-based or health-system-based studies conducted to date have reported point estimates suggesting elevation of the risk of COVID-19 hospitalization in people with RMD (329–332).The risk of hospitalization with COVID-19 was 46 percent higher for people with RMD than for the general population in a subsequent Danish data-linking study for a 6-month period starting in March 2020, but using a fully adjusted model, only people with RA still had an elevated risk of a severe outcome (HR 1.72; 95 percent CI 1.29-2.30) (333). Other studies have compared the IR of IRD with their reference population without differences (334–337) however some of these studies did not include patients with systemic autoimmune conditions (334,335).

Overall, the IR varies per region and period and the findings of the individual studies and the meta-analysis show that individuals with RMD are at an elevated risk of hospitalisation and maybe additional severe COVID-19 outcomes compared to the general population, with some of this risk being attributed to comorbidities. The high incidence of comorbidities among those

with RMD, comorbidities that are known to be linked to COVID-19 outcomes, indicates the need for a close examination of their effects.

In our investigation, comparing the features of patients who required hospital admission due to COVID-19 with those who did not, we found the following variables: admitted patients were older, a median age of 70 years, more frequently had baseline comorbidities and systemic autoimmune conditions (**article 1**). Interestingly, in the (**article 2**), we corroborated the role of age, male sex and comorbidities in the susceptibility of moderate–severe COVID-19 development (338,339). 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.

As it has been reported, comorbidities play an important role in the risk of hospital admission and clinical outcomes, a greater number of comorbidities correlate with poorer clinical outcomes. Diabetes is a major comorbidity in COVID-19, and the patient's history of diabetes is an independent risk factor for morbidity and mortality in this condition. Therefore, we adjusted for comorbidity in the multivariable analysis (340,341).

The multivariable regression model for hospital admission (adjusted for age, sex, and comorbidity) (**article 1**) showed that only age (increasing by 8% per year) and systemic autoimmune conditions continued to be risk factors for hospital admission related to COVID-19. We did not detect a higher risk of hospital admission in women, despite the fact that rheumatic disorders are more common in this population.

5.2.1 Influence of RMD treatment on hospital admission related to COVID-19

Our data (**article 1**) show that patients exposed to DMARDs, regardless of whether they were biological or synthetic, did not seem to be at higher risk of hospital admission related to COVID-19. Although we have to consider the limited number of patients in our study, our results are in concordance with data at the moment reported (342,343).

The (**article 2**) included a correct sample size with a broad spectrum of RMD treated with different DMARDs and glucocorticoids. With all this information, we have been able to evaluate the influence of ts/bDMARDs and csDMARDs on the risk of hospital admissions related to COVID-19. In this aspect, the crude IR of hospital admission was lower for those on anti-TNF and higher for those with non-TNF biologics, with 4 patients using rituximab and one tocilizumab, however in the multivariate analysis this slight statistical difference between

biologic agents disappeared. Although our data (**article 1 and article 2**) must be assumed with caution due to the number of patients on these drugs, not sufficient to draw specific conclusions, our findings are consistent with other studies affirming that DMARDs, and especially anti-TNF, do not seem to be associated with worse outcomes in RMD (344–346).

In this sense, important updated information has been provided by the studies from the C19-GRA, where researchers investigated the risk of poor outcomes as well as the impact of using ts/bDMARDs, in a group of RA patients in the C19-GRA registry (347). Patients with RA who were receiving a JAK inhibitor or rituximab prior to the COVID-19 outbreak, presented a higher risk of poor outcomes than those who were receiving TNF-inhibitor therapy. The association of rituximab use with poor outcomes was not unexpected, as it was similar to the findings in the main C19-GRA cohort study, where the risk of poor COVID-19 outcomes (combined end point of hospitalization, ventilatory support or death) with rituximab treatment was clear (OR 4.15; 95% CI 3.16–5.44) (347,348). Rituximab is a B cell-depleting therapy (BCDT), and BCDTs have been linked with poor outcomes for COVID-19 in people with conditions other than rheumatic diseases (349).

Despite conflicting evidence, existing large cohort studies imply that COVID-19 patients may experience worse outcomes for COVID-19 if they get immunosuppressive treatments like cyclophosphamide and mycophenolate, as well as BCDTs like rituximab. Because BCDTs impair humoral responses to vaccination, they are a particular source of worry (328,350–355).According to several studies, patients with COVID-19 infection who are treated with rituximab, including those with RA, are at an increased risk of of a more prolonged disease course, severe disease, and/or worse outcomes (356–359).

Regarding the possible benefit that anti-TNF agents might confer, in agreement with our results, the analysis of pooled data from the C19-GRA registry and from international registries for people with COVID-19 and inflammatory bowel disease or skin psoriasis, to outcomes for people on treatment with TNF inhibitors (360).In over 6,000 COVID-19 patients from 74 countries, those who received anti-TNF in addition to azathioprine or 6-mercaptopurine, azathioprine or 6-mercaptopurine monotherapy, methotrexate monotherapy, or JAKi inhibitor monotherapy had higher risks of hospitalisation or death than those who received only anti-TNF. In line with our findings (**articles 1 and 2**), these results suggest that anti-TNF monotherapy may confer some benefit with respect to COVID-19 outcomes in individuals with a variety of ARDs, and this possibility is currently being investigated in intervention studies of the use of TNF inhibitors to treat COVID-19 (361).

In the same line, concerning to other therapies (**article 2**), the crude IRs seems to be similar in patients with and without csDMARDs, higher in those on glucocorticoids, and lower in those

using NSAIDs. Nevertheless, none of them remained statistically significant after the multivariate analysis. According to the majority of international and specialty guidelines, patients with SARS-CoV-2 exposure would not use NSAIDs differently from other patients(362). The use of NSAIDs in patients with COVID-19 is not associated with any novel elevated risk, and numerous data support their safety (363,364).

In concordance with our analysis (**article 1 and article 2**), according to Favalli et al.(345), it seems that methotrexate, leflunomide, or azathioprine do not increase the risk of hospital admission related to COVID-19. In general, from previous evidence, treatment with methotrexate and leflunomide is also associated with a relatively low risk of serious infection, particularly when given as monotherapy (365,366). In agreement with other authors, we are not able to demonstrate the protective effect of the chronic use of antimalarials on moderate–severe infections related to COVID-19 (367,368).

Although glucocorticoids may be a useful intervention for severe COVID-19, limited observational data have prompted the question whether glucocorticoid therapy may also be associated with increased susceptibility to more severe disease in both rheumatologic and inflammatory bowel disease (369–371). In our studies, treatment with glucocorticoids lost statistical significance in the multiple regression model as a risk factor for hospital admission (**article 1 and article 2**). However, the dose was not recorded in our data, and in the case of this treatment, the risk could be dose-dependent. In a publication from the C19-GRA registry, the authors found that exposure to >10 mg/day was associated with a greater probability of hospitalisation (372). Another possible explanation for this result is that glucocorticoids in COVID-19 might have divergent effects, depending on the underlying disease, although this idea has not yet been confirmed.

Overall, the available data suggest that the use of csDMARDs and b/tsDMARDs does not appear to increase the risk of poor outcomes in COVID-19, which is consistent with the recommendations from the ACR and EULAR to continue current treatment with DMARDs in the absence of known exposure to SARS-CoV-2 in order to maintain good disease control (373,374). However, there are some notable exceptions such as rituximab (375,376), for which the risk of negative outcomes is becoming apparent. The use of rituximab is a complex subject and challenging, because the risk of poor outcomes from COVID-19 must be considered against the severity of the rheumatic disease that is being treated. Rituximab is most commonly used for the treatment of diseases such as vasculitis, complex SLE, and some RA.

5.2.2 Role of different RMD and hospital admission related to COVID-19

The type of RMD diagnosis appears to play an important role in the probability of hospital admission. In our data, patients with systemic autoimmune conditions seem to have the highest risk compared with CIA (**article 1**). The crude IR of hospitalization related to COVID-19 differs among RMD, being slightly higher in the systemic autoimmune conditions (**article 2**).

The multivariable regression model showed that only age and some systemic autoimmune conditions continued to be risk factors for hospital admission related to COVID-19 (**article 1 and article 2**). A stratification by type of ARD diagnosis was not made in (**article 1**). However, this aspect was assessed in (**article 2**), showing that the risk of severe COVID-19 remained statistically significant for Sjögren's syndrome, polychondritis, and MCTD and primary Raynaud phenomenon. Nevertheless, SLE had the same risk as RA and PsA without statistical significance. Other systemic autoimmune conditions did not reach statistically supported, but perhaps the number of patients was insufficient to detect those differences (**article 2**). Similar results were reported in a large Danish population-based study of 11,122 people with SARS-CoV-2 infection confirmed by PCR in early 2020, sing an unadjusted model, where individuals with RA or CTD had higher risk of hospital admissions than those without these diagnoses. However, after age, sex and comorbidity statistical adjustment, the probabilities of this poor outcome were not increased (377).

Abording patients with inflammatory arthritis and COVID-19, the disease course in a series of 86 patients with immune-mediated inflammatory diseases including 50 cases of inflammatory arthritis (RA, PsA, axial spondyloarthritis) with confirmed or highly suspected COVID-19 was analyzed (confirmed cases: total: 59, of which 37 inflammatory arthritis). A special interest was put on the comparison of patients with out-patient or in-patient management (16%) (378) and found that comorbidities (such as hypertension, diabetes, or COPD) were more prevalent in hospitalized patients than in outpatients. In our results (**article 1**) from a total of 123 individuals with RMD, the main diagnosis was RA (40.65%), followed by axial spondyloarthritis (14.63%). Many patients had at least one baseline comorbid condition, hypertension, diabetes, chronic kidney disease, and lung disease (ILD/COPD) was most prevalent in hospitalized patients, not resulting as a risk for hospital admission in the multivariable analysis.

Regarding to patients with CTD, there have been only incidental publications besides SLE, the most notable shared factor is about immunosuppressive treatment, such as rituximab therapy, which appears to cause a late worsening of symptoms that results in respiratory issues, even in patients without pre-existing lung disease (379,380). In our investigation, comparing RMD patients with COVID-19 that required hospital admission with those with not, we observed (**article 1**) that patients with a diagnosis of MCTD, SSc, vasculitis, polychondritis,

polymyositis and polymyalgia rheumatica trended to be admitted, and this was confirmed in the multivariate analysis concluding that systemic autoimmune conditions had more probability of hospital admissions, regardless of other factors.

