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Clinical Course and Predictors of Severe Coronavirus Disease 19 Among Patients with Rheumatic Diseases

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Abstract

Background and introduction: As of November 2020, more than 50.000.000 people have been diagnosed with coronavirus disease-2019 (COVID-19) worldwide. The impact of this pandemic on patients with rheumatic and musculoskeletal diseases (RMDs) has been a matter of much concern, not only because of their immunocompromised state, that represents a risk for serious infections, but also given the prospects for the use of immunomodulatory drugs, part of the therapeutic armamentarium of rheumatologists for many years, on the fight against severe forms of SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) infection. During the last months, various reports, from different parts of the world, have addressed this gap in knowledge, however, to date, many questions remain unanswered.

Objectives: To better characterize the epidemiological features and clinical outcomes of COVID-19 among patients with RMDs, analyzing which variables related to their rheumatologic diagnosis and baseline treatment might affect disease severity and the development of humoral immunity.

Method: We included patients with RMDs, followed in the Rheumatology department of Hospital Santa Maria, with confirmed or suspected infection by SARS-CoV-2, from March to September 2020. Demographics and clinical data concerning comorbidities, smoking status, baseline RMD and chronic treatment as well as data on evolution of COVID-19 were collected from Reuma.pt. Blood samples were collected for anti-SARS-CoV-2-IgG antibodies testing using ELISA. Multivariate logistic regression was used to identify predictors of severe disease, defined as hospitalization due to COVID-19. A factorial ANOVA was performed to identify main effects on anti-SARS-CoV-2 IgG titers. Association between age, glucocorticoid dose and anti-SARS-CoV-2 IgG titers was searched for using a Spearman correlation.

Results: Patients with inflammatory RMDs were not found to be at a higher risk of severe infection and chronic immunosuppressive treatment with csDMARDs, bDMARDs or glucocorticoids did not have a significant effect on hospitalization. Development of anti-SARS-CoV-2 IgG was not impacted by baseline disease activity or chronic immunosuppressive treatment nor by COVID-19 severity.

Keywords: SARS-CoV-2 infection; rheumatic patients; COVID-19 severity; humoral immunity

Resumo

Introdução: Em novembro de 2020, a COVID-19 já tinha afetado mais de 50.000.000 de pessoas. O impacto desta pandemia em doentes com patologia reumática e músculo-esquelética suscita particular preocupação, tendo em conta o compromisso imunitário que lhe é inerente e que aumenta consideravelmente o risco de infeção, mas também o interesse crescente na utilização de fármacos imunomoduladores, importantes armas terapêuticas da Reumatologia, no combate a formas graves de infeção a SARS-CoV-2. Nos últimos meses, relatos de diferentes partes do globo têm procurado dar resposta às muitas dúvidas que permanecem por responder.

Objetivos: Caracterizar a epidemiologia e evolução clínica da COVID-19 em doentes com doença reumática e músculo-esquelética, analisando a forma como esta doença e respetivo tratamento afetam a gravidade da infeção a SARS-CoV-2 e o desenvolvimento de imunidade humoral contra este vírus.

Métodos: Foram incluídos doentes com doença reumática e músculo-esquelética, acompanhados no Serviço de Reumatologia do Hospital Santa Maria, com infeção confirmada ou suspeita a SARS-CoV-2, entre março e setembro de 2020. A informação demográfica, relativa a comorbilidades, hábitos tabágicos, doença reumatológica e seu tratamento, bem como informação referente à evolução da COVID-19 foi recolhida da plataforma Reuma.pt. Foram colhidas amostras de sangue para pesquisa de anticorpos IgG anti-SARS-CoV-2 por ELISA. Realizou-se uma regressão logística multivariada para identificação de preditores de gravidade de doença, definida como necessidade de internamento. Foi realizada uma ANOVA para pesquisa dos efeitos de vários fatores nos títulos de IgG anti-SARS-CoV-2. Pesquisou-se também a associação entre idade, dose de glucocorticóides e títulos IgG anti-SARS-CoV-2 utilizando uma correlação de Spearman.

Resultados: O risco de internamento em doentes com patologia inflamatória não foi significativamente superior face a doentes com patologia não inflamatória, e este não foi significativamente influenciado pela imunossupressão com csDMARDs, bDMARDs ou glucocorticóides. O título de anticorpos IgG anti-SARS-CoV-2 não foi influenciado pela

atividade da doença de base, tratamento crónico com imunossupressores ou gravidade da doença a coronavírus-2019.

Palavras-chave: infeção SARS-CoV-2; doentes reumáticos; gravidade COVID-19; imunidade humoral

Índice

Introduction and Background:

In December 2019, a new coronavirus emerged in Wuhan, China. In the beginning of 2020, SARS-CoV-2 spread rapidly around the globe, imposing restraining strategies that were to change social interactions for an undetermined period of time and challenging health care services to a dangerous limit.

During this last year, knowledge on coronavirus disease-2019 (COVID-19) has grown at an incredible pace, much enabled by a remarkable sense of communion among scientific communities.

As of November 2020, nearly 45.000.000 people have been diagnosed with COVID-19 worldwide, approximately 150.000 in Portugal. At the same time-point, Portugal has a case fatality ratio of 1.7% but mortality rates vary greatly in different geographical areas. It is now clear that infection by the novel SARS-CoV-2 has distinct outcomes among different groups of patients and various risk factors have been identified based on strong scientific evidence. Age seems to be the most important determinant of severity, followed by previous diagnosis of cardiovascular, chronic kidney and chronic pulmonary diseases (1–4). This knowledge has now helped the definition of vaccination campaigns, our most promising hope in the struggle to protect the more vulnerable.

Soon in the course of this pandemic, the spotlight has turned to patients with rheumatic and musculoskeletal diseases (RMDs). The impact of this pandemic on this specific group of patients has been a matter of much concern, not only because of their immunocompromised state but also given the prospects for the use of immunomodulatory drugs, part of the therapeutic armamentarium of rheumatologists for many years, on the fight against severe forms of SARS-CoV-2 infection.

Patients with inflammatory RMDs have a well-known risk for various infectious diseases. Consequently, the emergence of a worldwide pandemic by a respiratory virus capable of life-threatening consequences in predisposed individuals raised particular concern among rheumatic patients and their doctors. What is more, second to their rheumatologic diagnosis and treatment strategies, these patients have a high prevalence of cardiovascular and renal comorbidities, which might impact their outcomes.

Based on our current knowledge, patients with RMDs have not been identified as a high

risk group for the development of severe forms of COVID-19 (5), nor are they being included in the first phases of vaccination campaigns around the world. However, nearly a year after the beginning of the pandemic, information is still scarce. A growing body of evidence has been collected by rheumatologic centers around the world sometimes from small samples of patients, with very different methodologies and thus producing conflicting results.

It has been claimed that prevalence of SARS-CoV-2 infection in rheumatic patients is not higher when compared to the general population of the same geographic area. (6–9) Nonetheless, a retrospective study with patients under follow-up in rheumatology departments from 7 hospitals in Spain, found a higher prevalence of hospital RT-PCR (Real Time-Polymerase Chain Reaction) confirmed cases compared with the reference population (10). Also, Gartshteyn et al. suggested a higher percentage of patients with Systemic Lupus Erythematosus (SLE) developed symptomatic COVID-19 when compared to the general population (11). Bearing in mind that the prevalence of infection is importantly affected by restraint measures, this comparison should be analyzed carefully as one could hypothesize a more pronounced lockdown effect in patients with RMDs, preventing exposure to infection.

