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Review Article

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Factors Associated with the Risk of Infection and Hospitalization by SARS-Cov-2 in Rheumatic Pacients: A Narrative Review

Fatores Associados ao Risco de Infecção e de Hospitalização pelo SARS-Cov-2 em Pacientes Reumáticos: uma Revisão Narrativa

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Abstract

INTRODUCTION: The severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) presents clinical heterogeneity, depending on the singularities of the individuals. Rheumatic diseases, which course with immunological alterations, in addition to requiring immunomodulatory therapy for their control, end up influencing the responsiveness to SARS-CoV-2 infection. However, this association, as well as the risk and severity factors, have not been clearly elucidated. PURPOSE: to analyze the factors associated with infection and hospitalization of rheumatologic patients by SARS-Cov-2. **MATERIALS AND METHODS:** This is a narrative literature review, which used the PUBMED, Science Direct and the Regional Portal of the Virtual Health Library (VHL) databases, with the descriptors “COVID-19”, “Rheumatic Disease”and "Immunosuppression". 11 scientific productions were selected to compose this review. **RESULTS:** Rheumatic disease was not associated with increased susceptibility to infection/hospitalization by SARS-Cov-2. Regarding demographic factors, the association with increased risk of illness/hospitalization due to COVID-19 was not convergent. Comorbidities were identified as a factor of greater propensity for viral infection, as for anti-rheumatic drugs, there were divergences. **CONCLUSIONS:** The present study found that rheumatologic patients had similar susceptibility to infection/hospitalization as the general population. Advanced age and the presence of comorbidities were associated with an increased risk of severe infection and hospitalization for COVID-19. As for immunosuppressive therapy, patients using rituximab or glucocorticosteroids chronically had a higher rate of hospitalization and severe infection by COVID-19, with the former still increasing the risk of death. The use of anti-TNF alpha presented a protective effect. However, it is noteworthy that the findings are preliminary and depend on new studies in the area for decision making.
Keywords: covid-19. rheumatic diseases. immunosuppression.

Resumo

INTRODUÇÃO: A síndrome respiratória aguda grave-coronavírus 2 (SARS-CoV-2), apresenta heterogeneidade clínica, a depender das singularidades dos indivíduos. As doenças reumatológicas, que cursam com alterações imunológicas, além de, necessitarem da terapia imunomodulatória para seu controle, acabam por influenciar na

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responsividade à infecção pelo SARS-CoV-2. Contudo, tal associação, bem como os fatores de risco e de gravidade, não estão claramente elucidados. **OBJETIVO:** analisar os fatores associados à infecção e à hospitalização de pacientes reumatológicos pelo SARS-CoV-2. **MATERIAIS E MÉTODOS:** Trata-se de uma revisão narrativa, que utilizou as bases de dados PUBMED, Science Direct e o Portal Regional da Biblioteca Virtual de Saúde (BVS), com os descritores "COVID-19", "Rheumatic Disease" and "Immunosuppression". Foram selecionadas 11 produções científicas para compor esta revisão. **RESULTADOS:** Doença reumatológica não foi associada à maior suscetibilidade à infecção/hospitalização por SARS-Cov-2. Em relação aos fatores demográficos, a associação com o aumento do risco de adoecimento/internação por COVID-19 não foi convergente. As comorbidades foram apontadas como fator de maior propensão para a infecção viral, já quanto às drogas antirreumáticas, houve divergências. **CONCLUSÕES:** O presente estudo verificou que pacientes reumatológicos apresentaram suscetibilidade semelhante à infecção/hospitalização da população geral. A idade avançada e a presença de comorbidades foram associados ao risco aumentado de infecção grave e hospitalização por COVID-19. Quanto à terapia imunossupressora, pacientes em uso de Rituximabe ou de glicocorticosteróides de forma crônica, apresentaram maior taxa de hospitalização e infecção grave por COVID-19, com aquele aumentando ainda o risco de morte. Já o uso de anti-TNF alfa apresentou efeito protetor. Entretanto, destaca-se que os achados são preliminares e dependem de novos estudos conduzidos na área para a tomada de decisão.
Palavras-chave: covid-19. doenças reumáticas. imunossupressão.

Introduction

Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) emerged in China in late December 2019[1]. COVID-19 is characterized by significant clinical heterogeneity, which can range from asymptomatic to life-threatening conditions, with the individual characteristics of infected patients related to the different outcomes observed[2]. The emergence and rapid global spread of the COVID-19-associated disease pandemic has raised several questions in the medical community about the risk of infection and risk factors in patients with autoimmune rheumatic diseases[3].

Autoimmune rheumatic diseases are characterized by irregular functioning of the immune system and immune-mediated inflammation in target tissues[4]. In this context, as COVID-19 is a new infectious disease, the response of the rheumatologic patient may be associated with an increased risk of severe infection, with pulmonary and severe systemic inflammatory manifestations related to a possible mechanism of hyperinflammation[5]. Thus, individuals with rheumatic diseases seem to have an increased risk of infection by SARS-Cov-2, with significant morbidity[6].

From this perspective, a great importance in the mortality associated with coronavirus infection in rheumatologic patients was given to the concomitant comorbidities of the patients. For COVID-19, a close correlation has been found with diabetes, hypertension, cardiovascular disease and, to a lesser extent, chronic obstructive pulmonary disease, chronic liver disease, and malignancies[7]. Thus, understanding the relationship between COVID-19 and the population of patients suffering from immuno-rheumatological diseases is of great importance.

However, understanding the factors associated with higher rates of SARS-CoV-2 infection and hospitalization in the context of rheumatologic diseases remains unclear, leading to uncertainties regarding the management of these patients, especially for those in use of immunosuppressants or immunomodulators[8]. In this sense, this work is justified in order to

investigate the response of rheumatologic patients to SARS-CoV-2 infection and the associated risk factors.

Thus, the present study aims to analyze, based on the current literature, the risk factors associated with infection and hospitalization of rheumatologic patients by SARS-Cov-2.

Materials and methods

Sample and type of study

This bibliographic research was conducted from a literature review, seeking a narrative approach. This type of research is based on the analysis of the material by the organization and the interpretation in order to satisfy the objective of the investigation[9].

Research design

The research sources used were the bibliographic databases MEDLINE via PUBMED, Science Direct, Scopus, in addition to the *"Portal Regional da Biblioteca Virtual de Saúde (BVS))"* database, using the following MeSH (Medical Subject Headings) descriptors: "COVID -19", "Rheumatic Disease", "Immunosuppression" and their combinations, using the Boolean operator "AND".

Inclusion and Exclusion Criteria

The inclusion criteria for the selection of scientific articles were: original articles with an approach related to the subject published between March 1, 2020 and June 15, 2021 (search period), written in Portuguese, English or Spanish. Productions involving the pediatric population, literature reviews, case series, expert opinions, editorials and articles in duplicate or with a subject different from the interest of the study in question were excluded. Thus, from the search through the descriptors, carried out from May 15 to June 15, 2021, and after applying the inclusion and exclusion criteria, 11 scientific productions were selected to compose this review (Figure 1). The numbers brought by each of the included articles can be seen in Table 1.

Figure 1. Flow diagram of the selection of articles for this narrative review.