In the same line, we observed in (**article 2**), that some systemic autoimmune conditions comparing CIAhad a trend of more risk of hospital admission except for SLE. Similar, Bozzalla et al. observed an overall mild course of COVID-19 in 12 patients of their cohort of 165 SLE patients, although the incidence of confirmed or suspected COVID-19 was higher in this cohort than in the general population of the area; nevertheless, this might be explained by a bias of higher testing as it happened in most of the real-life setting studies, during the first months of the pandemic(381).

In contrast, there was a report about the disease course of 17 French patients with SLE (median age: 53.5 (26.6-69.2) (382). 16 of the patients had quiescent rheumatic disease, with obesity (59%) and chronic kidney disease (47%), as well as secondary antiphospholipid syndrome (24%), as the major comorbidities. All were taking HCQ (different doses), 71% were taking glucocorticoids (mostly in doses less than 10 mg prednisone equivalent), and 41% were taking immunosuppressants. These patients' clinical outcomes were worse than expected; 65% of them showed symptoms of respiratory failure needing oxygen therapy. One third of these patients developed ARDS, and nearly half were admitted to intensive care. Two of the 17 patients died. Acute renal injury happened in three patients, while cardiac injury and venous thrombosis only affected one patient each. Five SLE patients from Michigan presented with a similarly dire picture, with one patient dying and three requiring mechanical ventilation (383). It is unclear why these SLE patients fared worse than those from other reports of the general population, but comorbidities and long-term glucocorticoid therapy may have contributed. The overexpression of ACE2 caused by DNA hypomethylation of ACE2 in the T cells of SLE patients has also been demonstrated. This epigenetic dysregulation may be maintained by the oxidative stress brought on by viral infections or SLE flares, which may explain why this SLE cohort has a worse prognosis (384).

Data specifically regarding patients with SLE and COVID-19 is scarce. Whether individuals with SLE have a higher risk of COVID-19 infection is unknown. In one large group of unvaccinated SLE patients in New York City, 4% experienced symptomatic COVID-19 infection, compared to an estimated 2% infection incidence in the general population (385). Immunosuppressive medication use at baseline did not appear to have an impact on the severity of infection. Despite previous interest in HCQ as a potential treatment for COVID-19 itself, a sizable proportion of patients in case series and both clinician- and patient-reported cohorts of rheumatologic disease consisting of unvaccinated patients with COVID-19 were nevertheless taking HCQ at the time of their infection diagnosis (386–388). Worse outcomes were linked to

older age, male sex, prednisone use, comorbidities such as kidney and cardiovascular diseases, and increased lupus disease activity in a registry analysis of 1606 SLE patients (389). Black and Hispanic SLE patients have been demonstrated to have more severe outcomes compared to White SLE patients, which is consistent with what is seen in the general population (390).

In summary, defining the role of the different RMD diagnoses, our results (**article 1 and article 2**) evidenced that patients with certain CTD presented more risk for hospital admission related to COVID-19 than those with chronic inflammatory arthritis.

5.2.3 Clinical and laboratory findings in RMD patients hospitalized with COVID-19

The clinical features of COVID-19 among patients with RMD are diverse and variable and are not known to be different than patients without these underlying conditions. There are insufficient data from reported cases to determine whether the type of RMD or the degree of immunosuppressive therapy influences the clinical presentation of COVID-19 in this population. However, it is probable that some features of rheumatologic disease may be difficult to distinguish from those of COVID-19.

Most of the patients included in our cohort presented respiratory symptoms, and almost 90% diagnosed with pneumonia at admission. 20 of the 123 patients included in the first analysis (**article 1**) developed relevant complications during the hospital admission, such as myocarditis, thrombosis, and kidney failure. Two patients were admitted to the intensive care unit during admission, one presented a diagnosis of MCTD who developed acute respiratory insufficiency and bilateral pneumonia, and another patient with SLE that presented and generalized urticaria and bilateral pneumonia.

Lymphopenia and high acute-phase reactants are the main features of the baseline laboratory results for patients included in our study, in fact, elevated blood levels of D-dimer and IL-6 were present in 75% of the patients (**article 1**), these findings do not differ from the general population and are consistent with what has been widely published on the subject (391–394).

In this aspect, it is important to mention that clinical features such fever, malaise, myalgias, and fatigue can imitate or be mirrored by COVID-19 in a number of rheumatologic disorders. Specific examples of such conditions include diseases that can manifest with fever (SLE); headache (GCA); gastrointestinal symptoms (spondyloarthritis, SSc, SLE, and Behçet syndrome); dyspnea (interstitial pulmonary disease due to RA, SSc, or SLE); stroke

(antiphospholipid syndrome); and a Kawasaki-like multisystem inflammatory syndrome in children, also referred to as pediatric multisystem inflammatory syndrome. Patients with severe COVID-19 may also experience cryptogenic stroke, systemic arterial and venous thromboemboli, and cutaneous vasculitis-like symptoms (395,396). In addition, laboratory abnormalities such as an elevated erythrocyte sedimentation rate, CRP levels, ferritin, IL-6, and creatine kinase levels can be seen in both COVID-19 and in association with various rheumatologic diseases.

Data regarding rheumatic disease activity was not available in our investigation, a variable that may potentially be related to the risk of hospitalization or death from COVID-19 (155,156). Although we gathered ESR data as a surrogate variable of disease activity, over 60% of the data was missing, not being possible to use this information.

5.2.4 Treatment of COVID-19 during the hospital admission

During the first months of the COVID-19 outbreak, treatment during admission varied widely as the disease proved challenging for the health care provider, prescribing different drugs and constantly updating management protocols, based on scant evidence published at that moment. Notable in our report (**article 1**), is the use of glucocorticoids as part of the treatment, in more than half of the patients, and tocilizumab, prescribed in almost 10% of the patients admitted, a recombinant humanized interleukin-6 (IL-6) receptor inhibitors, approved by the FDA for use in patients with rheumatologic disorders and cytokine release syndrome induced by chimeric antigen receptor T cell (CAR T-cell) therapy (397).

The basis on which the use of these drugs is based on the hyperactive inflammatory response to SARS-CoV-2 infection that plays a central role in the pathogenesis of COVID-19 (398,399). Multiple randomized trials indicate that systemic corticosteroid therapy improves clinical outcomes and reduces mortality in hospitalized patients with COVID-19 who require supplemental oxygen, presumably by reducing the systemic inflammatory response (400,401).

In contrast, in hospitalized patients who do not require supplemental oxygen, glucocorticoids have not demonstrated any benefit (402,403). In the same context, IL-6 is a pleiotropic, proinflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by SARS-CoV induces a dose-dependent production of IL-6 from bronchial epithelial cells (404). COVID-19-associated systemic inflammation and hypoxemic respiratory failure can be associated with heightened cytokine release, as indicated by elevated blood levels of IL-6, CRP, D-dimer, and ferritin (394,405,406).

It is hypothesized that modulating IL-6 levels or the effects of IL-6 may reduce the duration and/or severity of COVID-19 (407) .

5.3 Mortality related to COVID-19 in patients with RMD

The SARS-CoV-2 virus infection causes a self-limiting disease for most of the people affected. However, severe COVID-19 can result in pneumonitis, ARDS, renal failure, thrombotic complications, cytokine storm, multiorgan failure, and mortality (408,409). Factors other than the rheumatic condition might affect the risk of death from COVID-19 in people with RMD.

Early in the COVID-19 pandemic case series of rheumatic disease, patients with COVID-19 reported generally mild clinical courses in patients with inflammatory arthritis, SLE, and vasculitis (352,410,411). Early observational studies from longitudinal clinics reported similar incidence of COVID-19 among rheumatic disease patients vs. the general population (337,344,353).

Although these preliminary studies were reassuring, a cohort study in the UK (OpenSAFELY) with over 17 million patients revealed a greater risk of death from COVID-19 among those with RA, SLE or psoriasis (412) . Soon after, comparative cohort studies from Wuhan, and Boston, found that patients with RMD had higher odds of mechanical ventilation than their comparators without rheumatic diseases (413,414) These results increased worries that certain rheumatic disease patient-specific risk factors, like the use of DMARDs, may raise the likelihood of severe COVID-19 outcomes.

In this real-world longitudinal study, 44 deaths related to COVID-19 during the study period were recorded, the case fatality rate for COVID-19 was 10.86% in patients with RMD (12.7% for CTD and 12.15% for CIA) (**article 3**), being comparable to the reported in Spain general population and to the published in other cohorts of RMD patients during the same period of time (415). This study demonstrates that the total CMR in RMD is estimated in 6.8% patient-month and is a phenomenon that appears early in the course of the infection. In fact, and in line with other studies, the majority of COVID-19-related deaths occurred during the first 15 days of the SARS-CoV-2 infection (416,417)

Consistent with other investigations, our data demonstrate that CMR for COVID-19 resulted higher in men, older patients, and in specific concomitant comorbid conditions (**article 3**) (412,417–419). In the analysis of the cohort of 3,729 patients with RMD recorded in the C19-GRA registry up to June 2020 (2,315 (62%) from Europe and 1,105 (29.6%) from North America) in which COVID-19-related death was the outcome, the risk of death was associated with age

and comorbidity (420). According to the results obtained, patients who died had a median age older than 80 years (**article 1**), in line with data in general population, where over 95% of deaths occurred in individuals older than 60 years and more than 50% of all deaths were in people aged ≥ 80 years.

In this article, almost two-thirds of the patients had at least one baseline comorbidity and the most prevalent was hypertension, particulars comorbid conditions, such diabetes mellitus, heart disease, ischemic vascular disease, chronic liver disease, renal insufficiency, and lung disease specifically implied a higher risk of mortality (**article 3**). These comorbidities have previously been linked to a higher incidence of severe COVID-19 in RMD patients by the C19-GRA registry and a number of representative cohorts (419,421,422). Nevertheless, the final model in our analysis did not evidence statistical significant association between hypertension and mortality. A possible explanation is a control of this cardiovascular risk factor in the included patients, indicating that hypertension was not as important as the eventual impact of the cardiovascular continuum as represented by ischemic vascular disease, and chronic renal failure on death outcome. No deaths were associated with obesity and smoking; however, these were only reported in few patients in our cohort.