Moreover, there is some evidence supporting no significantly higher adjusted risk of hospitalization for COVID-19 among rheumatic patients (6,12,13). However, in a case series of 600 individuals with RMDs and COVID-19 from the COVID-19 Global Rheumatology Alliance registry nearly half of the cases were hospitalized (46%) (14) and a similar result was found by Freites Nuñez et al., with 44% of patients with autoimmune with RMDs and COVID-19 requiring hospital admission (15). Hospitalization rate in the general population varies greatly but is generally inferior. According to the CDC (Center for Disease Control and Prevention), along 2020, it has varied, in the US, between 5-20% (62).

Evidence from various cohorts has supported a not significantly increased mortality rate among rheumatic patients (12,14,16).

As of today, it is believed that the risk of severe outcomes and intensive care unit (ICU) admission in patients with rheumatic diseases and COVID-19 is largely mediated by age and comorbidities (12,17) As in the general population, hospitalization and mortality risk are higher in older patients (13,14,16,18) and rate of hospitalization was superior in male

patients, with cardiovascular disease, hypertension, diabetes, dyslipidemia, obesity, chronic renal disease or interstitial lung disease (7,13,16,19,20).

Evidence on the impact of rheumatologic diagnosis on the prognosis of COVID-19 has been conflicting, with some groups supporting that having a systemic connective tissue disease but not an inflammatory arthritis is an independent risk factor for poor COVID-19 outcomes (15,21); others suggesting a higher susceptibility to hospitalization among patients with rheumatoid arthritis (13) and others finding non-significant differences between hospitalized and non-hospitalized patients with regards to rheumatologic diagnosis (7). Santos and al. found that patients who died from COVID-19 are more likely to have moderate/high rheumatic disease activity prior to infection (19).

Susceptibility to infection in patients with RMDs is in part explained by the physiopathology of autoimmunity, which implies a dysregulation of immune responses, and common comorbidities but is much amplified by the immunosuppressive therapeutic strategies.

Whether background immunosuppressive medications confer individuals with rheumatic disease an increased or decreased risk for severe SARS-CoV-2 infection is unknown.

Disease Modifying Anti-Rheumatic Drugs (DMARDs) are immunomodulating and immunosuppressive treatments used in patients with systemic connective tissue diseases (systemic lupus erythematosus, Sjögren syndrome, systemic sclerosis, polymyalgia rheumatica and vasculitis) or inflammatory arthritis (rheumatoid arthritis, spondylarthritis) to control symptoms and, more importantly, to prevent disease progression. These drugs can be classified in three major groups: conventional synthetic (csDMARDS) which include drugs such as methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF) or hydroxychloroquine (HCQ); targeted synthetic (tsDMARDS) which are mainly represented by JAK kinase inhibitors (tofacitinib, baricitinib, upadacitinib); and biologic (bDMARDs), which includes anti-TNF agents (infliximab, etanercept, adalimumab, certolizumab, golimumab), anti-CD20 (rituximab), anti-BLyS (belimumab) CTLA4-Ig (abatacept), anti-IL6 receptor (tocilizumab, sarilumab), anti-IL1 receptor (anakinra, canakinumab), anti-IL17 (secukinumab, ixekizumab) or anti-IL12/23 receptor (ustekinumab).

Another cornerstone of the treatment of inflammatory RMDs are glucocorticoids, whose anti-inflammatory and immunosuppressive effects justify a massive utilization in this group of patients.

Although DMARDs' efficacy favors their utilization, in monotherapy or in different combinations, there are some non-negligible risks associated with their tolerance. The most relevant of which being their association with a higher risk of severe infections. This risk is transversal and largely incremented by the co-utilization of corticosteroids but moderately increased with bDMARDs compared with csDMARDs, with no differences found across bDMARDs. (22)

This justifies an extensive pre-treatment check-up, in search for pre-existent or latent infections (including Hepatitis B and C, HIV and tuberculosis workup) and vaccination strategies including anti-pneumococic and seasonal influenza vaccines. Furthermore, the development of any sign of infection under treatment with bDMARDs should prompt a halt in treatment and urge a medical consultation.

Evidence on the impact of background immunosuppressive therapy on the evolution of COVID-19 in patients with RMDs is still lacking to guide treatment decisions. The European Alliance of Associations for Rheumatology (EULAR) recommendations state that treatment changes in DMARDs should be discussed on a case-by-case basis (5). The American College of Rheumatology (ACR) more assertively suggests that, regardless of COVID-19 severity, HCQ, SSZ, MTX, LEF, non-IL-6R-inhibitor biologics and JAK inhibitors should be temporarily stopped or held (23). Both entities advise against glucocorticoids chronic treatment stop upon coronavirus-19 disease symptoms.

This has been a topic of much debate as many treatments commonly used in patients with rheumatic disease are being investigated as potential therapies for severe forms of COVID-19. The interest in these drugs as a promising therapeutic shed light on the impact of the pandemic on rheumatic patients, as they represented a chronically exposed group for the efficacy of this strategy.

In an initial phase of the pandemic, hydroxychloroquine, a csDMARD frequently used in patients with SLE, was suggested as a potential successful treatment for COVID-19 (24). In March 2020, a group of investigators from the Wuhan Institute of Virology, published results suggesting that HCQ could efficiently inhibit SARS-CoV-2 infection in vitro (25). This antiviral effect in cell culture systems had already been documented for SARS-CoV-

1 (Severe Acute Respiratory Syndrome Coronavirus 1) and MERS-CoV (Middle East Respiratory Syndrome-related Coronavirus) (26). This assumption was also supported by the initial lack of reported COVID-19 cases among SLE patients (27), a finding that was promptly contradicted (28). In line with this, data from the COVID-19 Global Rheumatology Alliance registry also supported no differences between individuals with systemic lupus erythematosus using antimalarials and non-users (14,26,29). In fact, in rheumatic patients, no beneficial effect of chronic antimalarial treatment on disease severity or mortality has been found (16,19,30), with some evidence even suggesting a higher susceptibility to hospitalization among hydroxychloroquine users (13).

HCQ used in the treatment of SLE is typically prescribed at doses of 5.0–6.5 mg/kg, with a maximum dose of 400 mg daily which might not be sufficient to achieve whole blood concentrations to the EC90 (90% effective concentration) for SARS-CoV-2 (27,31,26). Moreover, to date, no acute virus infection has been successfully treated by chloroquine in humans (32).

In June 2020, the enrollment of patients in the hydroxychloroquine group of the RECOVERY (Randomised Evaluation of COVid-19 thERapY) Trial was suspended, after an interim analysis determined that there was a lack of efficacy. Results from this randomized controlled trial suggested that, among patients hospitalized with COVID-19, those who received hydroxychloroquine did not have a lower incidence of death at 28 days than those who received usual care (33).

More recently, and although some health systems continue to support the use of HCQ monotherapy to reduce in-hospital mortality rate (34), the use of hydroxychloroquine in the treatment of SARS-Cov-2 severe forms of infection has been discouraged by most scientific societies (35,36).

In general, use of other csDMARD among rheumatic patients was not associated with a higher risk of contracting COVID-19 nor with a higher risk of hospitalization (10,29). However, use of methotrexate was found to be associated with a higher risk of hospitalization among some (13) but not all cohorts (16).

The impact of bDMARDS and tsDMARDS is controversial. As discussed above, risk of severe infection raises particular concern among bDMARDS users (22). However, some evidence from a time previous to COVID-19 pandemic, already supported a beneficial effect of bDMARDs on the risk of sepsis after severe infection suggesting that a

successful immunosuppression may prevent an unregulated host response, that is, the escalation to sepsis (37), and therefore justifying its utilization in conditions associated with massive cytokine production. Similarly, severe respiratory complications caused by coronaviruses are thought to be driven by the aberrant inflammatory and cytokine response perpetuated by the host immune system. TNF, IL-6 and IL-10 play a pivotal role in the so-called cytokine storm (38). Particularly, TNF is believed to importantly mediate pulmonary inflammatory damage in viral pneumonia (39,40). It follows that immunosuppression by tocilizumab (anti-IL6R), anakinra (anti-IL1), and adalimumab (anti-TNF) are currently being investigated as therapeutic approaches for reducing cytokine concentrations in severe forms of COVID-19, especially for patients developing acute respiratory distress syndrome (ARDS). The JAK inhibitor – baricitinib - has also been suggested as protective by reducing the ability of the virus to infect lung cells (41). Although chronic treatment with bDMARDs or JAK inhibitors was associated with a 1.60-fold increase in COVID-19 prevalence in patients with inflammatory arthritis from a Spanish cohort (10), to date, most published papers suggest that rheumatic patients receiving those treatments do not present a more severe clinical presentation of COVID-19 (6,12,13,17,19,21,42,43) with some works even supporting a beneficial impact of baseline treatment with anti-TNF on hospitalization rate (14–16).