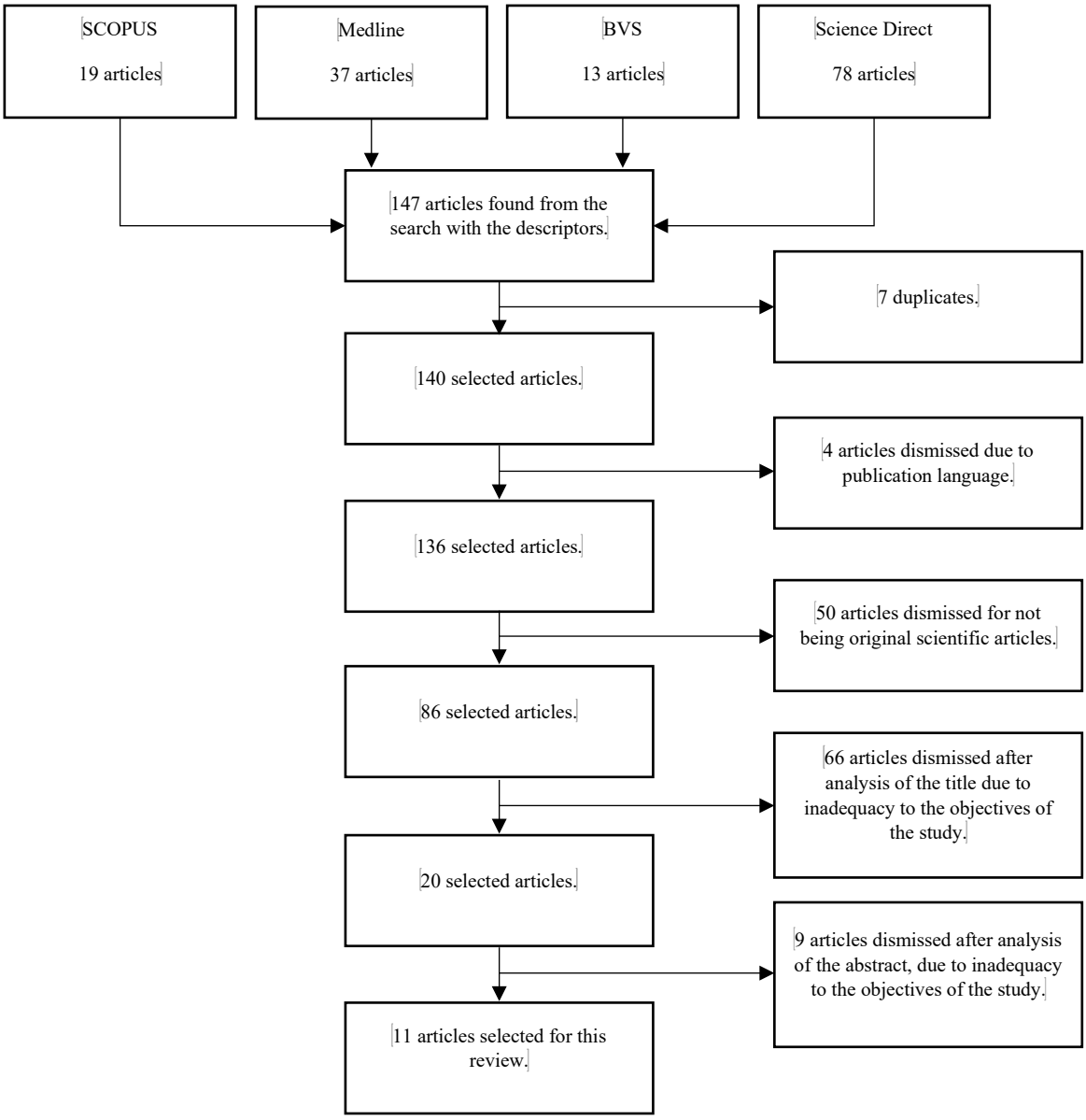

Table 1. Summary of the main characteristics of the studies selected for review.

Reference	Modelo of Study	Objetives	Number of Rheumatic Patients hospitalized for COVID-19	Number of Dead	Main Fidings
Arleo T. et al. Clin Rheumatol. 2021. 9:1–10[13].	Monocentric Cohort Study	Determine clinical course and outcomes in rheumatic disease patients with coronavirus disease 2019 (COVID-19) and compare outcomes with	48,6% (34/70)	8,6% (6/70)	• 49% of patients who were admitted used oral glucocorticoids more often than those treated as outpatients ($p < 0.01$) • All 10 patients using anti-TNFα drugs were treated

Reference	Modelo of Study	Objetives	Number of Rheumatic Patients hospitalized for COVID-19	Number of Dead	Main Fidings
		uninfected patients			on an outpatient basis ($p < 0.01$) • Those hospitalized with COVID-19 more often required ICU admission [17 (50%) vs 27 (26%), $p = 0.01$] and intubation [10 (29%) vs 6 (6%), $p < 0.01$] than uninfected patients and had higher mortality rates [6 (18%) vs 3 (3%), $p < 0.01$]. • Of the six COVID-19 patients who died, only one was of African descent ($p = 0.03$)
D'Silva KM et al. Ann Rheum Dis. 2020. Volume 79[14].	Multicenter Comparative Cohort Study	To investigate differences in the manifestations and outcomes of coronavirus disease 2019 (COVID-19) infection between those with and without rheumatic disease.	44,2% (23/52)	5,8% (3/52)	• Patients with and without rheumatic disease had similar symptoms and laboratory findings. • A similar proportion of patients with and without rheumatic disease were hospitalized [23 (44%) vs 42 (40%), p=0.50]. • Those with rheumatic disease required intensive care admission and mechanical ventilation more often [11 (48%) vs 7 (18%), OR 3.11 (95% CI 1.07 to 9.05)] • Mortality was similar between the two groups [3 (6%) vs 4 (4%), p=0.69]
Fredi M. et al. The Lancet Rheumatology. 2020. Volume 2[11].	Observational Study and Monocentric Case-Control Study	To analyze the course of severe acute respiratory syndrome from SARS-CoV-2 infection in patients with	72,3% (47/65)	15,4% (10/65)	• Of 1,525 patients with rheumatic and musculoskeletal diseases: 117 (8%) had symptoms consistent with COVID-19. 65

Reference	Modelo of Study	Objetives	Number of Rheumatic Patients hospitalized for COVID-19	Number of Dead	Main Fidings
		rheumatic and musculoskeletal diseases living in a district of Lombardy with a high prevalence of COVID-19			patients had a confirmation of SARS-CoV-2 infection by SWAB, while 52 had a spectrum of symptoms indicative of COVID-19 but were not tested. • 47 (72%) of 65 patients with confirmed COVID-19 developed pneumonia that required hospitalization • 12 (10%) deaths occurred among 117 patients with confirmed or suspected COVID-19 • Deceased patients with confirmed COVID-19 were older than survivors [median age 78.8 years (IQR 75.3–81.3) vs 65.5 years (53.3–74.0); p=0.0002] • No differences in sex, comorbidities or therapies were observed between deceased patients and survivors • The case-control study included 26 patients with rheumatic and musculoskeletal diseases and COVID-19 pneumonia and 62 matched controls • No significant differences were found between cases and controls in duration of COVID-19 symptoms prior to admission, duration of hospital