5.3.1 Influence of RMD treatment on mortality related to COVID-19

Patients with RMD and their physicians remain concerned regarding the potential heightened risk of severe COVID-19 due to immunosuppressive treatments needed to control autoimmune disease activity (423). During the pandemic, there has been considerable interest in the severity of COVID-19 and its relationship with exposure to different RMD therapies. Patients on DMARDs remain concerned about the potential risks of severe COVID-19 outcomes, in the meanwhile, a number of DMARDs have been suggested as potential COVID-19 treatments.

In this investigation, csDMARDs or anti-TNF drugs do not seem to be at higher risk of death related to COVID-19 (**article 3**), results that have been similarly published in other cohorts (350,424). Although we are unable to include JAKi or other biologics (others than anti-TNF) in this assumption, because of the limited number of patients using them in our cohort.

The C19-GRA physician-reported registry is one of the largest collection of patients with RMD and COVID-19, in this registry compared with methotrexate monotherapy, most DMARDs were not associated with higher odds of death, although sulfasalazine and rituximab were significant exceptions (370). Specifically, due to the fact that anti-TNF therapy is related with poor humoral immune responses in fatal disease and is overexpressed in patients with severe COVID-19, it has been suggested as a viable treatment for the hyperinflammatory phase

of the disease (425,426). In some registry studies, individuals on baseline TNF inhibitor therapy may also have a decreased risk of experiencing severe COVID-19 outcomes, although this this risk may be mediated by other variables such as adherence to social distancing.

Although we cannot draw firm conclusions from these observational findings, it is interesting to note that in our register less than 30% of patients with COVID-19 and none of the reported deaths were taking NSAIDs as regular treatment (**article 3**), this result may be cautiously in line with the findings of a published systematic review and meta-analysis, which concludes that the exposure to NSAIDs was not associated with SARS-CoV-2 infection, or an excessive risk of hospital admission, death, or serious outcomes in COVID-19 (346,427).

Regarding to the use of glucocorticoid, in this investigation, its exposure was associated to COVID-19-related deaths in the bivariate analysis, but it dropped from the final model (**article 3**). Previous studies have shown that long-term use of corticosteroids might increase the risk of severe COVID-19 and death, however, it is possible that the method by which this variable was collected in our research had an impact on the final result (323,428–431).

In the analysis of the C19-GRA registry, RMD factors that were associated with the risk of death included glucocorticoid use (≥10 mg prednisone equivalent daily), disease activity, rituximab and sulfasalazine use (350). A post hoc analysis's results suggested that underlying disease activity was influencing the risk of COVID-19-related death and that the association between glucocorticoid use and the risk of death might be the result of confounding by indication (432).

The RECOVERY study, however, shows that the corticosteroid benefit effect in COVID-19 is a matter of time use correctly (402). According to this finding, glucocorticoids may not be helpful for people with early-stage or mild illness but are useful in treating patients with severe COVID-19-related respiratory failure, remarkable in our reports (**article 1**), the use of glucocorticoids as part of the treatment was in more than half of the patients.

The registry studies of patients with autoimmune disorders revealed that glucocorticoid use at baseline was related with a higher risk of severe COVID-19, despite the overwhelming evidence from randomized clinical trials, that glucocorticoids are helpful in treating severe COVID-19. This may be because patients with more severe autoimmune diseases may be more likely to be on baseline glucocorticoids, and the severity of the autoimmune disease may put patients at higher risk of severe COVID-19 outcomes rather than the use of glucocorticoids itself. This may be due to confounding by indication in the registry studies. On the other hand, the timing of glucocorticoid exposure may have an impact on the results, making the

administration of glucocorticoids during the COVID-19 virus replication phase detrimental to the immune response.

Overall, in this investigation (**article 3**) DMARDs including biologic, targeted synthetic, and conventional synthetic DMARDs do not appear to be associated with significantly higher risk of fatal COVID-19 outcome in patients with RMD. However, registry studies have raised concerns regarding specific medications, such as sulfasalazine, rituximab, and certain immunosuppressants. Although the use of glucocorticoids, dropped out from the final statistical analysis, in individuals with autoimmune diseases, it uses at baseline is associated with severe COVID-19 outcomes. Given that dexamethasone reduces mortality in severe COVID-19, the finding in patients with autoimmune diseases may be related to the timing of exposure or confounding by indication.

5.3.2 Role of different RMD and death related to COVID-19

COVID-19 has been associated with increased morbidity and mortality globally. Epidemiological studies have investigated COVID-19 in patients with RMD, including the role of different types of autoimmune inflammatory rheumatic diseases, disease course and disease activity.

Early in the pandemic, it was emphasised that well-designed research were required to determine whether individuals with RMD were at elevated risk for COVID-19-related outcomes. According to our data analysis, the risk of death seemed to be similar between CTD, CIA, and non-ARD regardless of other factors (**article 3**). In our study, the CMR for COVID-19 was somewhat higher in patients with ARD compared to non-ARD, and subtly more in CTD however without statistical significance, in accordance with the results published by the French RMD COVID-19 cohort (433).

In South Korea, Youn Ho Shin and colleagues reported a population-based study that provides further real-world evidence of the association between ARD, drugs used to treat these diseases, and COVID-19 (434). The group included 133.609 South Korean patients aged 20 or older, providing an excellent nationwide cohort. They used a South Korean national health insurance claims-based database that was linked to general health examination records. The study included 8297 patients with ARD, including CIA (RA, psoriatic arthritis, and spondyloarthritis) and CTD, including SLE, Sjögren's syndrome, SSc, polymyalgia rheumatica, MCTD, dermatomyositis or polymyositis, polyarteritis nodosa, or vasculitis, based on ICD-10 codes, similar classification methods applied in this investigation (**article 3**) . After exposure-driven propensity score matching, patients with ARD showed an increased likelihood of COVID-19-related death (1.69, 1.01–2.84; p=0·046), compared with the general population.

A Swedish nationwide cohort study (435) revealed that patients with RA had higher COVID-19-associated mortality than people in general, but that patients with other types of inflammatory arthritis did not vary in this regard (including PsA, ankylosing spondylitis, other spondyloarthropathies, or juvenile idiopathic arthritis). Additionally, COVID-19-associated mortality was higher in patients with RA and SSc compared to matched referents from the general population, according to 12-month data derived from the interlinkage of electronic databases covering nearly 99% of the Greek population, or about 11 million people. No difference in mortality was found for SLE, ankylosing spondylitis, or PsA (436). In consonance with this finding in our study, 44 deaths related to COVID-19 during the study period were reported, 54.55% were women with a mean age of 81.61 (7.29) years and ARD was present in 45.45%, including nine patients with RA (**article 3**).

A study of 17 million persons in the UK primary care database examined factors associated with 10.926 COVID-19-related deaths (0.06% of the study population) over the first 3 months of the pandemic and found that the combined group of patients with RA, SLE, or psoriasis were marginally higher odds of COVID-19-related death than the general population (412). This observation is significant, but it is constrained by a frequent limitation of primary care data—the absence of more detailed understanding of the diseases at the individual level.

Contrasting with this, an analysis of more than 31,000 adults in a US electronic medical-record database (TriNetX) found no statistically significant increase in the probability of COVID-19 death for individuals with RMD and a meta-analysis of 13 studies published up to mid-February 2021 found a similar risk of death in people with and without RMD (437), and similar an American multicenter study and a smaller study from France reported equal mortality risk in individuals with or without ARD (438,439). Of note, a meta-analysis of observational or case–control studies, published in November 2021, reported an odds ratio for COVID-19-associated mortality of 1.74 (95% CI 1.08, 2.80) for SRD patients (440).

Putting all the studies mentioned together, the results are still somewhat conflicting. Ethnic discrepancies, including differences in the geoepidemiology and preventive measures implemented for SARS-Cov2, as well as variations in methodology, may be a contributing factor in this. Additionally, data from the Global Rheumatology Alliance Physician Registry for the COVID-19 has demonstrated that race and ethnicity may also be associated with COVID-19-related outcomes (441).

Due to these contrasts, information on current disease activity, particular disease-related comorbidities, and, most importantly, the use of glucocorticoids and/or DMARDs, all of which

are risk factors for significant infection, is crucial because rheumatic diseases are highly heterogeneous (442).

As in our investigation (**article 3**), adjustments for immunosuppressive treatment received were not conducted in most of these studies (443). Besides, rituximab and JAK inhibitors have been linked to an increased risk of COVID-19-related death (358,370,435), and some data also show a relationship between the risk of mortality and the use of various immunosuppressive drugs and/or glucocorticoids above certain dosages (369,370,439,443). Along the same lines, disease activity (for which it is particularly challenging to control in studies utilizing electronic records) has also been suggested as an adverse prognostic factor for COVID-19-related mortality.

Overall, although there is a slight tendency of higher risk of mortality in patients with ARD, there is not enough evidence in our study nor in other investigations, that an autoimmune condition presents a higher risk of death related to COVID-19, and as it has been previously described other factors such as age, comorbid conditions and certain treatments, have more influence in the risk of COVID-19 mortality.

5.4 Firsts months crisis during the COVID-19 outbreak

Wuhan, the capital of China's Hubei Province, reported the first instances of this novel pneumonia in the beginning of December 2019 (433). The novel disease, COVID-19, is characterized by signs and symptoms similar to other respiratory infections: fever, dry cough, myalgia, or fatigue are frequently seen, while sputum production, headache, hemoptysis, and diarrhea are less frequent (394,444). While the majority of patients have favorable outcomes (445,446), some develop severe pneumonia eventually leading to ARDS, respiratory failure, sepsis, and additional organ symptoms (272).

According to the first report of the Chinese Center for Disease Control, around 5% of patients out of 72,314 Chinese patients were critically ill, 14% of them had a severe course, while most patients (81%) presented no or mild pneumonic symptoms (271) . Compared to previous coronavirus outbreaks with SARS-CoV (9%) and MERS-CoV (36%) cases, the overall case-fatality rate was 2.3% (447).