The utilization of steroids along the progression of SARS-CoV-2 infection has also been a matter of much discussion. The chronic use of oral glucocorticoids was associated with higher odds of hospitalization (7,13,15–17,21). The analysis of data from the Global Rheumatology Alliance registry suggested that a high prednisone dose was detrimental (29) and Montero et al. found similar results with lower doses (7). Few studies found no significant impact of corticosteroids use in mortality (19).

These results are in line with recent finds on the impact of glucocorticoids in different stages of COVID-19 progression. Glucocorticoids seem to negatively influence viral clearance in the initial stages of disease (41). However, dexamethasone is to date one of the few treatments that has proven its efficacy in the late severe stages of disease, when acute respiratory distress syndrome (ARDS) overcomes. In June 2020, the RECOVERY trial found that low-dose dexamethasone reduced deaths by one-third in ventilated patients and by one fifth in other patients receiving oxygen only (44). Systemic

corticosteroids use is, nowadays, recommended in mechanically ventilated adults with COVID-19 and ARDS (35).

In face of these uncertainties on the impact of SARS-CoV-2 infection in rheumatic patients and the relevant doubts regarding their treatment, a path on prevention of disease and development of immunity starts to be made. Expectations on efficient vaccination campaigns raise the problem of acquisition of immunity as a significant one to address.

It seems today clear that most people who encounter SARS-CoV-2 display an antibody response between 10 and 14 days after infection (45). Also, most patients seroconvert for SARS-CoV-2-specific IgG antibodies within 2 weeks post-symptom onset (46). In hospitalized patients this humoral response seems more robust, including antibodies with virus neutralizing activity, when compared to milder forms of COVID-19, associated with a delayed antibody response, with minimal functional activity (47). Less than a year after the beginning of this pandemic, we have not yet had the time to learn about the longevity of the antibody response to SARS-CoV-2. However, it is known that antibody titer to MERS-CoV and SARS-CoV-1 virus were maintained for 1-2 years post-infection (46), waning over time. With those suffering more severe disease having higher titer antibody responses for longer (45). It has recently been proposed that circulating protective immunity might persist for up to 6 months after infection by SARS-Cov-2 (48). It remains uncertain if it is sufficient to preclude reinfection and longitudinal serological data is much needed.

To date, few studies have addressed post-infection long term immunity among rheumatic patients. There is some evidence suggesting an inhibitory effect of immunomodulatory drugs on SARS-CoV-2 seroconversion (48). Anti-SARS-CoV-2 IgG prevalence among patients with inflammatory RMDs treated with cytokine inhibitors was found to be inferior to healthy controls and this was not the case when not receiving cytokine blockade (49).

However hopeful, prospects of vaccination in patients with RMDs are still very much a matter of concern and doubt. Artificial creation of humoral immunity with other non-live vaccines has been proven to work for immune-suppressed patients (50) even if antibody responses to these vaccines can be poorer (51–53). In fact, vaccination against

Pneumococcus and Influenza is highly recommended in patients with RMDs, especially when under immunosuppressive treatment.

EULAR point of view on this matter is that approved anti-SARS-CoV-2 vaccines can be used safely in patients with RMDs even if under immunomodulation therapy, notwithstanding an expected reduced efficacy of the vaccine in those patients (63).

In Portugal, patients under bDMARDs or a daily prednisolone equivalent dose >15mg are considered a priority group and being included in the second phase of vaccination campaign. Information on this topic is expectedly scarce and awaits further investigation.

Objectives:

The aim of this study was to better characterize the epidemiological features and clinical outcomes of patients with RMDs infected by SARS-CoV-2. It was our goal to identify predictors of severe disease requiring hospitalization and to analyze the effect of demographic variables, comorbidities, rheumatic disease and chronic immunosuppressive treatment on disease course. It was also our intent to assess the development of antibodies against SARS-CoV-2 in patients with RMDs and how variables related to their rheumatologic diagnosis and baseline treatment might affect it.

Methods:

We conducted a study including adult and pediatric patients with inflammatory and non-inflammatory RMDs, followed in the Rheumatology Department of Hospital Santa Maria, with confirmed or suspected infection by SARS-CoV-2, from March 2 (first case diagnosed in the country) to September 30, 2020.

We collected the following data from Reuma.pt:

- Demographic characteristics: age (defined as continuous and as categorical ≥/<65 years) and sex.
- Comorbidities (cardiovascular disease, chronic pulmonary disease, chronic renal disease, obesity – defined as BMI > 30kg/m^2 - and hypertension) and smoking status (defined as current or past and never).

- Information concerning baseline RMD (defined as inflammatory and non-inflammatory) and disease activity (physician-reported and defined as remission, low, moderate and high activity).
- Chronic treatment: glucocorticoids (prednisone-equivalent dose, defined as continuous and as categorical ≤5, 7.5-10, >10mg), csDMARDs and/or bDMARDs.
- Information regarding COVID-19, namely diagnosis, reported symptoms, need for hospitalization, evolution and complications, laboratorial data, outcome and treatment.

Confirmed cases of SARS-CoV2 were considered if the patient had a positive RT-PCR test on respiratory samples or serological test compatible with acute infection. Suspected cases were based on clinical and epidemiological data.

To assess antibody responses against SARS-CoV-2, blood samples were collected from patients. IgG antibodies recognizing the SARS-CoV-2 receptor-binding domain were quantified using ELISA (Enzyme-Linked Immunosorbent Assay). After serological testing, samples were stored at a biobank (Biobanco-IMM, Lisbon Academic Medical Centre).

Statistical analysis:

Descriptive analysis of continuous variables are displayed as mean ± standard deviation (SD) and percentiles, as appropriate. Categorical variables' frequencies are displayed as absolute, relative and percentage.

Multivariate logistic regression analysis was used to identify predictors of severe disease, defined as hospitalization due to COVID-19. We estimated odds ratio and 95% confidence intervals for the following categorical and continuous covariates in the analysis: age (defined as continuous and as categorical ≥/<65 years), sex, baseline RMD, disease activity, chronic treatment with glucocorticoids (defined as continuous and as categorical ≤5, 7.5-10, >10mg), csDMARDs and/or bDMARDs, comorbidities and smoking status. All variables with $p<0.5$ in the univariate analysis were considered, through backward stepwise selection, to build a multivariable-adjusted model with independent predictors of severe disease.

Moreover, we used a factorial ANOVA analysis to identify main effects of categorical variables of interest on anti-SARS-CoV-2 IgG titers. Considered covariates were as

follows: age (defined as ≥ or <65 years), baseline RMD, disease activity, chronic treatment with glucocorticoids (defined as ≤5, 7.5-10 and >10mg), csDMARDs and/or bDMARDs and severe coronavirus-19 disease (defined as need for hospitalization). All variables with p<0.5 in the one-way ANOVA analysis were considered, through backward stepwise selection, to build a factorial ANOVA.

Finally, to search for association between continuous covariates age and glucocorticoid prednisone-equivalent dose and anti-SARS-CoV-2 IgG titers we plotted the variables and observed a non-linear relationship between them (**figures 1-3** in the annex). Therefore, we used a Spearman correlation coefficient for this purpose.