Reference	Modelo of Study	Objetives	Number of Rheumatic Patients hospitalized for COVID-19	Number of Dead	Main Fidings
					stay, or local chest X-ray scoring system • Glucocorticoids were used for severe respiratory manifestations related to lung involvement in 17 (65%) of 26 cases and tocilizumab in six (23%) of 26 cases. • Thrombotic events occurred in four (15%) of 26 cases • Four (15%) of 26 cases and six (10%) of 62 controls died during the study period
Marques CDL et al. RMD Open. 2021. Volume 7[5].	Multicenter Retrospective Observational Cohort Study	Assess risk factors associated with unfavorable outcomes: emergency care, hospitalization, intensive care unit (ICU) admission, mechanical ventilation, and death in patients with immune-mediated rheumatic disease (IMRD) and COVID-19	32,9% (110/334)	8,4% (28/334)	• 334 participants were enrolled, most of them women, with an average age of 45 years; Systemic lupus erythematosus was the most frequent IMRD (32.9%) • Emergency care was required in 160 patients, 33.0% were hospitalized, 15.0% were admitted to the ICU and 10.5% underwent mechanical ventilation; 28 patients (8.4%) died • In the multivariate fit model for emergency care, diabetes [prevalence ratio, PR 1.38; (95% CI 1.11 to 1.73); p=0.004], kidney disease [PR 1.36; (95% CI 1.05 to 1.77); p=0.020], oral glucocorticoids [PR 1.49; (95% CI 1.21 to 1.85); p<0.001] and pulse therapy with

Reference	Modelo of Study	Objetives	Number of Rheumatic Patients hospitalized for COVID-19	Number of Dead	Main Fidings
					methylprednisolone [PR 1.38; (95% CI 1.14 to 1.67); p=0.001] remained significant • For hospitalization, age >50 years [PR 1.89; (95% CI 1.26 to 2.85); p=0.002], no use of tumor necrosis factor inhibitor (TNFi) [PR 2.51; (95% CI 1.16 to 5.45); p=0.004] and pulsed methylprednisolone [PR 2.50; (95% CI 1.59 to 3.92); p<0.001] remained significant • For ICU admission, oral glucocorticoids [PR 2.24; (95% CI 1.36 to 3.71); p<0.001] and pulse therapy with methylprednisolone [RP 1.65; (95% CI 1.00 to 2.68); p<0.043] remained significant • The two variables associated with death were pulse therapy with methylprednisolone or cyclophosphamide [PR 2.86; (95% CI 1.59 to 5.14); p<0.018]
PAPA N. et al. Therapeutic Advances In Musculoskeletal Disease. 2020. Volume 12[7].	Monocentric Observational Study	To describe the prevalence and severity of COVID-19 in a large cohort of patients with Systemic Sclerosis during the SARSCOV-2 epidemic in an area of high prevalence of	100% (2/2)	50% (1/2)	• A total of 526 patients with SSc were contacted and interviewed. Of them, 270 and 256 had limited cutaneous and diffuse cutaneous SSc, respectively. • Interstitial Lung Disease was present in 45% of patients and the majority

Reference	Modelo of Study	Objetives	Number of Rheumatic Patients hospitalized for COVID-19	Number of Dead	Main Fidings
		the infection in Italy.			(68.2%) were treated with immunosuppressive therapy • Only two patients were hospitalized for COVID-19 pneumonia, and one of them died despite invasive ventilatory support • An additional 11 patients reported flu-like symptoms consistent with a mild form of COVID-19
Pistone A.; Tant, L.; Soyfoo, MS . Rheumatology Advances in Practice. 2020. Volume 4[1].	Monocentric Retrospective Observational Study	Little is known about the incidence and consequences of coronavirus disease 2019 (COVID-19) infection in patients with rheumatic diseases. To improve our knowledge in this field, we collected data from patients with inflammatory rheumatic diseases who developed COVID-19 infection.	30,4% (7/23)	4,3% (1/23)	• A total of 23 patients developed COVID-19 infection • Seven patients required hospitalization [female 57%, mean age 59 +/- 9 years], and 16 patients were followed up on an outpatient basis [female 80%, mean age 50 +/- 14 years] • All hospitalized patients had more than one comorbidity • At the time of infection, all patients were on immunosuppressive therapy consisting of conventional synthetic DARMDs and/or biotherapy, with or without Corticosteroids • The most common symptoms of patients infected with COVID-19 were fever, dyspnea, cough and fatigue • The average length of stay was 21 +/- 19 days • Three patients developed ARDS,

Reference	Modelo of Study	Objetives	Number of Rheumatic Patients hospitalized for COVID-19	Number of Dead	Main Fidings
					including one who died
SARZI-PUTTINI, Piercarlo et al. Journal of Autoimmunity. 2021. Volume 116[10].	Multicenter Retrospective Observational Study	To determine whether patients receiving biological or small molecule treatment are more susceptible to developing COVID-19 than the general population.	29,8% (14/47)	14,9% (7/47)	• All COVID-19 patients (47) had a history of 13.25 (SD 9.43) years of disease duration with moderate/high disease activity in 72.3%. • The most frequent comorbidities were hypertension (14 patients, 29.7%) and lung diseases (10 patients, 21.2%); comorbidity data were not different in rheumatic patients without COVID-19. Of the 47 subjects, 16 (34%) reported 2 medical comorbidities and 16 (31.9%) reported 3 or more comorbidities. • There was no statistically significant difference between the two groups regarding treatment with bDMARD or systemic corticosteroid; • 40% of patients in both groups were receiving monotherapy. • The overall infection rate was 0.65 and the crude case fatality risk (CFR) in COVID-19 patients was 14.9%. • There was no difference in the mortality rate between patients who received the different individual or small-molecule biologic drugs, but

Reference	Modelo of Study	Objetives	Number of Rheumatic Patients hospitalized for COVID-19	Number of Dead	Main Fidings
					there was a trend, although not significant, for more infections among patients who received tumor necrosis factor inhibitors.
Santos CS et al. Clin Rheumatol. 2020. Volume 39[6].	Monocentric Prospective Observational Study	To describe the epidemiological characteristics of patients with rheumatic diseases hospitalized with COVID-19 and to determine the risk factors associated with mortality in a third-level hospital setting in León, Spain.	100% (38/38)	26,3% (10/38)	• Patients who died of COVID-19 had higher markers of hyperinflammation than patients who survived: C-reactive protein [181 (IQR 120-220) vs 107.4 (IQR 30-150; p 0.05]; lactate dehydrogenase [641.8 (IQR 465.75-853.5) vs 361 (IQR 250-450), p 0.03]; serum ferritin [1026 (IQR 228.3-1536.3) vs 861.3 (IQR 389) - 1490.5), p 0.04]; D-dimer [12019.8 (IQR 843.5-25790.5) vs 1544.3 (IQR 619-1622), p 0.04]. • Risk factors that were associated with mortality: rheumatic disease activity (p 0.003), dyslipidemia (p 0.01), cardiovascular disease (p 0.02) and interstitial lung disease (p 0.02). • Rheumatic disease activity was significantly associated with fever (p 0.05), interstitial lung disease (p 0.03), cardiovascular disease (p 0.03) and dyslipidemia (p 0.01).
SANTOS C. et al. Rmd Open. 2021. Volume 7[12].	Monocentric Retrospective Observational Study	To estimate the rate of COVID-19 infection in patients treated	10% (4/10)	5% (2/40)	• 40 out of 820 patients with rheumatic diseases (4.8%) receiving

Reference	Modelo of Study	Objetives	Number of Rheumatic Patients hospitalized for COVID-19	Number of Dead	Main Fidings
		with biological disease-modifying drugs (bDMARDs) for inflammatory rheumatic diseases (RMD), determine the influence of treatment with biological agents as risk or protective factors, and study the prognosis of patients with rheumatic diseases diseases receiving biological agents compared to the general population in a third level hospital setting in León, Spain.			bDMARDs contracted COVID-19 and 4 required hospital care. • The crude incidence rate of COVID-19 requiring hospital care in the general population was 3.6% and was 0.89% in the group with underlying rheumatic diseases. • 90% of patients who received bDMARDS with COVID-19 did not require hospitalization. • Patients with rheumatic diseases who tested positive for COVID-19 were older [female: median age 60.8 IQR 46-74; male: median age 61.9 IQR 52-70.3] than those who were negative for COVID-19 [female: median age 58.3 IQR 48-69; male: median age 56.2 IQR 47-66].
SCIRE, C.A. et al. Clinical And Experimental Rheumatology. 2020. Volume 38[2.]	Multicenter Retrospective Observational Study	Monitor COVID-19 in patients with rheumatic and musculoskeletal diseases (RMDs).	69,8% (162/232)	19% (44/232)	• The population consisted mainly of elderly patients (mean age 62.2 years), who used corticosteroids (51.7%) and suffered from multimorbidities (median of comorbidities 2). • Rheumatoid arthritis was the most frequent disease (34.1%), followed by spondyloarthritis (26.3%), connective tissue disease (21.1%) and vasculitis (11.2%).