While COVID-19 comorbidities and risk factors for worse outcomes are consistent across international studies, mortality rates vary significantly by country, ranging from 0.06% in Singapore to 18.3% in France (448). Numerous factors, such as disease risk factors and population genetic susceptibility, as well as variations in healthcare delivery (such as the number

of tests performed and criteria for testing) and outcome reporting (specifically, who is counted as deceased due to or with COVID-19), may contribute to this disparity.

At the beginning of the pandemic, there was a concern among rheumatologists globally that patients with rheumatic diseases might be at particular risk for increased morbidity and mortality related to COVID-19. Several studies evaluating the effect of COVID-19 on patients with RMD have been published more than 2 years after the pandemic began, but only a small number of them are of good quality and/or powerful enough to answer these concerns.

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 (415). The IR for hospital admission had been increasing throughout the first month of the study, the IR from 1 March to 15 March was 1.01 per 1000 and for the latter two weeks of March, it was 6.3 per 1000 (**article 2**). Interestingly, patients diagnosed in March had independently more risk of death compared to those diagnosed in April or May (**article 3**). In the absence of a vaccine, the mortality risk decreased after the first month in our report, this might be explained by diverse factors, including the healthcare measures applied during the outbreak and some psychological factors, like the delay in consulting emergency services. Additionally, this fact might have led to selection bias in individuals who didn't need hospital admission. (449–451).

During the pandemic first months, data on COVID-19 patients with underlying RMD emerged mostly in the form of small case series and one global registry. This investigation (**article 1, article 2, and article 3**) contributed at that moment with the preliminary data, where a few parts of the world were still grappling with the pandemic at its peak. Published evidence to guide treatment decisions was lacking and doubts regarding continuation and initiation of immunosuppressants remained.

5.5 Limitations and strength

This study has some limitations, the main ones are those that affect any observational retrospective study in a single center, with data recorded in routine clinical practice, particularly impacted by a high workload environment as a result of COVID-19's first peak. In this sense, rheumatic disease activity, some analytical parameters, or treatment dosage data were not available, variables that may potentially be related to the risk of hospitalization or death from COVID-19.

Regarding to patients with COVID-19 who did not require admission, some contacted with the rheumatology department to report the disease and others were detected through the COVID-19 discharge reports by primary care. Elderly people and homemakers who did not

contact with the department, deaths or severe COVID-19 experienced at home, and patients admitted to other hospitals, can be considered missing data. Although we consider these few cases, we are fully aware that the number of COVID-19 cases could be underestimated. Consequently, there may be some selection bias between those admitted and those not admitted, however, this problem was addressed by adjusting for confounders in the multivariable analysis.

SARS-CoV-2 PCR diagnostic test was not required as a part of the inclusion criteria definition, due to the lack of available tests and extreme healthcare overload at that time, in this sense if we had not included cases with not test, the hospital admission and mortality rate would be overestimated. Nevertheless, all cases included were clinically compatible and managed as COVID-19.

However, the main strength is that this is a real-world setting investigation performed during the peak of the pandemic, in a period of maximum health emergency in Madrid, the epicenter of the COVID-19 pandemic in Spain. The articles conducted were part of the first scientific evidence on the topic with global scope. The thesis includes a representative number of non-selected patients with a wide range of different RMD, sociodemographic, and clinical features, and with no standardized immunosuppressive therapy, reflecting clinical practice through the whole first wave of the pandemic. We analyzed the differences between rheumatic diseases, saw the effect of time in the analysis, and adjusted by confounders factors.

These studies have been pioneers in this matter and their findings have been useful in the development of first recommendations regarding alerts on infection risk, prevention measures, and management in RMD patients.

Thus, we believe, this study contributes to solving gaps of knowledge in the management of patients with RMD and COVID-19, prepares the health system for challenges with similar characteristics, and improves the ongoing patient registries and administrative databases. Our study aimed to shed light on rheumatologists' concerns regarding their patients in those difficult moments.

CHAPTER 6

6 Conclusions

This thesis includes real-world longitudinal studies conducted during the first wave of the COVID-19 pandemic in Madrid, epicenter of the outbreak in Spain, and performed in a period of maximum health emergency. The investigation includes a representative sample size and a spectrum of RMD with different treatments, giving a picture of the situation in patients with RMD infected by SARS-CoV-2.

- Demographic and disease characteristics of individuals with RMD diagnosed with COVID-19 are comparable to those reported by rheumatologic global registries, almost 70% were women with a mean age of 59 years.

- A third of patients with RMD and COVID-19 presented comorbidities, especially cardiovascular risk factors, they were more prevalent in individuals with CTD.

- AIRDs are at an elevated risk of hospitalisation and severe COVID-19 outcomes compared to the reference population, with part of this risk being attributed to comorbidity presence.

- Around forty percent of patients with AIRD and COVID-19 required hospital admission with an incident rate IR of 9.15 per 1000 patient-months.

- Patients who required hospital admission due to COVID-19, were older, median age of 70 years, frequently had baseline comorbidities and systemic autoimmune conditions. The role of age, male sex, and comorbidities in the susceptibility of moderate–severe COVID-19 was corroborated.

- RMD patients exposed to DMARDs, regardless of whether they were conventional synthetic, biological, or targeted synthetic, did not seem to be at higher risk of hospital admission due to COVID-19. DMARDs do not seem to be associated with poor outcomes in RMD.

- The crude IR of hospital admission was higher for those patients on non-TNF biologics, however in the multivariate analysis this difference between biologic agents disappeared.

- The crude IRs of hospital admission resulted higher in those patients on glucocorticoids, and lower in those using NSAIDs, however, none of them remained statistically significant after the multivariate analysis.

- The type of RMD diagnosis appears to play an important role in the probability of hospital admission. Patients with systemic autoimmune conditions seem to have the highest risk compared with chronic inflammatory arthritis.

- Clinical and laboratory findings in RMD patients hospitalized for COVID-19 did not differ from the general population.

- More than half of the RMD patients received glucocorticoids as part of the COVID-19 treatment, and tocilizumab was prescribed in almost 10% of the patients admitted.

- The case fatality rate for COVID-19 was 10.9% in RMD patients, resulted comparable to the reported in Spain general population and to the published in other cohorts of RMD patients during the same period of time.

- The CMR in RMD patients was estimated in 6.8% patients-month and is a phenomenon that appears early in the course of the infection.

- The CMR for COVID-19 resulted higher in older patients (median age older than 80 years), men, and in specific concomitant comorbid conditions. Diabetes mellitus, heart disease, ischemic vascular disease, chronic liver disease, renal insufficiency, and lung disease specifically implied a higher risk of COVID-19 mortality.

- Overall, classes of DMARDs, including csDMARDs and anti-TNF drugs, were not associated with a significantly higher risk of death due to COVID-19 in patients with RMD. We are aware that have raised concerns regarding specific medications, such as rituximab and certain immunosuppressants, drugs that we were not able to analyze separately.

- The use of glucocorticoids was associated to COVID-19-related deaths in the bivariate analysis, however it dropped from the final model. None of the reported deaths were taking NSAIDs as regular treatment for the RMD.

- The CMR for COVID-19 was somewhat higher in patients with ARD compared to non-ARD, and subtly more in CTD however without statistical significance.

- The first contact with COVID-19 represented a difficult health situation in Madrid, CMR decreased over time, mortality risk was lower in April or May compared to March, regardless of other factors.

This thesis based on real-life studies have provided useful insights to increase the knowledge in the management of patients with RMD and COVID-19. The landscape of COVID-19 research is constantly evolving, and recommendations will continue to change over time based on emerging evidence.

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8 Supplementary Material

Supplementary Material 1. **Table S1 Rosser Classification Index**

Rosser	Disability	Distress
1.0	1	A
0.995	1	B
0.990	1	C
0.967	1	D
0.990	2	A
0.986	2	B
0.973	2	C
0.932	2	D
0.980	3	A
0.972	3	B
0.956	3	C
0.912	3	D
0.964	4	A
0.956	4	B
0.942	4	C
0.870	4	D
0.946	5	A
0.935	5	B
0.900	5	C
0.700	5	D
0.875	6	A
0.845	6	B
0.680	6	C
0.0	6	D
0.677	7	A
0.564	7	B
0.0	7	C
-1.486	7	D
-1.28	8	A
*	8	B
*	8	C
	8	D

Supplementary Material 2. Table S2 Disability levels

Code	Description
1	No disability
2	Slight social disability
3	Severe social disability and slight physical disability or decrease in mobility. Slight work impairment. Homemakers can perform house chores except for the heavier ones.
4	” Work alternatives may be limited or present work may be performed with many limitations. Elderly persons and home- makers can perform only light chores but are able to go shopping. Moderate decrease in mobility”
5	” Unable to perform paid work or to continue studying if student. Elderly persons stay at home or go out for short walks accompanied. Inability to go shopping. Home worker can only perform a few chores. Severe decrease in mobility.”
6	” Confined to a chair or a wheelchair. Able to walk at home only with an aid. Almost dependent.”
7	In bed
8	Unconscious

Supplementary Material 3. Table S3 Distress levels

Code	Description
0/A	None (No distress)
1/B	Slight (Mild)
2/C	High (Moderate)
3/D	Very high (Severe)

EPIDEMIOLOGICAL SCIENCE

Risk factors for hospital admissions related to COVID-19 in patients with autoimmune inflammatory rheumatic diseases

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ABSTRACT

Objectives To describe patients with autoimmune inflammatory rheumatic diseases (AIRD) who had COVID-19 disease; to compare patients who required hospital admission with those who did not and assess risk factors for hospital admission related to COVID-19.

Methods An observational longitudinal study was conducted during the pandemic peak of severe acute respiratory syndrome coronavirus 2 (1 March 2020 to 24 April). All patients attended at the rheumatology outpatient clinic of a tertiary hospital in Madrid, Spain with a medical diagnosis of AIRD and with symptomatic COVID-19 were included. The main outcome was hospital admission related to COVID-19. The covariates were sociodemographic, clinical and treatments. We ran a multivariable logistic regression model to assess risk factors for the hospital admission.