Statistical analysis was performed in the SPSS® v.26 (Statistical Package for the Social Sciences) and p-value was considered significant at $p<0.05$ (except when otherwise stated).

This study was approved by the Ethics Committee of Centro Académico de Medicina de Lisboa. All patients participated after informed consent. Gathered clinical information and collected blood samples were anonymized.

Results:

We identified 40 patients diagnosed with COVID-19 between March 2 and September 30, 2020 with a follow-up at the Rheumatology Department of Hospital Santa Maria for inflammatory and non-inflammatory RMDs.

Patient's mean age was 53.50 years (SD = 15.908). A pediatric patient, aged 8 years, was included. The rest of the sample was composed by adult patients. The sample was mainly composed by female patients (n= 30, 75% of the sample).

The great majority of patients had an inflammatory RMD (n= 34, 85% of the sample). Most common rheumatologic diagnosis among sampled patients was Systemic Lupus Erythematosus (n= 6, 15%) followed by Psoriatic Arthritis (n= 5, 13%) and Rheumatoid Arthritis (n=4, 10%). Most patients were at a period of either low disease activity (n= 17, 43%) or remission (n= 11, 28%).

As far as chronic treatment is concerned, 24 patients were treated with csDMARDs (60%), 22 patients were treated with glucocorticoids (53%) and 8 patients received treatment with bDMARDs (20%). Among patients who take glucocorticoids (n=21), most

common dosages were above 5mg/day (n=10, 47th percentile) or between 7.5 and 10 mg/day (n=9, 90th percentile).

Most common comorbidities identified in this cohort were hypertension (n=12, 30%) and obesity (n= 9, 23%). Other reported previous medical conditions were chronic pulmonary disease (n = 6, 15% of the sample), cardiovascular diseases (n = 5, 13%) and chronic renal disease (n=2, 5% of the sample). 25% of the patients were smokers or former smokers (n=10). Patient characteristics are presented in **tables 1** to **9** of the supplementary tables.

Most commonly reported symptoms of COVID-19 were malaise (n= 25, 63%) and fever (n= 24, 60%). More than half of the patients also presented headache (n= 22, 55%), fatigue (n= 22, 55%) and cough (n= 21, 53%). Other common symptoms were dysgeusia (n=18, 45%) and myalgia (n= 17, 43%). Asymptomatic cases were rare (n= 2, 5%). Frequency of symptoms is detailed in **table 10** below. Diagnosis of SARS-CoV-2 infection was performed by RT-PCR test in 90% of the patients (n=36), 2 patients had a serological diagnosis (5%) and 2 others a presumptive diagnosis based on clinical and epidemiological data (5%) – detailed in **table 11** of the annex.

Concerning evolution of COVID-19, in this cohort, 10 patients (25%) were hospitalized and 30 were followed-up at in-home isolation (75%). None of the patients included were admitted to an ICU nor were there any deaths. Most patients suffered no complications from COVID-19 (n = 32, 80%) - **tables 12** and **13.** Eight patients (20%) experienced a more severe course of infection: bacterial pneumonia was the most reported adverse evolution, affecting 6 patients. Of note, one patient suffered a type 2 acute myocardial infarction and another presented a leukocytoclastic vasculitis.

Table 10

Frequency of Symptoms of COVID-19 Among Patients with RMDs

Symptoms	*f*	Rel *f*	%
Malaise	25	.625	63
Fever	24	.600	60
Headache	22	.550	55
Fatigue	22	.550	55
Cough	21	.525	53
Dysgeusia	18	.450	45
Myalgia	17	.425	43
Anosmia	14	.350	35
Diarrhea	13	.325	33
Arthralgia	11	.275	28
Rhinorrhea	10	.250	25
Odynophagia	10	.250	25
Abdominal Pain	9	.225	23
Thoracalgia	7	.175	18
Nausea	7	.175	18
Vomiting	6	.150	15
Dyspnea	5	.125	13
Altered Mental Status	5	.125	13
Asymptomatic	2	.050	5

Table 12 and 13

Hospitalization Rate from COVID-19 Among Patients with RMDs (N=40)

	f	Rel *f*	%
Non-Hospitalized	30	0,750	75
Hospitalized	10	0,250	25

Complication Rate Following COVID-19 Among Patients with RMDs (N=40)

	f	Rel *f*	%
No Complications	32	0,800	80
Complications	8	0,200	20

Note. Reported complications include bacterial pneumonia, type 2 acute myocardial infarction and leukocytoclastic vasculitis.

Results from multivariate analyses revealed no statistically significant differences between hospitalized and non-hospitalized patients with regard to age, sex, baseline RMD, disease activity, chronic treatment with glucocorticoids, csDMARDs and/or bDMARDs, comorbidities and smoking status. None of the variables in study were found to be predictive of a more severe infection requiring hospital admission. The estimated odds ratio (OR) and respective *p*-values are shown in **table 14** below.

Table 14

Univariate and Multivariate Logistic Regression Predicting Hospitalization from COVID-19 among Patients with RMDs

Variables	Univariate analyses		Multivariate analyses	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age	1.02 [.97-1.07]	.464	1,00 [.92-1.08]	.991
Age ≥ 65 years	2.79 [.50-15.46]	.241	1,04 [.04-27.25]	.98
Men[a]	1.71 [.34-8.68]	.515	-	-
Inflammatory RMDs[b]	0.65 [.07-6.41]	.712	-	-
Smoking[c]	0.82 [.14-4.80]	.827	-	-
Obesity	1.71 [.03-8.68]	.515	-	-
Hypertension	1.83 [.41-8.23]	.429	.94 [.09-9.55]	.957
CRD	3.22 [.18-56.88]	.424	19*10^7 [.00-]	.998
CV disease	0.69 [.07-7.07]	.758	-	-
CPD	0.53 [.6-5.21]	.589	-	-
bDMARD	1.00 [.15-5.99]	1	-	-
csDMARD	1.00 [.23-4.31]	1	-	-
Glucocorticoids	1.50 [.35 -6.42]	.585	-	-
Glucocorticoid Dose[d]	1.09 [.97-1.22]	.159	13*10^5 [.00-]	.997
GC Dose Group[e]	1.44 [.68-3.05]	.336	.00 [.00-]	.997
Disease Activity[f]	.98 [.46-2.10]	.961	-	-

Note. Multivariate Logistic Regression: R^2 = 0,275 (Nagelkerke) Model $\chi 2$ = 0,222.
CRD – chronic renal disease; CV disease – cardiovascular disease; CPD – chronic pulmonary disease; GC – glucocorticoid.
[a] women as reference; [b] non-inflammatory disease as reference; [c] includes smokers and former smokers [d] defined as continuous variable [e] defined as categorical variable ≤5, 7.5-10 and >10mg [f] defined as remission, low, moderate and high activity.

Blood samples were collected from 27 patients (68%). Median of anti-SARS-CoV-2 IgG titer was 800, interquartile range (IQR) = 3200 – 200. Three patients (n=3, 11%) were negative for anti-SARS-CoV-2 IgG antibodies. Distribution of frequencies is shown in **table 15** below. Outliers were winsorized.

In the interpretation of the conducted factorial ANOVA, allowing for a non-normally distributed sample, a *p* value of 0.01 was defined a priori.

Results from factorial ANOVA, shown in **table 16**, support no statistically significant effect of age, baseline RMD, disease activity or chronic treatment with bDMARD, csDMARD and glucocorticoids on Anti-SARSCov2 IgG titers. Only main effects were studied, interaction effects were not considered given the small size of the sample.