Reference	Modelo of Study	Objetives	Number of Rheumatic Patients hospitalized for COVID-19	Number of Dead	Main Fidings
					• Most cases had active disease (69.4%). • Clinical presentation of COVID-19 was typical, with both systemic (fever and asthenia) and respiratory symptoms. • The overall outcome was severe, with high frequencies of hospitalization (69.8%), respiratory support oxygen (55.7%), non-invasive ventilation (20.9%) or mechanical ventilation (7.5%) and 19 % of deaths. • Male patients generally had a worse prognosis.
ZHONG J. et al. The Lancet Rheumatology. 2020. Volume 2[4].	Multicenter Retrospective Observational Study	Investigate COVID-19 susceptibility in patients with autoimmune rheumatic diseases during the COVID-19 pandemic.	Not informed	Not informed	• The overall rate of COVID-19 in patients with autoimmune rheumatic disease in the study population was 0.43% (27 of 6,228 patients). • COVID-19 was diagnosed in 27 (63%) of 43 patients with rheumatic disease and in 28 (34%) of 83 without rheumatic disease [OR 2.68 (95% CI 1.14-6.27); p=0.023]. • Patients with rheumatic disease who were taking hydroxychloroquine had a lower risk of COVID-19 infection than patients taking other disease-modifying

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					antirheumatic drugs [OR 0.09 (95% CI 0.01-0.94); p = 0.044]. • In addition, the risk of COVID-19 increased with age [OR 1.04 (95% CI 1.01-1.06); p=0.0081].
TOTAL			47,4% (441/930)	12% (112/930)	

Table 2. Summary of main results with statistical significance by article included in the study

Reference	Variables with Statistical Significance
Arleo T. et al. Clin Rheumatol. 2021. 9:1–10[13].	**Need for Hospitalization** - Age (being older) (p <0.01) - Comorbidity: Kidney Disease (p<0.01) - Comorbidity: Heart Failure (p=0.02) - Type of Rheumatic Disease: Polymyalgia Rheumatica or Giant Cell Arteritis (p<0.01) - Chronic Use of Glucocorticoids (p<0.01) - Protective Factor: Inflammatory Bowel Disease (0=0.03), use of biological DARMD (p=0.02), use of anti-TNFalpha (p<0.01) **Hospitalized Patients with COVID-19 vs. Hospitalized Patients without COVID-19** - More patients with Polymyalgia Rheumatica or with Giant Cell Arteritis in the COVID-19 group (p=0.04) - Uninfected patients received hydroxychloroquine more frequently (p=0.03) - Patients in the COVID-19 group had higher C-Reactive Protein peaks (p<0.01) and lower albumin trough values (p=0.02) during their first hospitalization - Patients with COVID-19 had a longer hospital stay (p=0.03), more ICU admissions (p=0.01) and a greater need for intubation (p<0.01) - Patients with COVID-19 required more ventilator days (p=0.02) and died more during hospitalization (p<0.01) **Admitted COVID-19 Patients: Survivors vs Those Who Died** - Patients who died were older (p<0.01) - Protection factor: African-American race (p=0.03) - ICU admission and death (p<0.01) - Need for ventilation and death (p=0.03)
D'Silva KM et al. Ann Rheum Dis. 2020. Volume 79[14].	**Patients with COVID-19: Carriers of Rheumatic Disease vs Non-Carriers of Rheumatic Disease** - Comorbidities: Coronary Artery Disease (p=0.03), Interstitial Lung Disease (p=0.01) and Obstructive Sleep Apnea (p=0.03) were more common in the group with rheumatic disease - Need for ICU Admission/Mechanical Ventilation was higher in the group with rheumatic disease (p=0.01) - Greater need for Mechanical Ventilation in the group with rheumatic disease (p=0.02) **Rheumatic Patients with COVID-19: Need for Hospitalization** - Group that required hospitalization was older (older) (p=0.05), more comorbidities (p=0.03) and more diabetes (p=0.04)

Reference	Variables with Statistical Significance
Fredi M. et al. The Lancet Rheumatology. 2020. Volume 2[11].	**Patients with Rheumatic Disease: Confirmed cases of COVID-19 vs Suspected cases of COVID-19** - Confirmed cases were older (p=0.001) and had higher rates of comorbidities such as Systemic Arterial Hypertension (p=0.031) and obesity (p=0.059) **Among patients with rheumatic disease with confirmed COVID-19** - The group that required hospitalization was older (p=0.036) - The group of those who died were older (p=0.0002) **Case-Control Study Among Patients Hospitalized for COVID-19 With Rheumatic Disease (Cases) vs Without Rheumatic Disease (Control)** - The lowest number of lymphocytes recorded (deeper lymphopenia) was recorded in the Case group (p=0.021)
Marques CDL et al. RMD Open. 2021. Volume 7[5].	**Need for Emergency Department Care for Rheumatic Patients with COVID-19 Confirmed** - Inactivity at work (p=0.002), presence of diabetes (p=0.008), hypertension (p=0.020), hypothyroidism (p=0.030), kidney disease (p=0.046), use of oral corticosteroids (p<0.001) and pulse therapy with methylprednisolone (p=0.018) were implicated in a greater need for care in the Emergency Department - Considering multivariate adjustment using the Poisson model, diabetes, kidney disease, use of oral glucocorticoids, and pulse therapy with methylprednisolone remained significant **Rheumatic Patients with Confirmed COVID-19: Need for Hospitalization** - Not using TNFalpha inhibitors was associated with a greater need for hospitalization (p=0.007) - Considering binary associations, a greater need for hospitalization was associated with age > 50 years (p=0.002), not using a TNF inhibitor (p=0.005), use of oral glucocorticoids (p=0.005), use of oral glucocorticoids in doses greater than 20mg/day (p=0.007) and pulse therapy with methylprednisolone as treatment for rheumatic disease (p=0.014) - Considering the multivariate analysis using the Poisson model, age > 50 years, not using TNF inhibitor and pulse therapy with methylprednisolone remained statistically significant **Rheumatic Patients with Confirmed COVID-19: ICU Admission** - Use of oral glucocorticoids (p=0.001), not using TNF inhibitor and pulse therapy with methylprednisolone or cyclophosphamide as treatment for rheumatic disease (p=0.042) - Considering the multivariate analysis using the Poisson model, the use of oral corticosteroids and pulse therapy with methylprednisolone remained statistically significant, while the disease Systemic Lupus Erythematosus proved to be a possible protective effect for ICU admission **Rheumatic Patients with Confirmed COVID-19: Risk of Death** - Not using TNF inhibitors and pulse therapy with methylprednisolone or cyclophosphamide as treatment of rheumatic disease were associated with increased risk of death (P 0.018)
PAPA N. et al. Therapeutic Advances In Musculoskeletal Disease. 2020. Volume 12[7].	**Article Did Not Present Statistical Analysis**
Pistone A.; Tant, L.; Soyfoo, MS . Rheumatology Advances in Practice. 2020. Volume 4[1].	**Article Did Not Present Statistical Analysis**
SARZI-PUTTINI, Piercarlo et al. Journal of	**Article did not present results with statistical significance**