Results The study population included 123 patients with AIRD and COVID-19. Of these, 54 patients required hospital admission related to COVID-19. The mean age on admission was 69.7 (15.7) years, and the median time from onset of symptoms to hospital admission was 5 (3–10) days. The median length of stay was 9 (6–14) days. A total of 12 patients died (22%) during admission. Compared with outpatients, the factors independently associated with hospital admission were older age (OR: 1.08; p=0.00) and autoimmune systemic condition (vs chronic inflammatory arthritis) (OR: 3.55; p=0.01). No statistically significant findings for exposure to disease-modifying antirheumatic drugs were found in the final model.

Conclusion Our results suggest that age and having a systemic autoimmune condition increased the risk of hospital admission, whereas disease-modifying antirheumatic drugs were not associated with hospital admission.

Key messages

What is already known about this subject?
- The epidemiological scenario is changing daily. There is little evidence for risk factors of poor outcome with COVID-19 specific to autoimmune inflammatory rheumatic diseases.

What does this study add?
- Patients with an autoimmune systemic condition have a higher risk of hospital admission related to COVID-19 compared with those with chronic inflammatory arthritis.
- Disease-modifying agents were not associated with a higher risk of hospital admission related to COVID-19.

How might this impact on clinical practice or future developments?
- Our data show that, in a real-world setting, a high percentage of patients with autoimmune inflammatory rheumatic diseases and COVID-19 required hospital admission. The patients were mainly elderly, with comorbidities and a systemic autoimmune condition.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a myriad of clinical signs and symptoms, together with typical laboratory abnormalities, that manifest as the disease COVID-19.[1]

Since the confirmation of the first patient infected with SARS-CoV-2 in Spain in January 2020, the current COVID-19 outbreak has had a considerable impact, especially in the Madrid region, where the highest incidence of COVID-19 cases has been recorded, with more than 41 304 patients admitted to the hospital until the first week of May.[2]

The incidence and severity of COVID-19 disease seem to be higher in patients with risk factors, such as advanced age and associated comorbidities, mainly hypertension, diabetes, heart disease and previous respiratory diseases.[3] It is not clear whether patients with rheumatic diseases are more susceptible to SARS-CoV-2 infection, or, when they are infected, whether they have more severe disease or a poorer outcome. Previous outbreaks caused by coronaviruses did not yield overwhelming evidence that patients with rheumatic diseases are at an increased risk,[4] although some patients are candidates for a higher number of infections owing to their rheumatic disease (predominantly systemic) or the treatment they are receiving for rheumatic diseases.[5] Preliminary experiences in patients with COVID-19 show that those with chronic arthritis treated with synthetic conventional or targeted synthetic/biologic disease-modifying antirheumatic

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drugs (DMARDs) do not seem to be at a greater risk of respiratory or life-threatening complications from SARS-CoV-2 than the general population.[6 7]

The epidemiological scenario is changing, and evidence on the risk factors of poor outcome with COVID-19 specific to inflammatory rheumatic disease is scarce. In addition, there are little data on how the hospital admissions of these patients with severe COVID-19 infection have evolved.[8]

The aim of our study was to describe patients with autoimmune inflammatory rheumatic diseases (AIRD) who had COVID-19 during the pandemic peak. We also explored possible risk factors associated with hospital admission related to COVID-19 disease in patients with AIRD from a tertiary hospital in Madrid, Spain.

METHODS

Setting, study design and patients

The study was performed in a public tertiary hospital, Hospital Clínico San Carlos (HCSC), in Madrid, Spain. The catchment area is home to almost 400 000 people.

We performed a prospective observational study from 1 March 2020 (when our health area had the first hospital admission related to COVID-19) to 24 April 2020. We preselected all patients attended at the rheumatology outpatient clinic of our centre during the study period whose data were recorded in the electronic clinical history of our department (HCR Penelope). The inclusion criteria were age >16 years, a medical diagnosis (according to International Classification of Diseases (ICD-10)) of inflammatory rheumatic disease and symptomatic COVID-19 disease assessed by medical diagnosis or confirmed with a positive SARS-CoV-2 PCR diagnostic test.

Patient data were obtained during routine clinical practice. The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice and was approved by the HCSC Ethics Committee (approval number 20/268-E-BS).

Variables

The primary outcome was admission to hospital with a medical diagnosis of COVID-19 and/or a positive PCR result between 1 March and 15 April compared with outpatients with symptomatic COVID-19 disease.

The covariables recorded were as follows: (1) sociodemographic baseline characteristics including sex, age and rheumatic disease duration. (2) Type of AIRD, including systemic autoimmune conditions (polymyalgia rheumatica, mixed connective tissue disease, systemic sclerosis, Sjogren's syndrome, vasculitis, Raynaud phenomenon, polymyositis, polychondritis, sarcoidosis, antiphospholipid syndrome, autoinflammatory syndromes and systemic lupus erythematosus) and chronic inflammatory arthritis (rheumatoid arthritis, inflammatory polyarthritis, juvenile idiopathic arthritis, psoriatic arthritis, axial spondyloarthritis, uveitis and inflammatory bowel disease). (3) Baseline comorbid conditions, including hypertension, dyslipidaemia, depression, diabetes mellitus, smoking habit, kidney disease, chronic liver disease, respiratory diseases (chronic obstructive pulmonary disease and interstitial lung disease), thyroid disease, heart disease (valve disease, arrythmias, cardiomyopathy, heart failure and pericarditis), ischaemic vascular disease (stroke, cardiovascular and peripheral vascular disease), venous thrombosis/lung embolism and cancer. (4) Treatment for inflammatory rheumatic disease: (a) glucocorticoids, (b) nonsteroidal anti-inflammatory drugs (NSAIDs), (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 (ts/bDMARDs) including: (1) antitumour necrosis factor (TNF)-alpha drugs (infliximab, adalimumab, etanercept, certolizumab and golimumab); (2) other biologics: anti-interleukin (IL)-6 (tocilizumab and sarilumab); rituximab; abatacept; belimumab; anti-IL-17/23; anti-IL-17 (ustekinumab, ixekizumab and secukinumab); (3) Janus kinase (JAK) inhibitors (tofacitinib and baricitinib).

Treatment had to start at least 1 month before the beginning of the study and continue during the study period until the end of the study or hospital admission for antimalarial therapy, glucocorticoids, sulfasalazine, NSAIDs or colchicine. Regarding csDMARDs and ts/bDMARDs, treatment had to start at least 1 month before the beginning of the study and continue until at least 21st March, the end of the study or hospital admission. In the case of rituximab, the last infusion had to be at least in January.

Data sources

Patient sociodemographic, clinical, laboratory and data on treatment of rheumatic disease were obtained through HCR Penelope.

Patients with COVID-19 were detected by warning calls to our rheumatologists or nurses or via routine telephone consultation. Other infected patients were detected through their sick leave forms for COVID-19. The results of SARS-CoV-2 PCR diagnostic assays were obtained from the microbiology/infectious service of HCSC. In addition, our Hospital Central Services registered all medical admissions to HCSC. This information was provided from 1 March to 15 April.

The researchers carried out an exhaustive review of the clinical histories of admitted patients to identify COVID-19 cases and rule out patients admitted for other reasons. Once the COVID-19 cases were identified, we collected clinical, laboratory and treatment data during admission until the end of admission (either discharge or death) in order to describe the progress of the disease. The review was performed until 24th April in order to include follow-up data from patients admitted to the hospital with COVID-19.

Statistical analysis

Patient characteristics are expressed as mean and SD or median and IQR for continuous variables; categorical variables are expressed as percentages. Statistical tests were performed to compare characteristics between patients admitted with COVID-19 and those without hospital admissions. Continuous variables were analysed using the Mann-Whitney test or t-test, and discrete variables were analysed using the χ^2 or Fisher exact test. Univariable logistic regression analyses were performed to assess differences between hospital admissions related to COVID-19 risk and covariates. Multivariable logistic regression models (adjusted for age, sex and comorbidity) were run in a stepwise manner to examine the possible effect of sociodemographic, clinical and therapeutic factors on hospital admissions related to COVID-19 The model also included csDMARDs and all other variables with a $p<0.2$ from the simple regression analysis. The results were expressed as the OR with its respective 95% CI.

All analyses were performed in Stata V.13 statistical software (Stata Corp). A two-tailed p value <0.05 was considered to indicate statistical significance.

RESULTS

A total of 123 patients with AIRD with symptomatic COVID-19 disease were included in the study (table 1). The tests were performed as an exploratory measure of the association between a variable and the outcome.

Most of the patients were women, with a mean age of 59.88 (14.9) years and a mean time since diagnosis of 10.65 (8.31) years. The main diagnosis was rheumatoid arthritis (40.65%), followed by axial spondyloarthritis (14.63%). Many patients had at least one baseline comorbid condition, the most prevalent being hypertension, dyslipidaemia and lung disease. Most patients were taking csDMARDs (71.54%). Half of the patients were taking glucocorticoids (49.59%), a quarter were taking NSAIDs (24.39%) and 21.14% were taking ts/bDMARDs, of which adalimumab was the most frequently prescribed (6.50%), followed by rituximab (4.07%). Only one patient was taking a JAK inhibitor. Interestingly, 14.63% of the patients taking ts/bDMARDs were taking the drug in combination with a csDMARD.

A total of 54 patients had to be admitted to the hospital because of COVID-19. Of these, 51 were evaluated in the HCSC Emergency Department (49 were admitted to HCSC and 2 were transferred to the Institucion Ferial de Madrid (IFEMA) support hospital owing to the lack of capacity in our hospital at that time). The remaining three patients were evaluated and admitted to other hospitals in the Autonomous Community of Madrid. Table 2 presents data for the 51 patients admitted to HCSC.

Of the patients admitted to our hospital, 59.2% were women, with a mean age at admission of 69.7 (15.7) years and median lag time from the onset of symptoms to the admission of 5 (3–10) days. The median length of stay was 9 (6–14) days (table 2).

At admission, the median haemoglobin was 12.9 (12.4–13.8) g/dL and the median total lymphocyte count was 700 (500–1200) ng/mL. The median D-dimer value was 727 (487–1091) ng/mL. In 10% of patients, median interleukin (IL)-6 levels were 213 (43–383) pg/mL. Patients received various antibiotics (mainly azithromycin, levofloxacin and third-generation cephalosporins).