Table 15

Distribution of Anti-SARS-CoV-2 IgG titers (N=27)

IgG titers	*f*	Rel *f*	%	Cum *f*	Percentile
0	3	0,111	11	27	100
100	2	0,074	7	24	89
200	3	0,111	11	22	81
400	4	0,148	15	19	70
800	2	0,074	7	15	56
1600	1	0,037	4	13	48
3200	6	0,222	22	12	44
6400	6	0,222	22	6	22

Table 16

One-way ANOVA and Main Effects Factorial ANOVA on Anti-SARS-Cov2 IgG titers

Variables	Bivariate analyses		Multivariate analyses	
	F	*p* value	F	*p* value
Age ≥ 65	1.03	.264	.84	.37
Baseline RMD	.03	.861	-	-
bDMARD	.93	.343	1,61	.219
csDMARD	1.42	.245	.02	.901
Glucocorticoid	.05	.833	-	-
GC Dose Group	.21	.892	-	-
Disease Activity	3.49	.032	3,47	.036
Severe COVID-19[a]	0	.965	-	-

Note. [a] defined as need for hospitalization

Spearman's rho correlation coefficient results, shown in **table 17**, indicated a significant positive correlation between age and Anti-SARSCoV2 IgG titers. No significant association was found between age and chronic glucocorticoid prescribed dose nor between chronic glucocorticoid prescribed dose and Anti-SARSCoV2 IgG titers.

Table 17

Spearman Correlation Between Anti-SARSCov2 IgG titers, Age and Glucocorticoid Dose

Variables	*n*	*M*	*SD*	IgG titers [a]	Age	GC dose [b]
IgG titers [a]	27	2340,74	483,17	-	-	-
Age	27	55,04	2,85	0,42*	-	-
GC dose [b]	27	3,98	0,83	0,08	-0,13	-

Note. * Correlation is significant at the 0.05 level (2-tailed): rs(27) = 0.42 and p = .029.
[a] anti-SARS-CoV-2 IgG titers
[b] Glucocorticoid dose

Interestingly, nearly half of the patients in this sample (n= 19, 48%) changed their chronic treatment in some way due to COVID-19 diagnosis. This phenomenon was particularly relevant among patients taking csDMARDs and bDMARD – detailed figures in **table 18** below.

Table 18

Attitude Towards Chronic Rheumatologic Treatment after COVID-19 Diagnosis (N=40)

	f	Rel *f*	%
Unchanged	21	.525	53
Changed	19	.475	48
Changes in Glucocorticoid treatment (N=21)			
Dose unchanged	14	.667	67
Reduction of dose	4	.19	19
Interruption of treatment	2	.095	10
Augmentation of dose	1	.048	5
Changes in csDMARDs treatment (N=24)			
Interruption of treatment	13	.542	54
Dose unchanged	11	.458	46
Changes in bDMARDs treatment (N=8)			
Interruption of treatment	5	.625	63
Dose unchanged	3	.375	38

Discussion:

In the present study, we report how patients with RMDs followed in the Rheumatology Department of Hospital Santa Maria were affected by SARS-CoV-2 infection.

Most commonly reported symptoms of COVID-19 were malaise and fever, fatigue and cough were also frequent. In a systematic review including 148 studies from 9 countries, Grant et al. presented these as some of the most frequently reported symptoms of SARS-CoV-2 infection (54). Asymptomatic cases were expectedly rare in our sample given our inclusion method. Diagnosis of SARS-CoV-2 infection was mainly performed by RT-PCR test.

Concerning evolution of COVID-19, in this cohort, 25% of the patients were hospitalized. This rate is consistent with previous findings from different groups (6,12,13). Most patients suffered no complications from COVID-19, none of the patients included were admitted to an ICU nor were there any deaths**.** Among patients who experienced a more severe course of infection, bacterial pneumonia was the most reported adverse evolution.

Our results support a non-statistically significant difference between hospitalized and non-hospitalized patients with regards to age, sex, comorbidities or smoking status.

Patients with inflammatory RMDs were not found to be at a higher risk of severe infection when compared to patients with non-inflammatory RMDs. Also, disease activity was not identified as a predictor of severity, which contrasts with previous publications (19).

Our results suggest no detrimental nor beneficial effect of chronic immunosuppressive treatment on COVID-19 severity, as hospitalization risk did not differ significantly between patients under bDMARDs or csDMARDs and patients not taking those drugs. Similar results have been previously described in the literature (6,12,13,17,19,21,42,43).

Likewise, chronic treatment with glucocorticoids was not found to be a significant predictor of severe disease nor did patients taking higher glucocorticoid doses had a significantly higher hospitalization rate. Although Santos et al., 2020 described similar results (19), chronic use of oral glucocorticoids was associated with higher odds of hospitalization in most other published works (7,13,15–17,21) with higher doses associated with worse prognosis (29).

As far as development of antibodies against SARS-CoV-2 is concerned, the great majority of patients (89%) were positive for anti-SARS-CoV-2 IgG antibodies.

Results support a non-statistically significant effect of age ≥ 65, baseline RMD, disease activity or chronic treatment with bDMARD, csDMARD and glucocorticoids on Anti-SARSCov2 IgG titers. These were not impacted by the severity of coronavirus-19 disease either, which is contrary to what was previously supported by Zhang et al. (55). It would have been interesting to study expected interaction effects of variables in study were we to have a larger sample.

Although IgG titers did not differ significantly between patients aged 65 or more and younger ones, age was positively correlated with anti-SARS-CoV-2 IgG titers. This is not in agreement with previously published literature (56,57) and thus awaits further investigation. No significant association was found between chronic glucocorticoid prescribed dose and anti-SARS-CoV-2 IgG titers. In fact, in our sample, most patients (90^{th} percentile) were taking lower daily glucocorticoid doses (< 10 mg), expected not to impact antibody production (58–60).

Serological testing was performed at different times post-infection, limiting assumptions concerning long term immunity against the virus. What is more, the presence of the antibodies is not reflective of the effectiveness of immunity were there to be a second contact with this viral agent.

Of note is also the fact that nearly half of the patients in this sample changed their chronic treatment in some way upon COVID-19 diagnosis. This phenomenon was particularly relevant among patients taking csDMARDs and bDMARD, but also occurred in patients chronically treated with glucocorticoids, who suspended their treatment or decreased habitual dose. This evidence deserves careful consideration given the persistent incertitude concerning treatment guidance in these circumstances and the utmost importance of immunosuppressive treatments not only on symptomatic relief but also on long-term prognosis. What is more, when discontinuing or tapering these treatments, patients might experience rheumatic disease flare, which has been identified as a risk factor for infection (19,61).

As discussed above, there are several limitations to our study. As it is a single-center study, sample size was small, limiting the interpretation of our results. What is more, assumptions on long term immunity are limited by the different post-infection periods

at the time of serological testing.

It would have been interesting to estimate the prevalence of SARS-CoV-2 infection among patients followed at our Rheumatology Department at the period of time in study. Another relevant analysis would be to compare COVID-19 hospitalization rates between rheumatic patients and patients followed up by other specialties of the same hospital.

Although many doubts remain and research on this topic is still much needed, a weekly growing body of evidence is assisting in a more and better-informed management of these patients.

In conclusion, patients with inflammatory RMDs were not found to be at a higher risk of severe infection and chronic immunosuppressive treatment with csDMARDs, bDMARDs or glucocorticoids did not have a significant effect on hospitalization.

Also, development of anti-SARS-CoV2 IgG was not impacted by baseline disease activity or chronic immunosuppressive treatment nor by COVID-19 severity.

Bibliography

1. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in wuhan, china. JAMA Intern Med. 2020 Jul 1;180(7):934–43.

2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 28;395(10229):1054–62.