Reference	Variables with Statistical Significance
Autoimmunity. 2021. Volume 116[10].	
Santos CS et al. Clin Rheumatol. 2020. Volume 39[6].	**Patients with rheumatic disease and confirmed COVID-19 survivors vs. patients with rheumatic disease and confirmed COVID-19 deceased: comorbidities.** - Arterial hypertension [9 (90%) vs 14 (50%); OR 9 (95% CI 1.0 - 80.8); p 0.049], dyslipidemia [9 (90%) vs 12 (43%); OR 12 (95% CI 1.33-108); p 0.03], diabetes [9 (90%) vs 6 (28%); OR 33 (95% CI 3.46 - 314.55); p 0.002], interstitial lung disease [6 (60%) vs 6 (21%); OR 5.5 (95% CI 1.16 - 26); p 0.03], cardiovascular disease [8 (80%) vs 11 (39%); OR 6.18 (95% CI 1.10 - 34.7); p 0.04] were associated with higher mortality in rheumatic patients with confirmed COVID-19. **Patients with rheumatic disease and confirmed COVID-19 survivors vs. patients with rheumatic disease and confirmed COVID-19 deceased: disease activity.** - A moderate/high rate of rheumatic disease activity [7 (25%) vs 6 (60%); OR 41.4 (4.23 - 405.23), p 0.04] was associated with a higher risk of mortality in rheumatic patients with confirmed COVID-19. - Rheumatic disease activity was significantly associated with fever (p 0.05), interstitial lung disease (p 0.03), cardiovascular disease (p 0.03) and dyslipidemia (p 0.01). **Patients with rheumatic disease and confirmed COVID-19 survivors vs. patients with rheumatic disease and confirmed COVID-19 deceased: markers of inflammation.** - Patients who died of COVID-19 had higher markers of hyperinflammation than patients who survived: C-reactive protein [181 (IQR 120-220) vs 107.4 (IQR 30-150; p 0.05]; lactate dehydrogenase [641.8 (IQR 465.75-853.5) vs 361 (IQR 250-450); p 0.03]; serum ferritin [1026 (IQR 228.3-1536.3) vs 861.3 (IQR 389) - 1490.5); p 0.04]; D-dimer [12019.8 (IQR 843.5-25790.5) vs 1544.3 (IQR 619-1622); p 0.04].
SANTOS C. et al. Rmd Open. 2021. Volume 7[12].	**Rheumatic patients with confirmed COVID-19 vs discarded COVID-19: comorbidities** - Among the comorbidities evaluated, patients with hypertension [45% vs 26%, OR 2.25 (95% CI 1.18 - 4.27), p 0.02] and patients with cardiovascular disease [23% vs 9.6 %, OR 2.73 (95% CI 1.25 - 5.95), p 0.02] had a higher risk of infection by Sars-CoV-2 in the study population. **Rheumatic patients with confirmed COVID-19 vs discarded COVID-19: smoking** - Smokers [13% vs 4.6%, OR 2.95 (95% CI 1.09 - 7.98), p 0.04] are at increased risk for SARS-CoV-2 infection in the study population. **Rheumatic patients with confirmed COVID-19 vs discarded COVID-19: specific therapy** - Patients using rituximab [20% vs 8%, 2.28 (95% CI 1.24 - 6.32); p 0.02] and a higher dose of glucocorticoids [OR 2.5 (95% CI 1.3 - 10.33); p 0.02] were more prone to SARS-CoV-2 infection. - Patients treated with IL-6 inhibitors [2.5% vs 14%, OR 0.16, (95% CI 0.10 - 0.97); p 0.03] were less likely to be infected with Sars-CoV-2.
SCIRE, C.A. et al. Clinical And Experimental Rheumatology. 2020. Volume 38[2].	**Article did not present results with statistical significance**
ZHONG J. et al. The Lancet Rheumatology. 2020. Volume 2[4].	**Patients with rheumatic disease and with COVID-19 vs. Patient without rheumatic disease and with COVID-19: age** - The risk of COVID-19 increased with age after adjusting for sex and rheumatic disease [OR 1.04 (95% CI 1.01 - 1.06); p=0.0081]. **Patients with rheumatic disease and with COVID-19 vs. Patient without rheumatic disease and with COVID-19: risk of infection.**

Reference	Variables with Statistical Significance
	- Patients with rheumatic disease had a higher risk of SARS-CoV-2 infection compared to patients without rheumatic disease in the study. [OR was 2.68 (95% CI 1.14 - 6.27; p=0.023] **Patients with rheumatic disease and with COVID-19 vs. Patient without rheumatic disease and with COVID-19: specific therapy.** - Patients with rheumatic disease using hydroxychloroquine had a lower risk of COVID-19 than those taking other DMARDs [OR 0.09 (95% CI 0.01 - 0.94); p=0·044].

Results

Factors associated with increased risk of SARS-COV-2 infection and/or worse prognosis

Rheumatic disease

Rheumatic patients were considered a vulnerable group for SARS-COV-2 infection[4]. In this study, 27/43 (63%) of patients with rheumatic disease and 28/83 (34%) of patients without rheumatic disease developed COVID-19 (OR 3.32; 95% CI 1.54-7.14; p =0.0023], which demonstrates a greater propensity for infection after exposure in the group of rheumatic patients. However, other studies showed that the population of rheumatic patients was not particularly susceptible to the new coronavirus in relation to the general population, so that other risk factors seem to be more involved in this association[6, 7, 10, 11].

Neither did the type of rheumatic disease prove to be relevant with regard to the significance of association with risk of infection by SARS-Cov-2[12]. However, it was observed that patients with Polymyalgia Rheumatica (PMR) or with Giant Cell Arteritis (GCA) were more frequent in the COVID-19 group (p=0.04)[13].

Gender

The gender variable did not show statistical significance among rheumatic patients[4, 12], which determined a similar odds ratio for men and women (OR 0.6; 95% CI 0.26-1.35; p=0.22)[4]. In disagreement, a greater proportion of men developed pneumonia when infected with SARS-Cov-2, although this subgroup, in their study, presented a series of particularities, such as being older, having more comorbidities and being heavier smokers[2] when compared to women.

Age

Still addressing demographic variables, age > 65 years was a characteristic that showed significance for the risk of infection, even after a multivariate analysis study[12]. In agreement, rheumatic patients aged > 50 years were associated with higher prevalences of unfavorable outcomes from COVID-19[5]. On the other hand, another study denied a significant difference in the ages of those with and without rheumatic disease diagnosed with COVID-19 [49.2 (+/-11.6) years vs. 48.4 (+/-19.1) years; p=0.82][4].

Race/Ethnicity

The last subgroup variable approached by the studies, race/ethnicity, showed a similar distribution in both groups (patients with and without disease, both with COVID-19 (p=0.2 in both).