Most patients were treated with hydroxychloroquine during admission (86%). About half received glucocorticoids (52%). Eighteen were treated with lopinavir/ritonavir and 3 received the anti-IL-6R antibody tocilizumab (table 2).FEDER

A total of 20 patients (44%) developed relevant complications during admission, the most frequent being myocarditis, thrombosis and kidney failure. Only two patients were admitted to the intensive care unit during admission. The first was a patient in 50s with mixed connective tissue disease and associated comorbidities who developed acute respiratory insufficiency and bilateral pneumonia. The patient was treated with antibiotic therapy, lopinavir/ritonavir, hydroxychloroquine and β-interferon. Finally, the patient was extubated 40 days later and is recovering. The other was a young adult patient with systemic lupus erythematosus treated with methotrexate, rituximab, hydroxychloroquine and glucocorticoids, who, days after being diagnosed with COVID-19 (PCR+), developed an erythematous rash and generalised urticaria requiring hospitalisation in the intensive care unit owing to general clinical and laboratory worsening (elevated D-dimer values). The patient was treated with methylprednisolone, heparin and a cephalosporin. A few days later, the patient's condition improved and he recovered completely at discharge.

Of the 49 patients admitted to HCSC, 5 were sent to another care centre (converted-hotel hospital/IFEMA support hospital) when their condition improved. A further 29 patients (53.7%) were discharged home to continue self-isolation after improvement. At the end of the study, five patients remained in hospital (9.26%). A total of 12 patients died (22%) during admission (6 men and 6 women), with a median age of 81 (76.5–87) years. Of the patients who died, 87% had relevant comorbidity (diabetes mellitus, pulmonary disease, ischaemic vascular disease, hypertension, venous thrombosis/lung embolism, lung disease and or liver disease). The main diagnoses were rheumatoid arthritis (6), followed by spondyloarthritis (2), polymyalgia rheumatica (2), vasculitis (1) and Sjogren's syndrome (1).

The results of the univariable analysis are shown in table 3. Older age, systemic autoimmune conditions (vs chronic inflammatory arthritis) (OR: 2.65; 95% CI 1.22–5.7, p=0.014), hypertension, diabetes mellitus, lung disease, heart disease and glucocorticoids were associated with statistically significant greater risk of admission to the hospital. Female sex, NSAIDs and anti-TNF drugs (vs non-use) were associated with a statistically significant lower risk. The differences reported for the remaining variables did not reach statistical significance.

The multivariable analysis was adjusted for gender, age and comorbidities related to COVID-19. These comorbidities were diabetes mellitus, pulmonary disease, ischaemic vascular disease, hypertension, venous thrombosis/lung embolism, lung disease and/or liver disease (table 4). Age and systemic autoimmune conditions had more probability of hospital admissions, regardless of other factors. Differences in exposure to glucocorticoids were not statistically significant. The type of exposed DMARDs did not reach statistical significance in the multivariate model. In fact, long-term treatment with antimalarials (OR: 0.76; 95% CI 0.26–2.53; p=0.66), other csDMARDs (including methotrexate, leflunomide and azathioprine) (OR: 0.95; 95% CI 0.36–2.51; p=0.9) and NSAIDs (OR: 1.49; 95% CI 0.42–5.23; p=0.5) dropped from the final model. The variable ts/bDMARDs was also eliminated from the final model (anti-TNF vs none: OR: 0.29; 95% CI 0.05–1.66; p=0.16; and non-anti-TNF vs none: OR: 2.21; 95% CI 0.47–10.2; p=0.3).

DISCUSSION

Our study aims to shed light on rheumatologists' concerns regarding their patients. We found that, in a real-world setting, 44% of patients with AIRD and COVID-19 required hospital admission. These were mainly elderly patients, with more comorbidities and systemic autoimmune conditions. Our data show that patients exposed to disease-modifying agents do not seem to be at higher risk of hospital admission related to COVID-19.

Of the 123 patients included in the study with COVID-19, 54 required hospital admission. Comparison of the characteristics of patients admitted to hospital because of COVID-19 and those who did not require hospital admission were as follows: admitted patients had a median age close to 70 years, that is, more than 15 years older than patients who were not admitted. Moreover, those who were admitted more frequently had baseline comorbidities and systemic autoimmune conditions. As for therapy, admitted patients were less frequently exposed to antimalarial and anti-TNF-alpha agents.

The median lag time from onset of symptoms to admission was 5 days, and almost 90% of patients had pneumonia at admission. The baseline laboratory results for admitted patients in our study are consistent with those published elsewhere[9–12] and are characterised by lymphopenia and elevated acute-phase reactants. In fact, 75% of the patients had elevated D-dimers (normal, <500) and elevated IL-6 (normal, <7 pg/mL). Treatment during admission varied widely as the disease proved

Table 1 Baseline demographic and clinical characteristics of patients with AIRD and with COVID-19 (admitted vs no admitted at the hospital)

Variable	AIRD–COVID-19 patients (N=123)	AIRD–COVID non-admitted patients (N=69)	AIRD–COVID admitted patients (N=54)	P value
Women, n (%)	86 (69.92)	54 (78.26)	32 (59.26)	0.02
Age (years), mean (SD)	59.88 (14.90)	52.91 (9.58)	68.78 (15.79)	0.0001
Time since diagnosis (years), mean (SD)	10.65 (8.31)	10.37 (7.99)	11 (8.77)	0.8
PCR test, n (%)				0
Positive	58(47)	17(25)	41(76)	
Negative	3 (2)	0	3 (5)	
Not performed	62(51)	52(75)	10 (19)	
Smoking habit (active vs none)	4 (3.25)	1 (1.45)	3 (5.56)	0.31
Diagnosis (AIRD), n (%)				0.01
Rheumatoid arthritis	50 (40.65)	32 (46.38)	18 (33.33)	
Axial spondyloarthritis	18 (14.63)	11 (15.94)	7 (12.96)	
Polymyalgia rheumatica	6 (4.88)	0	6 (11.11)	
Psoriatic arthritis	6 (4.88)	3 (4.35)	3 (5.56)	
Systemic lupus erythematosus	8 (6.50)	6 (8.70)	2 (3.70)	
Mixed connective tissue disease	6 (4.88)	2 (2.90)	4 (7.41)	
Sjogren's syndrome	9 (7.32)	5 (7.25)	4 (7.41)	
Vasculitis	2 (1.63)	0	2 (3.70)	
Uveitis	1 (0.81)	1 (1.45)	0	
Systemic sclerosis	1 (0.81)	0	1 (1.85)	
Inflammatory polyarthritis	8 (6.50)	6 (8.70)	2 (3.20)	
Polychondritis	1 (0.81)	0	1 (1.85)	
Polymyositis	1 (0.81)	0	1 (1.85)	
Raynaud phenomenon	3 (2.44)	0	3 (5.56)	
Other*	3 (2.44)	3 (4.35)	0	
Comorbidities, n (%)				
Hypertension	40 (32.52)	14 (20.29)	26 (48.15)	0.002
Dyslipidaemia	27 (21.95)	12 (17.35)	15 (27.38)	0.19
Depression	9 (7.32)	8 (11.59)	1 (1.85)	0.039
Diabetes mellitus	17 (13.82)	4 (5.80)	13 (24.07)	0.007
Heart disease	15 (12.20)	5 (7.25)	10 (18.52)	0.09
Vascular disease	8 (6.50)	2 (2.90)	6 (11.11)	0.13
Liver disease	7 (5.69)	3 (4.35)	4 (7.41)	0.69
Kidney disease	6 (4.88)	0	6 (11.11)	0.006
Lung disease (ILD/COPD)	19 (15.45)	6 (8.70)	13 (24.07)	0.02
Cancer	5 (4.07)	1 (1.45)	4 (7.41)	0.16
Venous thrombosis/lung embolism	3 (2.44)	0	3 (5.56)	0.08
Thyroid disease	17 (13.8)	12 (17.39)	5 (9.26)	0.29
NSAIDs, n (%)	30 (24.39)	22 (31.88)	8 (14.81)	0.03
Glucocorticoids, n (%)	61 (49.59)	29 (42.03)	32 (59.26)	0.07
csDMARDs, n (%)				
Methotrexate–leflunomide–azathioprine	68 (55.28)	40 (57.97)	28 (51.85)	0.49
Sulfasalazine	9 (7.32)	5 (7.25)	4 (7.41)	0.97
Antimalarials	27 (21.95)	18 (26.09)	9 (16.67)	0.21
Ts/bDMARDs, n (%)	26 (21.14)	19 (27.54)	7 (12.96)	0.04
Anti-TNF-alpha agent	17 (13.82)	15 (21.74)	2 (3.70)	0.004
Other biologics	9 (7.32)	4 (5.80)	5 (9.26)	0.4
Abatacept	1 (0.81)	1 (1.45)	0	0.99
Tocilizumab	2 (1.63)	1 (1.45)	1 (1.85)	0.99
Belimumab	1 (0.81)	1 (1.45)	0	0
Rituximab	5 (4.07)	1 (1.45)	4 (7.41)	0.16
JAKi, n (%)	1 (0.89)	0	1 (2)	0.43

*Others: inflammatory bowel disease, antiphospholipid syndrome, juvenile idiopathic arthritis, autoinflammatory syndromes and sarcoidosis.
†Heart disease: arrhythmias,valve disease, cardiomyopathy and heart failure. Ischaemic vascular disease: stroke, cardiovascular and peripheral vascular disease.
AIRD, autoimmune inflammatory rheumatic disease; Anti-TNF, tumour necrosis factor-alpha; COPD, chronic obstructive pulmonary disease; csDMARD, conventional synthetic disease-modifying antirheumatic drug; ILD, interstitial lung disease; JAKi, JAK inhibitor; ts/bDMARDs, target synthetic/biologic disease-modifying antirheumatic drug.