3. Goodman KE, Magder LS, Baghdadi JD, Pineles L, Levine AR, Perencevich EN, et al. Impact of Sex and Metabolic Comorbidities on COVID-19 Mortality Risk Across Age Groups: 66,646 Inpatients Across 613 U.S. Hospitals. Clin Infect Dis. 2020 Dec 18;

4. ERA-EDTA Council, ERACODA Working Group. Chronic kidney disease is a key risk factor for severe COVID-19: a call to action by the ERA-EDTA. Nephrol Dial Transplant. 2021 Jan 1;36(1):87–94.

5. Landewé RB, Machado PM, Kroon F, Bijlsma HW, Burmester GR, Carmona L, et al. EULAR provisional recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2. Ann Rheum Dis. 2020 Jun 5;79(7):851–8.

6. Michelena X, Borrell H, López-Corbeto M, López-Lasanta M, Moreno E, Pascual-Pastor M, et al. Incidence of COVID-19 in a cohort of adult and paediatric patients with rheumatic diseases treated with targeted biologic and synthetic disease-modifying anti-rheumatic drugs. Semin Arthritis Rheum. 2020 May 16;50(4):564–70.

7. Montero F, Martínez-Barrio J, Serrano-Benavente B, González T, Rivera J, Molina Collada J, et al. Coronavirus disease 2019 (COVID-19) in autoimmune and inflammatory conditions: clinical characteristics of poor outcomes. Rheumatol Int. 2020 Oct;40(10):1593–8.

8. Zen M, Fuzzi E, Astorri D, Saccon F, Padoan R, Ienna L, et al. SARS-CoV-2 infection in patients with autoimmune rheumatic diseases in northeast Italy: A cross-sectional study on 916 patients. J Autoimmun. 2020 Jun 8;112:102502.

9. Emmi G, Bettiol A, Mattioli I, Silvestri E, Di Scala G, Urban ML, et al. SARS-CoV-2 infection among patients with systemic autoimmune diseases. Autoimmun Rev. 2020 Jul;19(7):102575.

10. Pablos JL, Abasolo L, Alvaro-Gracia JM, Blanco FJ, Blanco R, Castrejón I, et al. Prevalence of hospital PCR-confirmed COVID-19 cases in patients with chronic inflammatory and autoimmune rheumatic diseases. Ann Rheum Dis. 2020 Jun 12;79(9):1170–3.

11. Gartshteyn Y, Askanase AD, Schmidt NM, Bernstein EJ, Khalili L, Drolet R, et al. COVID-19 and systemic lupus erythematosus: a case series. Lancet Rheumatol. 2020 Aug;2(8):e452–4.

12. Serling-Boyd N, D'Silva KM, Hsu TY, Wallwork R, Fu X, Gravallese EM, et al. Coronavirus disease 2019 outcomes among patients with rheumatic diseases 6 months into the pandemic. Ann Rheum Dis. 2020 Nov 30;

13. Haberman R, Axelrad J, Chen A, Castillo R, Yan D, Izmirly P, et al. Covid-19 in Immune-Mediated Inflammatory Diseases - Case Series from New York. N Engl J Med. 2020 Jul 2;383(1):85–8.

14. Gianfrancesco M, Yazdany J, Robinson PC. Epidemiology and outcomes of novel coronavirus 2019 in patients with immune-mediated inflammatory diseases. Curr Opin Rheumatol. 2020;32(5):434–40.

15. Freites Nuñez DD, Leon L, Mucientes A, Rodriguez-Rodriguez L, Font Urgelles J, Madrid García A, et al. Risk factors for hospital admissions related to COVID-19 in patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2020 Aug 7;79(11):1393–9.

16. FAI2R /SFR/SNFMI/SOFREMIP/CRI/IMIDIATE consortium and contributors. Severity of COVID-19 and survival in patients with rheumatic and inflammatory diseases: data from the French RMD COVID-19 cohort of 694 patients. Ann Rheum Dis. 2020 Dec 2;

17. D'Silva KM, Jorge A, Cohen A, McCormick N, Zhang Y, Wallace ZS, et al. COVID-19 Outcomes in Patients with Systemic Autoimmune Rheumatic Diseases (SARDs) Compared to the General Population: A US Multi-Center Comparative Cohort Study. Arthritis Rheumatol. 2020 Dec 10;

18. Fredi M, Cavazzana I, Moschetti L, Andreoli L, Franceschini F, Brescia Rheumatology COVID-19 Study Group. COVID-19 in patients with rheumatic diseases in northern Italy: a single-centre observational and case-control study. Lancet Rheumatol. 2020 Sep;2(9):e549–56.

19. Santos CS, Morales CM, Álvarez ED, Castro CÁ, Robles AL, Sandoval TP. Determinants of COVID-19 disease severity in patients with underlying rheumatic disease. Clin Rheumatol. 2020 Sep;39(9):2789–96.

20. Hasseli R, Mueller-Ladner U, Schmeiser T, Hoyer BF, Krause A, Lorenz H-M, et al. National registry for patients with inflammatory rheumatic diseases (IRD) infected with SARS-CoV-2 in Germany (ReCoVery): a valuable mean to gain rapid and reliable knowledge of the clinical course of SARS-CoV-2 infections in patients with IRD. RMD Open. 2020;6(2).

21. Pablos JL, Galindo M, Carmona L, Lledó A, Retuerto M, Blanco R, et al. Clinical outcomes of hospitalised patients with COVID-19 and chronic inflammatory and autoimmune rheumatic diseases: a multicentric matched cohort study. Ann Rheum Dis. 2020 Aug 12;79(12):1544–9.

22. Sepriano A, Kerschbaumer A, Smolen JS, van der Heijde D, Dougados M, van Vollenhoven R, et al. Safety of synthetic and biological DMARDs: a systematic literature

review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2020 Feb 7;79(6):760–70.

23. Mikuls TR, Johnson SR, Fraenkel L, Arasaratnam RJ, Baden LR, Bermas BL, et al. American College of Rheumatology Guidance for the Management of Rheumatic Disease in Adult Patients During the COVID-19 Pandemic: Version 3. Arthritis Rheumatol. 73(2):e1–12.

24. Colson P, Rolain J-M, Raoult D. Chloroquine for the 2019 novel coronavirus SARS-CoV-2. Int J Antimicrob Agents. 2020 Feb 15;55(3):105923.

25. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020;6:16.

26. Konig MF, Kim AH, Scheetz MH, Graef ER, Liew JW, Simard J, et al. Baseline use of hydroxychloroquine in systemic lupus erythematosus does not preclude SARS-CoV-2 infection and severe COVID-19. Ann Rheum Dis. 2020 May 7;79(10):1386–8.

27. Joob B, Wiwanitkit V. SLE, hydroxychloroquine and no SLE patients with COVID-19: a comment. Ann Rheum Dis. 2020 Apr 15;79(6):e61.

28. Romão VC, Cruz-Machado AR, Fonseca JE. No evidence so far on the protective effect of hydroxychloroquine to prevent COVID-19: comment by Joob and Wiwanitkit. Ann Rheum Dis. 80(2):e22.

29. Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis. 2020 May 29;79(7):859–66.

30. Sbidian E, Penso L, Herlemont P, Botton J, Baricault B, Semenzato L, et al. Comment on “Baseline use of hydroxychloroquine in systemic lupus erythematosus does not preclude SARS-CoV-2 infection and severe COVID-19” by Konig et al. Long-term exposure to hydroxychloroquine or chloroquine and the risk of hospitalisation with COVID-19: a nationwide, observational cohort study in 54 873 exposed individuals and 155 689 matched unexposed individuals in France. Ann Rheum Dis. 2020 Aug 28;

31. Balevic SJ, Hornik CP, Green TP, Clowse MEB, Gonzalez D, Maharaj AR, et al. Hydroxychloroquine in Patients with Rheumatic Disease Complicated by COVID-19: Clarifying Target Exposures and the Need for Clinical Trials. J Rheumatol. 2020 May 11;

32. Touret F, de Lamballerie X. Of chloroquine and COVID-19. Antiviral Res. 2020 Mar 5;177:104762.

33. RECOVERY Collaborative Group, Horby P, Mafham M, Linsell L, Bell JL, Staplin N, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med. 2020 Nov 19;383(21):2030–40.