Comorbidities

Most patients with more than one comorbidity had more severe damage from infection with the new coronavirus[1]. In contrast, in another study, it was observed that the mean number of comorbidities was similar in both groups in patients with COVID-19 and rheumatic disease vs in patients with COVID-19 and without rheumatic disease (p=0.3)[14].

In the group of patients using b-DARMDs who had COVID-19, the comorbidities that showed significance for the risk of acquiring the infection were hypertension, cardiovascular disease and smoking. However, only the last two remained relevant after multivariate analysis[12]. In addition, diabetes and kidney disease were reported to be the conditions associated with higher prevalence of unfavorable outcomes of COVID-19 in rheumatic patients[5]. Furthermore, an increased frequency of hypertension and obesity was noted in patients with confirmed SARS-Cov-2 virology, considering these risk factors associated with more severe symptoms of COVID-19[11].

Medications in use for underlying rheumatic disease

Regarding the chronic therapy of underlying rheumatic diseases, the prognosis of COVID-19 infection is more related to the presence of other risk factors than to the rheumatic disease itself, or to the therapy of this disease[6, 11]. From this perspective, it was not possible to evaluate the association of COVID-19 with the combined use of different immunosuppressants or combinations of DARMDs[5].

Opinions about the influence of corticosteroid use were quite conflicting. Prednisone users showed an increased risk of adverse outcomes in SARS-Cov-2 infection, compared to patients who did not use it[2]. In addition, another study ensures that both the use of oral corticosteroids and pulse therapy with methylprednisolone are associated with higher prevalence of unfavorable outcomes when the infection in question is acquired[5]. To end this viewpoint, the use of high doses of glucocorticoids showed significance for the risk of acquiring the infection, although it did not remain so when performing the multivariate analysis[12]. In an opposite view to what has been proposed so far, there was no statistically significant difference regarding the use of low/moderate dose corticosteroids (5 - 15 mg/day) between the group of infected and non-infected by COVID-19[4, 10].

When comparing hospitalized patients with and without COVID-19, it was noticed that uninfected patients received hydroxychloroquine more frequently (p=0.03)[13]. In addition, rheumatic disease patients taking hydroxychloroquine had a lower risk of COVID-19 than those taking other DARMDs [OR 0.09; IC 95% 0.01-0.94; p=0.044]4. However, a protective effect of hydroxychloroquine was not observed in relation to COVID-19, so that this group of users are likely to develop the disease and be at risk of unfavorable outcomes[5, 14].

Chronic biologic drug therapies for underlying rheumatic disease were associated with a lower risk of adverse outcomes from novel coronavirus infection[2]. On the other hand, there was no statistically significant difference for the use of b-DARMDs between the COVID-19 infected and non-infected groups[10]. In addition, drugs other than hydroxychloroquine showed similar prevalence of use among the group of hospitalized rheumatic patients with and without COVID-19[13].

Specifically, TNF-alpha inhibitor drugs showed a protective effect for favorable outcomes of SARS-Cov-2[5] infection. On the same category as biological drugs, the use of rituximab

(anti-CD20) was a characteristic of the group of patients using b-DARMDs who had COVID-19 and the use of IL-6 inhibitors (sarilumab and tocilizumab) was a relevant feature among the group of patients with rheumatic disease using b-DARMDs who did not acquire COVID-19 infection. It is noteworthy that none of these associations remained significant after multivariate analysis[12].

The last class of drugs used in the treatment of the underlying rheumatic disease addressed in this review, the ts-DARMDs, were identified as having a potential protective effect, although, after adjusted for age, gender and comorbidities, such treatment did not remain significantly associated with the outcome[2].

Factors associated with the need for hospitalization

Rheumatic Disease

Regarding the need for hospitalization, neither differences were found between the various types of rheumatic disease nor in the severity of such underlying diseases in the group of hospitalized patients[14].

Age

Regarding demographic factors, the most cited was the age of the patients. It was found that age over 50 years (PR 1.91; 95% CI 1.26-2.91; p=0.002) is a statistically significant factor associated with the need for hospitalization[5]. In addition, the mean age of the group of patients who were hospitalized was almost 10 years older than the group that did not need such procedure (mean age of 59 years vs. 50 years)[1, 14]. In another study, such difference between the mean age was even higher: 16.8 years between the groups (65.2 years vs. 48.4 years for those who did not require hospitalization; p<0.01)[13]. Confirming this association, another study highlighted that age was the only significant difference, greater between the hospitalized group [mean age 70 years (ranging from 60.5-76 years) vs. 54 years (ranging from 47.0-73.8 years; p=0.036][11].

Gender

A single study found that men have a higher proportion of hospitalization than women. However, this subgroup of the study had a higher mean age than the women in the study, in addition to higher rates of comorbidities (particularly cardiovascular diseases) and a higher frequency of smoking (14.5% vs. 7.4%)[2].

Race/Ethnicity

Still on demographic factors, there was a higher proportion of African Americans who needed hospitalization vs. those who did not (30% vs. 14%)[14]. In disagreement, another study found that the hospitalization rate among African-Americans was similar to the general rate[13].

Comorbidities

Another category of variables that is very important to be evaluated, comorbidities, were not identified as statistically relevant for greater chances of hospitalization[11]. However, it was observed that, among patients with rheumatic disease, those hospitalized had more comorbidities [2(1-2) vs. 1(0-1); p=0.03], in addition to the fact that all hospitalized patients had more than one comorbidity[1,14].

Specifically regarding comorbidities, when comparing hospitalized and non-hospitalized patients with COVID-19, it was concluded that those had more comorbidity of kidney disease (p<0.01) and heart failure (p=0.02)[13]. In turn, most patients admitted to hospital had important comorbidities: hypertension (60%), dyslipidemia (55%), diabetes (32%), cardiovascular disease (50%) and interstitial lung disease (32%)[6]. In this context, the most common disease in the group of hospitalized rheumatic patients

was diabetes [9 (39%) vs. 4(14%); p=0.04][14]. Besides, another study indicates that 1/3 of the obese patients included required hospitalization[1].

Medications in use for underlying rheumatic disease

When analyzing the medications used for the treatment of underlying rheumatic disease, some authors deny differences between hospitalized and patients treated at home[11, 14].

Regarding corticosteroids, there are differences in the studies addressed in this review. Hospitalized patients tended to receive more corticosteroids in chronic therapy (71% vs. 36% among the non-hospitalized group; p<0.01)[13]. In addition, the use of oral corticosteroids (PR 1.82; 95% CI 1.1-2.74; p=0.005), oral corticosteroids at doses > 20mg/day (PR 2.18; 95% CI 1.29 -3.66; p=0.007) and pulse therapy with methylprednisolone (PR 2.90; 95% CI 1.73-4.87; p=0.014) led to a greater need for hospitalization[5]. Another author, in his study, reports that, among his patients, the use of corticosteroids was less frequent among those admitted to hospital (2 vs. 3)[1].

The use of b-DARMDs has a protective effect against the need for hospitalization, since hospitalized patients tended to receive fewer b-DARMDs (p=0.02), and that, of these, no patient using a TNF-alpha inhibitor was hospitalized (p<0.01)[13]. Likewise, it was observed that biologicals (5 vs. 12) were less frequently used among hospitalized patients[1]. Besides, it was found that not using TNF-alpha inhibitors was a factor statistically associated with hospital admission (PR 2.69; 95% CI 1.26-2.91; p=0.005)[5].