Table 2 Hospital admissions related to COVID-19 among patients with AIRD

Variable	Value
Admissions, n	54
Lag time from onset of symptoms to admission (days), median (IQR)	5 (3–10)
Pneumonia at admission, n (%)	47 (87)
Systemic autoimmune conditions, n (%)	24 (44.4)
Laboratory data at admission, median (IQR)	
Haemoglobin (g/dL)	12.9 (12.4–13.8)
D-dimer (ng/mL)	727 (487–1091)
Neutrophil count (×10^9/L)	4500 (3500–5700)
Lymphocyte count (×10^9/L)	700 (500–1200)
CRP (mg/dL)	9.19 (2.9–14.6)
LDH (U/L)	618 (489–919)
Platelet count (×10^9/L)	199 000 (158 000–267 000)
Creatinine (mg/dL)	0.86 (0.76–1.28)
Ferritine (ng/mL)	319 (151–885)
COVID-19-related treatments during admission*, n (%)	
Azithromycin	17 (34)
Other antibiotics	29 (58)
Glucocorticoids	26 (52)
Lopinavir/ritonavir	18 (6)
Remdesivir	0
Darunavir/cobicistat	4 (8)
Tocilizumab	3 (6)
Interferon	4 (8)
HCQ	43 (86)
Immunoglobulin	0
Admitted by intensive care unit during hospital admission	
No	52 (96.29)
Yes	2 (3.71)
Length of stay (days), median (IQR)	9 (6–14)
Discharge reason, n (%)	
Improvement, home isolation	29 (53.70)
Other care centre (medicalised hotel/IFEMA hospital)	8 (14.82)
Death	12 (22.22)
End of study (no discharge)	5 (9.26)

*Data for 50 patients (4 patients were treated in other support centres after referral or admission in other centres).
CRP, C reactive protein; HCQ, hydroxychloroquine; LDH, lactate dehydrogenase.

Table 3 OR of hospital admission related to COVID-19 in patients with AIRD (univariable analysis)

Variable	OR	95% CI	P
Gender, women	0.4	0.18–0.988	0.02
Age (years)	1.09	1.05–1.14	0
Diagnosis (AIRD: one category vs the rest)*			
Rheumatoid arthritis	0.57	0.27–1.20	0.14
Inflammatory polyarthritis	0.4	0.07–2.08	0.27
Systemic lupus erythematosus	0.4	0.07–2.08	0.27
Psoriatic arthritis	1.29	0.25–6.68	0.7
Spondyloarthritis	0.78	0.28–2.18	0.64
MTCD	2.68	0.47–15.2	0.26
Sjogren syndrome	1.02	0.26–4.01	0.93
Disease duration	1.01	0.96–1.05	0.67
Smoking habit (active vs none)	3.99	0.40–39.58	0.23
Comorbidities (yes)			
Hypertension	3.64	1.65–8.06	0.001
Dyslipidaemia	1.82	0.77–4.32	0.17
Depression	0.14	0.01–1.18	0.07
Diabetes mellitus	5.15	1.5–16.8	0.007
Heart disease	2.9	0.93–9.09	0.06
Vascular disease	4.18	0.81–21.64	0.09
Liver disease	1.76	0.37–8.22	0.47
Kidney disease	1	–	–
Lung disease (ILD/COPD)	3.32	1.17–9.45	0.02
Cancer	5.4	0.58–50.1	0.13
Venous thrombosis/lung embolism	1	–	–
Thyroid disease	0.48	0.15–1.47	0.2
NSAIDs	0.37	0.15 –0.91	0.03
Glucocorticoids	2.01	0.97–4.13	0.05
csDMARDSs			
Methotrexate–leflunomide–azathioprine	0.78	0.38–1.59	0.49
Sulfasalazine	1.02	0.26–4.01	0.97
Antimalarial agents	0.56	0.23–1.38	0.21
Ts/bDMARDs	0.39	0.15–1.01	0.05
None	1	–	–
Anti-TNF agents	0.13	0.03–0.63	0.01
Other biologics	1.65	0.46–6.49	0.46
JAKis	1	–	–

Other biologics: anti-IL-6 (tocilizumab, sarilumab); rituximab (Rtx); anti-IL-17/23; anti-IL-17.
*Othercategories could not be represented: polymalgia rheumatica, systemicsclerosis, vasculitis, Raynaud phenomenon, polychondritis, Behçet disease,polymyositis, uveitis inflammatory boweldisease, antiphospholipid syndrome, juvenile idiopathic arthritis, autoinflammatorysyndromes and sarcoidosis.
AIRD, autoimmune inflammatory rheumatic disease; anti-TNF, tumour necrosis factor; csDMARD, Conventional synthetic disease-modifying antirheumatic drug; IL-6, interleukin-6; JAKi, JAK inhibitors; ts/bDMARDs, target synthetic/biologic disease-modifying antirheumatic drug.

challenging for specialists, who prescribed various combinations of drugs based on little published evidence. In this sense, the anti-IL-6R antibody tocilizumab has proven to be beneficial in patients with COVID-19.[12] Treatment may also be successful in the early stages of cytokine release syndrome, if it can effectively block the signal transduction pathway of IL-6; therefore, tocilizumab and sarilumab are likely to emerge as effective drugs for patients with moderate to severe COVID-19.[13 14] In our study, almost 10% of the patients were treated with tocilizumab.

The patients who eventually died had a median age of >80 years. This finding is in line with data for the general population, where over 95% of deaths occurred in persons >60 years and more than 50% of all deaths were in people aged ≥80 years.[7]

The multivariable regression model showed that only age (increasing by 8% per year) and systemic autoimmune conditions continued to be risk factors for hospital admission related to COVID-19.

As for the association between sex and risk of hospital admission, we did not find a higher risk of admission in women, despite the fact that rheumatic diseases are more prevalent in this group. The type of diagnosis seems to play an important role in the probability of hospital admission, and patients with systemic autoimmune conditions seem to have the highest risk compared with chronic inflammatory arthritis.

As it has been reported elsewhere, comorbidities play an important role in the risk of hospital admission.[15] Clinical outcomes are poorer in patients with COVID-19 with a comorbid condition than in those without, and a greater number of comorbidities correlates with poorer clinical outcomes.[16] Diabetes is a major comorbidity in COVID-19, and patient's history of diabetes is an independent risk factor for morbidity and mortality in this condition.[17 18] Diabetes has been associated with admissions to

Table 4 Multivariable analysis. risk factors for hospital admission related to COVID-19 in patients with AIRD

Variable	OR	95% CI	P value
Gender, women	0.45	0.15–1.29	0.14
Age (years)	1.08	1.04–1.13	0
AIRD (systemic autoimmune conditions vs chronic inflammatory arthritis)	3.55	1.30–9.67	0.01
COVID comorbidities (yes)	1.82	0.69–4.80	0.22
Glucocorticoids	1.97	0.77–5.01	0.15

Systemic autoimmune conditions (polymyalgia rheumatica; mixed connective tissue disease, systemic sclerosis, Sjogren's syndrome, vasculitis, Raynaud, polymyositis polychondritis, sarcoidosis, antiphospholipid syndrome; autoinflammatory syndromes and systemic lupus erythematosus) vs chronic inflammatory arthritis (rheumatoid arthritis; inflammatory polyarthritis; juvenile idiopathic arthritis, psoriatic arthritis, axial spondyloarthritis, uvetis and inflammatory bowel disease). Comorbidities including the presence of at least one of the follows: hypertension, heart disease, vascular disease, diabetes mellitus, venous thrombosis/lung embolism, chronic kidney disease, liver disease and lung disease (ILD/COPD). AIRD, autoimmune inflammatory rheumatic disease; ;COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease.

the intensive care unit due to COVID-19 in recent series[19 20] and has been shown to increase mortality.[6] Therefore, we adjusted for comorbidity in the multivariable analysis.

Treatment with glucocorticoids lost its statistical significance in the multiple regression model. However, the dose was not reported in our data, and in the case of these agents, the risk could be dose-dependent. In a recent publication from a European registry, the authors found that exposure to >10 mg/day was associated with a greater probability of hospitalisation.[21]

The exposure to DMARDs, regardless of whether they were biological or synthetic, does not seem to be associated with a higher hospital admission related to COVID-19. Although we have to consider the limited number of patients in our study, our results are in concordance with data reported elsewhere.[8 20]

Our results should be interpreted taking into account other limitations. First, patients were included from a single centre. Second, of all the patients with COVID-19 19 who did not require admission, one-third contacted the rheumatology service to report the disease and the remainder were detected through the COVID-19 discharge reports sent to their primary care physician. Elderly persons and homemakers who did not contact us can be considered missing. Consequently, there may be some selection bias between those admitted and those not admitted, although this problem was addressed by adjusting for confounders in the multivariable analysis. Third, while it is acknowledged that clinical suspicion must be confirmed by PCR assay, almost 20% of patients admitted did not undergo PCR owing to the lack of tests or the extreme healthcare overload. Nevertheless, all cases included were clinically compatible and managed as COVID-19.

The key strength of our study is that it was performed in real-life conditions during then pandemic peak, with access to complete sociodemographic and clinical data from our rheumatology electronic clinical history, including thorough hospital admission data such as laboratory abnormalities and COVID-19 treatment data from the hospital computer services. Consequently, this has allowed us to analyse the risk of hospital admission related to COVID-19 adjusted for confounders, thus avoiding possible bias.

Although we are unable to modify the factors reported here, knowing them can help rheumatologists to treat and advise their patients during this new and challenging period. Results provided by our study are preliminary and should be corroborated with other real-life studies, but we consider our findings helpful to increase the knowledge in the management of patients with AIRD and COVID-19.

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Contributors BF-G, LL, JAJ, LR-R and LA conceived and designed the study. DDFN, JFU, AMG, JIC and LL collected data. LA and LL performed the data analysis and interpreted the data. All of the authors were involved in the drafting and/or revising of the manuscript.

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Patient consent for publication Not required.

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

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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.

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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

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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 ⩾ 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).