34. Catteau L, Dauby N, Montourcy M, Bottieau E, Hautekiet J, Goetghebeur E, et al. Low-dose hydroxychloroquine therapy and mortality in hospitalised patients with COVID-19: a nationwide observational study of 8075 participants. Int J Antimicrob Agents. 2020 Oct;56(4):106144.

35. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). Crit Care Med. 2020;48(6):e440–69.

36. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC-C, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Clin Infect Dis. 2020 Apr 27;

37. Richter A, Listing J, Schneider M, Klopsch T, Kapelle A, Kaufmann J, et al. Impact of treatment with biologic DMARDs on the risk of sepsis or mortality after serious infection in patients with rheumatoid arthritis. Ann Rheum Dis. 2016 Sep;75(9):1667–73.

38. Pedersen SF, Ho Y-C. SARS-CoV-2: a storm is raging. J Clin Invest. 2020 May 1;130(5):2202–5.

39. Hussell T, Pennycook A, Openshaw PJ. Inhibition of tumor necrosis factor reduces the severity of virus-specific lung immunopathology. Eur J Immunol. 2001 Sep;31(9):2566–73.

40. Peper RL, Van Campen H. Tumor necrosis factor as a mediator of inflammation in influenza A viral pneumonia. Microb Pathog. 1995 Sep;19(3):175–83.

41. Favalli EG, Ingegnoli F, De Lucia O, Cincinelli G, Cimaz R, Caporali R. COVID-19 infection and rheumatoid arthritis: Faraway, so close! Autoimmun Rev. 2020 May;19(5):102523.

42. Conticini E, Bargagli E, Bardelli M, Rana GD, Baldi C, Cameli P, et al. COVID-19 pneumonia in a large cohort of patients treated with biological and targeted synthetic antirheumatic drugs. Ann Rheum Dis. 80(2):e14.

43. Monti S, Balduzzi S, Delvino P, Bellis E, Quadrelli VS, Montecucco C. Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. Ann Rheum Dis. 2020 Apr 2;79(5):667–8.

44. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021 Feb 25;384(8):693–704.

45. Kellam P, Barclay W. The dynamics of humoral immune responses following SARS-CoV-2 infection and the potential for reinfection. J Gen Virol. 2020;101(8):791–7.

46. O Murchu E, Byrne P, Walsh KA, Carty PG, Connolly M, De Gascun C, et al. Immune response following infection with SARS-CoV-2 and other coronaviruses: A rapid review. Rev Med Virol. 31(2):e2162.

47. Rijkers G, Murk J-L, Wintermans B, van Looy B, van den Berge M, Veenemans J, et al. Differences in antibody kinetics and functionality between severe and mild severe acute respiratory syndrome coronavirus 2 infections. J Infect Dis. 2020 Sep 14;222(8):1265–9.

48. Figueiredo-Campos P, Blankenhaus B, Mota C, Gomes A, Serrano M, Ariotti S, et al. Seroprevalence of anti-SARS-CoV-2 antibodies in COVID-19 patients and healthy volunteers up to 6 months post disease onset. Eur J Immunol. 2020 Dec;50(12):2025–40.

49. Simon D, Tascilar K, Krönke G, Kleyer A, Zaiss MM, Heppt F, et al. Patients with immune-mediated inflammatory diseases receiving cytokine inhibitors have low prevalence of SARS-CoV-2 seroconversion. Nat Commun. 2020 Jul 24;11(1):3774.

50. Nakafero G, Grainge MJ, Myles PR, Mallen CD, Zhang W, Doherty M, et al. Effectiveness of inactivated influenza vaccine in autoimmune rheumatic diseases treated with disease-modifying anti-rheumatic drugs. Rheumatology (Oxford). 2020 Dec 1;59(12):3666–75.

51. Bühler S, Jaeger VK, Adler S, Bannert B, Brümmerhoff C, Ciurea A, et al. Safety and immunogenicity of tetanus/diphtheria vaccination in patients with rheumatic diseases-a prospective multi-centre cohort study. Rheumatology (Oxford). 2019 Sep 1;58(9):1585–96.

52. Intongkam S, Samakarnthai P, Pakchotanon R, Narongroeknawin P, Assavatanabodee P, Chaiamnuay S. Efficacy and Safety of Hepatitis B Vaccination in Rheumatoid Arthritis Patients Receiving Disease-Modifying Antirheumatic Drugs and/or Biologics Therapy. J Clin Rheumatol. 2019 Dec;25(8):329–34.

53. Sousa S, Duarte AC, Cordeiro I, Ferreira J, Gonçalves MJ, Meirinhos T, et al. Efficacy and Safety of Vaccination in Pediatric Patients with Systemic Inflammatory Rheumatic Diseases: a systematic review of the literature. Acta Reumatol Port. 2017 Mar;42(1):8–16.

54. Grant MC, Geoghegan L, Arbyn M, Mohammed Z, McGuinness L, Clarke EL, et al. The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): A systematic review and meta-analysis of 148 studies from 9 countries. PLoS ONE. 2020 Jun 23;15(6):e0234765.

55. Zhang B, Zhou X, Zhu C, Song Y, Feng F, Qiu Y, et al. Immune Phenotyping Based on the Neutrophil-to-Lymphocyte Ratio and IgG Level Predicts Disease Severity and Outcome for Patients With COVID-19. Front Mol Biosci. 2020 Jul 3;7:157.

56. Capai L, Ayhan N, Masse S, Canarelli J, Priet S, Simeoni M-H, et al. Seroprevalence of SARS-CoV-2 IgG Antibodies in Corsica (France), April and June 2020. J Clin Med. 2020 Nov 5;9(11).

57. Stringhini S, Wisniak A, Piumatti G, Azman AS, Lauer SA, Baysson H, et al. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study. Lancet. 2020;396(10247):313–9.

58. Batu ED. Glucocorticoid treatment in juvenile idiopathic arthritis. Rheumatol Int. 2019;39(1):13–27.

59. Heijstek MW, Ott de Bruin LM, Bijl M, Borrow R, van der Klis F, Koné-Paut I, et al. EULAR recommendations for vaccination in paediatric patients with rheumatic diseases. Ann Rheum Dis. 2011 Oct;70(10):1704–12.

60. Groot N, Heijstek MW, Wulffraat NM. Vaccinations in paediatric rheumatology: an update on current developments. Curr Rheumatol Rep. 2015 Jul;17(7):46.

61. Au K, Reed G, Curtis JR, Kremer JM, Greenberg JD, Strand V, et al. High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. Ann Rheum Dis. 2011 May;70(5):785–91.

62. Centers for Disease Control and Prevention. (2020). COVID Data Tracker Weekly Review. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html.

63. EULAR Viewpoints on SARS-CoV-2 vaccination in patients with RMDs. EULAR. (2020) https://www.eular.org/eular_sars_cov_2_vaccination_rmd_patients.cfm.