Still on the pharmacological therapies commonly prescribed for rheumatic patients, the use of cs-DARMDs was shown to be less common in hospitalized patients (4 vs 11)[1]. Other authors have not noticed a relationship between the previous use of antimalarials (eg, hydroxychloroquine) and hospitalization[6, 13].

Discussion

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with droplets and contact being the main routes of transmission[15]. In addition, patients with severe COVID-19 are characterized by an acute systemic inflammatory response and cytokine storm, which can result in multiple organ damage. Systemic cytokine storm is associated with considerable mortality. Pro-inflammatory cytokines (IL-1β, IL-18, IFN-γ, and IL-6) are induced by excessive innate immune activation resulting from delayed or impaired early immune responses and are key mediators of late-phase hyperinflammation in COVID-19[3].

From this, it was suggested a greater susceptibility of rheumatic patients to COVID-19 and a severity of the disease in these patients. However, the impact of SARS-CoV-2 infection in patients with chronic rheumatic disease is still unclear. Rheumatic patients may be susceptible to infections due to their immunosuppressive treatments or their underlying condition. According to Parr et al., 2014[16], rheumatic patients are at greater risk for developing infectious lung diseases which management depends on the cessation of immunosuppressive therapy. Patients with rheumatoid arthritis are twice as likely to develop infection, being this risk associated with the use of glucocorticoids and TNF-alpha inhibitors[17].

Findings from preliminary studies suggest that rheumatic patients are no more susceptible to COVID-19 than the general population[7,10]. Thus, some studies show that a higher rheumatic disease activity was

associated to a higher probability to develop SARS-Cov-2 infection, being moderate/high disease activity significantly associated to death related to COVID-19[8,10,13].

Regarding the need for hospitalization, studies have shown a greater chance of hospitalization in patients with rheumatic disease, with a greater number of hospitalizations of these patients globally and nationally[24,25].

With regard to the severity of SARS-Cov-2 infection in rheumatic patients, patients with rheumatic disease had symptoms and odds of hospitalization and mortality similar to the general population, but three times greater odds of admission to intensive care unit/mechanical ventilation compared to patients without rheumatic disease[14]. In agreement, a higher rate of ICU admission, mechanical ventilation and death was observed among rheumatic patients with COVID-19, suggesting a worse clinical performance[13]. Furthermore, among people with rheumatic disease, death related to COVID-19 was associated with known general factors (advanced age, male gender, and specific comorbidities) and disease-specific factors (disease activity and specific medications)[8, 13].

On the other hand, it has been proposed that the use of immunosuppressive therapies by rheumatic patients would be beneficial in the treatment of COVID-19, with studies demonstrating a lower incidence of COVID-19 in patients receiving immunosuppressants than in the general population[1, 6, 7, 13, 15]. In addition, the potential benefit of biologics in the treatment of COVID-19 is highlighted by those with more severe disease and higher levels of cytokines, including IL-6 and TNF[6]. In agreement, it was observed that the chances of hospitalization for COVID-19 of rheumatic patients would be reduced by the use of anti-TNF treatments[1].

Another explanation for the improved outcomes in patients using DMARDs is that these patients follow their rheumatologist more closely and have better control of their underlying disease[7, 13]. Furthermore, these patients typically require less chronic use of steroids, which is a known risk factor for worse outcomes[1, 13].

The relationship of SARS-Cov-2 infection in rheumatic patients with the sex of patients remains unclear. Some studies have shown that among the factors associated with death, being male increases the chance of death related to COVID-19 in these patients[8, 10]. On the other hand, another study found no significant differences in sex and in rheumatologic disease among patients with the test positive for COVID-19 and patients testing negative[6].

Regarding the demographic factor “age of patients”, it was established in our study that advanced age, in particular over 60 years, is a factor for the increased risk of hospitalization in rheumatic patients, which is consistent with several previously reported studies[18-21]. Still on demographic factors, there was a greater proportion of African Americans who needed hospitalization versus those who did not (30% vs. 14%)[14]. In disagreement, another study showed that the hospitalization rate among Afro-Americans was similar to the general population[13].

In our study, patients' comorbidities were associated with a higher chance of severe manifestation of COVID-19 and hospitalization in the group of rheumatologic patients, especially in those who had more than one comorbidity[1, 14]. Among the comorbidities, hypertension, cardiovascular disease, heart failure, diabetes, preexisting lung disease, renal failure, dyslipidemia and obesity stood

out[1, 6, 13, 14]. Such results were also found in other studies, which strengthens the premise that comorbidities are one of the factors associated with greater chances of hospitalization in rheumatic patients[19, 22]. However, in one of the studies, no statistical relevance was observed for greater chances of hospitalization regarding the presence of comorbidities[11].

In respect of the basic treatment of rheumatologic diseases, we have the disease-modifying antirheumatic drugs (DARMDs). They can be categorized into conventional (cs-DARMDs) and biological (b-DARMDs) synthetics. In general, these drugs do not change the chances of hospitalizations or mortality rates, suggesting little influence of these immunosuppressive medications on COVID-19 infection and its severity[11, 14, 20]. This fact is disputed, since, in the study of these drugs, it was established that patients who undergo treatment with Rituximab (RTX), a representative of the non-TNF alpha inhibitor b-DARMDs class, have a significantly higher rate of hospitalizations, serious infections and deaths from COVID-19 in rheumatologic patients, this finding being justified by the fact that RTX has a direct effect reducing mature B lymphocytes and an indirect effect on T lymphocytes, inducing a reduction in CD4 and CD8 cells, resulting in severe lymphopenia and dysregulation between innate and adaptive immunity, predisposing to a worse prognosis[19]. In addition, there is an association between the use of Rituximab and an increased chance of hospitalization and death in rheumatologic patients[19]. Regarding anti-TNF alpha, it was observed that they have a protective effect on the need of hospitalization, as none of the patients using anti-TNF alpha were hospitalized during the studies[13, 18, 22]. In addition, not using TNF alpha inhibitors was found to be a factor associated with hospital admission[5].

Still on the pharmacological therapies commonly prescribed for rheumatic patients, the use of cs-DARMDs was less common in hospitalized patients, that is, it was associated with a reduced risk of hospitalization[1], however, some studies did not perceive a relationship between the previous use of antimalarials, such as hydroxychloroquine and hospitalization[6, 13]. On the other hand, the use of Sulfasalazine and other potent immunosuppressants (cyclophosphamide, azathioprine, mycophenolate, cyclosporine and tacrolimus) are specific risk factors for hospitalization in patients with rheumatic disease[17].

Regarding the use of glucocorticoids, it is observed that chronic therapy is twice as common in the group of rheumatic patients who were hospitalized for COVID-19[13], as well as that the use of oral corticosteroids at a dose > 20 mg/day and/or pulse therapy with methylprednisolone is statistically significant for greater need for hospital admission[5]. In addition, the use of corticosteroids was less frequent among those admitted to hospital[1]. The chronic use of oral glucocorticoids, such as prednisone, at a dose equivalent to ≥ 10 mg/day is associated with a greater chance of hospitalization in patients with rheumatologic diseases[19], different from what was found in the RECOVERY study, which evaluated the efficacy of acute glucocorticoid therapy for COVID-19, reducing the number of hospitalizations. However, initial treatment with glucocorticoids at doses ≥ 5 mg/day is associated with a greater chance of a more severe COVID-19 infection, requiring hospitalization[21, 23].

Conclusions

In conclusion, the present study found that patients with rheumatologic diseases were not more susceptible to

SARS-Cov-2 related infection and hospitalization when compared to the general population, as long as the underlying disease is controlled, as moderate/severe rheumatic disease activity was associated with higher mortality related to COVID-19. Furthermore, rheumatic patients showed a worse clinical performance when hospitalized, presenting a three times greater chance of admission to intensive care unit/mechanical ventilation.