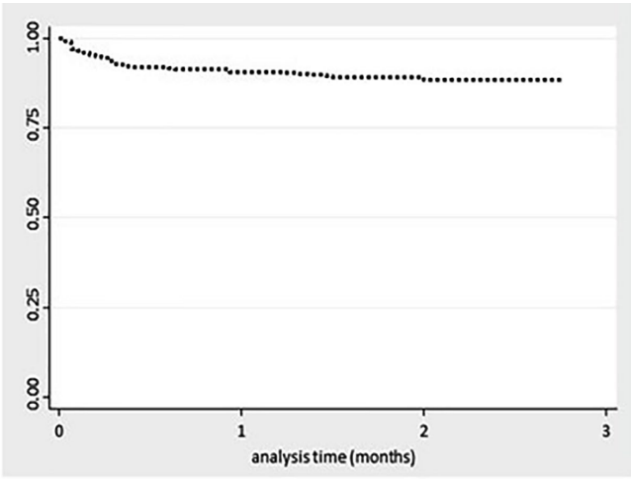

Figure 1. Cumulative incidence of deaths related to COVID-19 over time in patients with RMD during the study period. Kaplan–Meier survival estimate curve.

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.

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

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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.

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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.

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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.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	Retrospective observational study
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3	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.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5	Included in introduction section
Objectives	3	State specific objectives, including any prespecified hypotheses	5,6	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. To 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				
Study design	4	Present key elements of study design early in the paper	6	Retrospective observational study
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6	Patients attended in a rheumatology outpatient clinic of tertiary hospital in Madrid, during the first wave of the COVID-19 pandemic from March 1st to May 20th, 2020.

Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6	The inclusion criteria were patients older than 16 years old with a medical diagnosis of RMD and diagnosed with COVID-19 according to a medical diagnosis and/or confirmed with a positive SARS-CoV-2 PCR diagnostic test. All patients were included since the date of COVID-19 diagnosis until death or end of study (May 20th). Patient data were obtained during routine daily clinical practice through EHR Penelope.
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7	The main outcome was mortality related to COVID-19 in patients with RMDs. The independent variable was type of RMD: (a) Autoimmune Rheumatic Diseases (ARD), including (a1) chronic inflammatory arthritis (CIA) and (a2) connective tissue diseases (CTD) and b) Non-Autoimmune Rheumatic Diseases (non-ARD)

				The covariables recorded at baseline were the following: 1) sociodemographic characteristics 2) Disability 3) Comorbid conditions: 4) Erythrocyte Sedimentation Rate 5) Stable treatments for RMDs and 6) COVID-19 diagnosis date.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	NA	
Bias	9	Describe any efforts to address potential sources of bias	7,8	- Erythrocyte Sedimentation Rate (ESR) as a surrogate variable of disease activity (mean value, at least three months previous of COVID-19 infection). However, we had almost 60% of missing data, not being possible to use this data. - All treatments were considered stable in terms of prescription and dose at least one month prior the diagnosis of COVID-19. -Multivariate models were performed adjusted for age, sex, comorbidity related to COVID-19, and calendar time
Study size	10	Explain how the study size was arrived at	6	We performed a retrospective observational and we preselected all patients attended at our rheumatology outpatient clinic during the study period whose data were recorded in our departmental

		electronic health record (EHR Penelope).

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7,8	Included in covariables and statistical section
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8	A descriptive analysis was performed for the sociodemographic and clinical characteristics of the study population and for the main outcome. 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 $\chi 2$ 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), survival over time was evaluated using Kaplan-Meier curves. Cox regression analysis was conducted to determine the risk factors for death related to COVID-19.
		(*b*) Describe any methods used to examine subgroups and interactions	NA	
		(*c*) Explain how missing data were addressed		Data was obtained from clinical practice. We had almost 60% of missing data on Erythrocyte Sedimentation Rate (ESR) not being possible to use this data. Rest of variables were complete.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	NA	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy		
		(*e*) Describe any sensitivity analyses	NA	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA	
		(b) Give reasons for non-participation at each stage	NA	
		(c) Consider use of a flow diagram	NA	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA	
		(b) Indicate number of participants with missing data for each variable of interest	NA	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA	
		Cross-sectional study—Report numbers of outcome events or summary measures	NA	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8,9,10	Unadjusted estimates are included in table 3 and results section. Adjusted estimates are included in table 4 and results section.
		(*b*) Report category boundaries when continuous variables were categorized	8,9,10	Reported in table 2-5.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA	
Discussion				
Key results	18	Summarise key results with reference to study objectives	10,11	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 vs CIA nor CTD vs non-ARD. Age, certain comorbidities, and being diagnosed in March compared to April/May (HR: 2.43 [1.1-5.55]) increased the mortality risk. Glucocorticoids and DMARDs dropped from the final model.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12	Limitations are those that affect any observational retrospective study in a single center. SARS-CoV-2 PCR diagnostic test was not required as a part of the inclusion criteria definition.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10,11,12	It seems that predisposition for COVID-19 fatal outcome is, at expenses of age and certain comorbidities, as 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, health care, social and political measures

Supplementary Material 7. Response to correspondence one

Response to: 'Correspondence on 'Risk factors for hospital admissions related to COVID-19 in patients with autoimmune inflammatory rheumatic diseases" by Schulze-Koops *et al*

We appreciate the interest of Dr Schulze-Koops and colleagues in our article.[1] The role of the inflammatory rheumatic diseases (IRDs), their therapies and other potential factors in the risk of SARS-CoV-2 infection and course of COVID-19 disease are a topic in a constant update. In this sense, we consider that our study provides additional evidence in patients with IRD regarding susceptibility to moderate-severe infection related to COVID-19.[2]

It is important to note that SARS-CoV-2/COVID-19 is a very changing epidemiological scenario. Our manuscript is a real-world longitudinal study performed during the period of maximum health emergency due to the COVID-19 pandemic in Madrid, the epicentre of the outbreak in Spain. We included all patients with IRD, attended and followed-up at the rheumatology outpatient clinic of our centre with clinical symptoms of COVID-19 during the study period. Our main results showed that 44% of them required hospital admission, mainly at the expense of systemic autoimmune diseases rather than chronic inflammatory arthritis. In addition, we corroborated the role of advanced age and certain comorbidities as important risk factors of moderate-severe COVID-19.[3] Regarding therapies, we did not found association between exposition to disease-modifying agents and more risk of hospital admission related to COVID-19.[4–7]

Our key messages are in consonance with the different professional societies' guidance for the management of patients with IRD during the SARS-CoV-2/COVID-19 pandemic, which have recommend maintaining treatment with disease-modifying agents in the absence of infection or unknown COVID-19 exposure.[8–11]

We fully agree with Dr Schulze-Koops and colleagues that patients with IRDs and COVID-19 have a high risk of hospitalisation due to parameters that cannot be easily influenced. In this sense and due to the novelty and the impact of the pandemic, a well disease control and a close monitoring carried out by the rheumatologist and team is mandatory, as well as a strict adherence to the hygiene, mask-wearing and social distance measures of patients with rheumatic disease.[8–11]

Finally, the authors contemplate that all their comments were very accurate and in line with our results. Therefore, until more definite data are available, the authors consider that SARS-CoV-2 infection should be carefully avoided in patients with IRD.

To conclude, we appreciate the opportunity to share our experience regarding risk factors for hospital admissions related to COVID-19 in patients with IRD,[2] hoping this article can be a step to improve gaps of knowledge, and thus help clinicians in the management of these patients.

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Correspondence response

Response to: 'Correspondence on 'Risk factors for hospital admissions related to COVID-19 in patients with autoimmune inflammatory rheumatic diseases" by Aydin *et al*

We appreciate the interest of Aydin *et al*[1] in our study about risk factors for hospital admissions related to COVID-19 in patients with inflammatory rheumatic diseases (IRD).[2] COVID-19 pandemic is a matter in constant update and certainly an enormous challenge for researchers, clinicians, healthcare workers and epidemiologists. In this sense, all together are making enormous efforts in their fields to overcome this global crisis. In relation to research advances, there has been an explosion in the publication of articles related to COVID-19. In this pandemic situation, it is true that it has been a challenge and a race against the clock for researchers and some publications could be less rigorous than expected.[3] For this reason, and according to Aydin *et al*,[1] the critical reading it is important to interpret the results, paying special attention to the limitations of each study.

The role of IRD, their therapies and other potential factors in the risk of SARS-CoV-2 infection and course of COVID-19 disease is a topic of major interest for health professionals in rheumatology and rheumatic patients. Similar to previous research, we concluded that patients with an autoimmune systemic condition have a higher risk of hospital admission related to COVID-19 compared with those with well-controlled chronic inflammatory arthritis in a real-world setting. Those patients were mainly elderly and with certain comorbidities. Regarding therapies, our data show that patients exposed to disease-modifying agents do not seem to be at higher risk of hospital admission related to COVID-19.[2 4–7]

The first concern of Aydin *et al*[1] regarding to the way of COVID-19 infectious status confirmation and that it was not clearly explained in the study and that might generate confusion. It is important to note that SARS-CoV-2/COVID-19 is a very changing epidemiological scenario. Our manuscript is a real-world longitudinal study performed during the period of maximum health emergency due to the first wave pandemic COVID-19 in Madrid, epicentre of the outbreak in Spain. In consonance with other similar studies,[8] PCR tests were not performed at primary care and they were only carried out in hospitals at the emergency room or once the patient was admitted. At emergency room, the patient was evaluated, and PCR test was performed if they were available. The patient was discharged or admitted based on patient's health situation and clinical parameters regardless to the PCR test result that was obtained 24–72 hours later. In this sense, the decision to admit a patient was not affected by the positive test itself. Therefore, we did not consider necessary the inclusion of this parameter in the multivariate analysis. Moreover, with such a high percentage of missing values in PCR test, it was not a variable candidate for such analysis.

The second concern of Aydin *et al*[1] regarding to the terminology used to describe the study design. It was an observational longitudinal study, and in fact it can be classified as retro prospective. Then we began to collect data, thus those study patients included on March were retrospective and those included until 15 April were prospective. For those admitted patients, we collected data until 24 April to obtain a more detailed clinical description for their hospital admission.

Finally, we appreciate the opportunity to share our experience regarding risk factors for hospital admissions related to COVID-19 in patients with IRD, and we welcome the comments by Aydin *et al*[1] in our real-world setting study. The authors hope this article, despite their limitations described, can be a step to improve gaps of knowledge regarding susceptibility to moderate–severe infection related to COVID-19, and thus helping clinicians in the management of these patients.

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