Supplementary Tables:

Table 1

Age Frequencies of Patients Included in the Study (N=40)

Age	*f*	Rel *f*	c*f*	Percentile
90	1	.025	40	100
88	1	.025	39	97.5
80	1	.025	38	95
75	1	.025	37	92.5
69	1	.025	36	90
68	1	.025	35	87.5
66	1	.025	34	85
64	1	.025	33	82.5
63	2	.05	32	80
61	1	.025	30	75
60	1	.025	29	72.5
59	2	.05	28	70
58	1	.025	26	65
57	1	.025	25	62.5
56	2	.05	24	60
55	1	.025	22	55
54	1	.025	21	52.5
53	1	.025	20	50
52	2	.05	19	47.5
50	1	.025	17	42.5
49	1	.025	16	40
47	2	.05	15	37.5
46	1	.025	13	32.5
45	1	.025	12	30
44	2	.05	11	27.5
41	3	.075	9	22.5
39	1	.025	6	15
38	1	.025	5	12.5
35	1	.025	4	10

31	1	.025	3	7.5
25	1	.025	2	5
8	1	.025	1	2.5

Table 2

Measures of Central Tendency - Age of Participants (N=40)

	Age
Mean	53.23
Median	53.50
SD	15.91

Table 3

Distribution by Sex in the Sample (N=40)

	f	Rel *f*	%
F	30	.750	75
M	10	.250	25

Table 4

Frequencies of Rheumatologic Diagnosis (N=40)

	f	Rel *f*	%
Inflammatory	34	.850	85
Non-Inflammatory	6	.150	15

Table 5

Distribution of RMDs Among Patients in the Sample (N=40)

	f	Rel *f*	%
SLE	6	.150	15
PsA	5	.125	13
RA	4	.100	10
GCA	3	.075	8
EnA	3	.075	8
SS	3	.075	8
UEIA	3	.075	5
JA	2	.050	5
MCTD	2	.050	5
Fibromyalgia	2	.050	5
Gout	2	.050	5
CPCDD	1	.025	3
Osteoporosis	1	.025	3
APLS	1	.025	3
AOSD	1	.025	3
OS	1	.025	3

Note. AOSD - Adult-onset Still's disease; APLS - Antiphospholipid syndrome; ; CPCDD - Calcium pyrophosphate crystal deposition disease; EnA – Entheropathic arthritis; GCA – Giant Cell Arthritis; JA – Juvenile Arthritis; MCTD – Mixed connective tissue disease; OS – Overlap Syndrome; PsA – Psoriatic Arthritis; RA – Rheumatoid Arthritis; SLE – Systemic Lupus Erythematous SS – Systemic Sclerosis; UEIA - Undifferentiated early inflammatory arthritis.

Table 6

Physician-reported Rheumatologic Disease Activity at the time of SARS-CoV-2 infection (N=40)

	f	Rel *f*	%
Low activity	17	.425	43
Remission	11	.275	28
Moderate activity	7	.175	18
High Activity	5	.125	13

Table 7

Distribution of Chronic Rheumatologic Treatment Among Participants

	f	Rel *f*	%
csDMARD	24	.600	60
Glucocorticoid	21	.525	53
bDMARD	8	.200	20

Table 8

Distribution of Prescribed Glucocorticoids Dose (N=21)

Dose GC	*f*	Rel *f*	%	c*f*	Percentile
>10.0 mg	2	.050	5	21	100
7.5-10 mg	9	.225	23	19	91
≤5.0 mg	10	.250	25	10	48

Table 9

Comorbidities and Smoking Status Among Participants

	f	Rel *f*	%
Hypertension	12	.300	30
Smoker or Former Smoker	10	.250	25
Obesity	9	.225	23
Chronic Pulmonary Disease	6	.150	15
Cardiovascular Diseases	5	.125	13
Chronic Renal Disease	2	.050	5

Note. Cardiovascular Diseases - cardiomyopathy, ischemic stroke or transient ischemic attack, Chronic Pulmonary Disease: COPD, Asthma and Obstructive Sleep Apnea Syndrome.

Table 11

Distribution of Procedure for Diagnosis SARS-CoV-2 (N=40)

	f	Rel *f*	%
RT-PCR Test	36	.90	90
Presumptive Diagnosis	2	.05	5
Serologic Test	2	.05	5

Note. Presumptive Diagnosis was based on clinical and epidemiological data.

Figure 1

Correlation Between Age and Chronic Glucocorticoid Dose (n=27)

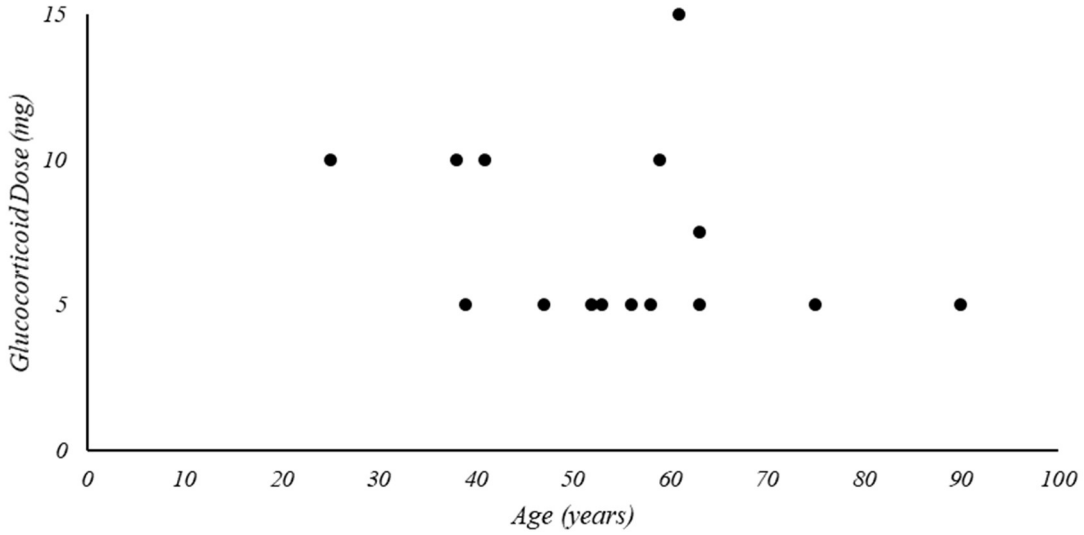

Figure 2

Correlation Between Age and Anti-SARS-CoV-2 IgG titers (n=27)

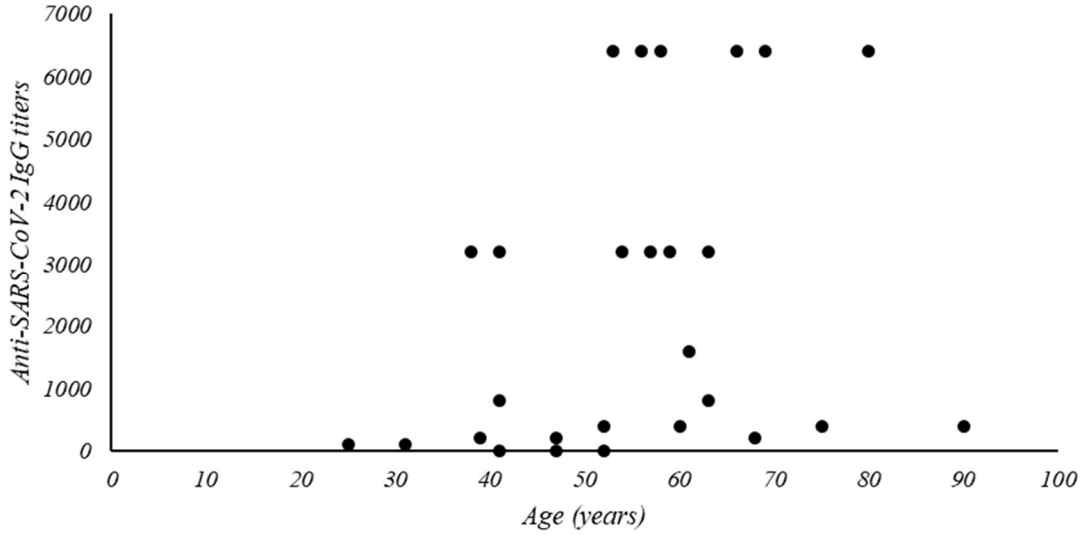

Figure 3

Correlation Between Chronic Glucocorticoid Dose and Anti-SARS-CoV-2 IgG titers (n=27)