Among the group of rheumatic patients, advanced age, over 60 years old, was associated with an increased risk of more severe infection and hospitalization for COVID-19, which was also valid for the presence of comorbidities in this group of patients, especially cardiovascular and pulmonary diseases. Regarding the impact of baseline therapy for rheumatological diseases on the risk of infection and hospitalization for COVID-19, patients using rituximab and on chronic therapy with glucocorticoids at a dose ≥ 5 mg/day were at increased risk, unlike patients using anti-TNF alpha that had a protective effect.

However, it is noteworthy that such findings are preliminary and that they depend on new studies that are being conducted in this theme to confirm the data obtained and the consequent preemptive measures.

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Bibliographical References

1. Pistone A, Tant L, Soyfoo MS. Clinical course of COVID-19 infection in inflammatory rheumatological patients: a monocentric belgian experience. *Rheumatology Advances In Practice*. 2020; 4(2): 1-8.
2. Scirè CA, Carrara G, Zanetti A, Landolfi G, Chighizola C, Alunno A, et al. COVID-19 in rheumatic diseases in Italy: first results from the Italian registry of the Italian Society for Rheumatology (CONTROL-19). *Clinical And Experimental Rheumatology*. 2020; 38(4): 748-753.
3. Thanou A, Sawalha AH. SARS-CoV-2 and Systemic Lupus Erythematosus. *Current Rheumatology Reports.* 28 jan. 2021; 23(2): 4-5.
4. Zhong J, Shen G, Yang H, Huang A, Chen X, Dong L, et al. COVID-19 in patients with rheumatic disease in Hubei province, China: a multicentre retrospective observational study. *The Lancet Rheumatology*. set. 2020; 2(9): 557-564.
5. Marques CDL, Kakehasi AM, Pinheiro MM, Mota LMH, Albuquerque CP, Silva CR, et al. High levels of immunosuppression are related to unfavourable outcomes in hospitalised patients with rheumatic diseases and COVID-19: first results of reumaCoV Brasil registry. *Rmd Open*. jan. 2021; 7(1): 1461-73.
6. Santos CS, Morales CM, Álvarez ED, Castro CÁ, Robles AL, Sandoval TP. Determinants of COVID-19 disease severity in patients with underlying rheumatic disease. *Clinical Rheumatology*. 27 jul. 2020; 39(9): 2789-96.
7. Del Papa N, Sambataro G, Minniti A, Maglione W, Pignataro F, Caminati A, et al. Impact of COVID-19 outbreak in an Italian cohort of patients with systemic sclerosis. *Therapeutic Advances In Musculoskeletal Disease*,. jan. 2020; 12: 1-8.

8. Strangfeld A, Schäfer M, Gianfrancesco MA, Lawson-Tovey S, Liew JW, Ljung L, et al. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the covid-19 global rheumatology alliance physician-reported registry. *Annals Of The Rheumatic Diseases*. 27 jan. 2021: 1-13.
9. Taquette SR, Minayo MCDS, Rodrigues ADO. Percepção de pesquisadores médicos sobre metodologias qualitativas. *Cadernos de Saúde Pública*. 2015; 31(4): 722-32.
10. Sarzi-Puttini P, Marotto D, Caporali R, Montecucco CM, Favalli EG, Franceschini F, et al. Prevalence of COVID infections in a population of rheumatic patients from Lombardy and Marche treated with biological drugs or small molecules: a multicentre retrospective study. *Journal Of Autoimmunity*. jan. 2021; 116: 102545.
11. Fredi M, Cavazzana I, Moschetti L, Andreoli L, Franceschini F, Airò P, et al. COVID-19 in patients with rheumatic diseases in northern Italy: a single-centre observational and case–control study. *The Lancet Rheumatology*. 2020; 2(9): e549-e556.
12. Santos CS, Férnandez XC, Morales CM, Álvarez ED, Castro CÁ, Robles AL, et al. Biological agents for rheumatic diseases in the outbreak of COVID-19: friend or foe?. *RMD open*. 2021; 7(1): e001439.
13. Arleo T, Tong D, Shabto J, O'Keefe G, Khosroshahi A. Clinical course and outcomes of COVID-19 in rheumatic disease patients: a case cohort study with a diverse population. *Clinical Rheumatology*. 9 jan. 2021; 40(7): 2633-42.
14. D'Silva KM, Serling-Boyd N, Wallwork R, Hsu T, Fu X, Gravallese EM, et al. Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: a comparative cohort study from a US 'hot spot'. *Annals Of The Rheumatic Diseases.* 26 maio 2020; 79(9): 1156-62.
15. Quartuccio, L., Valent, F., Pasut, E., Tascini, C., & De Vita, S.. Prevalence of COVID-19 among patients with chronic inflammatory rheumatic diseases treated with biologic agents or small molecules: a population-based study in the first two months of covid-19 outbreak in italy. *Joint Bone Spine.* out. 2020; 87(5): 439-443.
16. Parr JB, Gill RR, Katz, JT. Respiratory Infections in the Rheumatic Disease Patient. In: Dellaripa, P., Fischer, A., Flaherty, K. (eds) Pulmonary Manifestations of Rheumatic Disease. Springer, New York, NY. 2014.
17. Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. *Rheumatology (Oxford*). Jan 2013; 52(1):53-61.
18. Bachiller-Corral J, Boteanu A, Garcia-Villanueva MJ, de la Puente C, Revenga M, Diaz-Miguel MC, et al. Risk of severe coronavirus infection (COVID-19) in patients with inflammatory rheumatic diseases. *The Journal of Rheumatology.* jul. 2021; 48(7): 1098-1102.
19. Goldman JD, Robinson PC, Uldrick TS, Ljungman P. COVID-19 in immunocompromised populations: implications for prognosis and repurposing of immunotherapies. *Journal for immunotherapy of cancer*. 2021; 9(6).
20. Alzahrani ZA, Alghamdi KA, Almaqati AS. Clinical characteristics and outcome of COVID-19 in patients with rheumatic diseases. *Rheumatology international*. 2021; 41(6), 1097-1103.
21. Hasseli R, Mueller-Ladner U, Hoyer BF, Krause A, Lorenz HM, Pfeil A, et al.. Older age, comorbidity, glucocorticoid use and disease activity are risk factors for COVID-19 hospitalisation in patients with inflammatory rheumatic and musculoskeletal diseases. *Rmd Open*. 2021; 7(1), e001464.
22. Wang Q, Liu J, Shao R, Han X, Su C, Lu W. Risk and clinical outcomes of COVID-19 in patients with rheumatic diseases compared with the general population: a systematic review and meta-analysis. *Rheumatology international*. 9 mar. 2021: 1-11.

23. Montero F, Martínez-Barrio J, Serrano-Benavente B, González T, Rivera J, Collada JM, et al. Coronavirus disease 2019 (COVID-19) in autoimmune and inflammatory conditions: clinical characteristics of poor outcomes. *Rheumatology international.* 2020; 40(10): 1593-98.
24. Gianfrancesco M, Hyrich KL, Al-Adely S, 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
25. NORMANDO, Paulo G et al. Redução na Hospitalização e Aumento na Mortalidade por Doenças Cardiovasculares durante a Pandemia da COVID-19 no Brasil. Arquivos Brasileiros de Cardiologia, [S.L.], 4 fev. 2021.

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