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Systematic Review

Rheumatoid arthritis, multiple sclerosis and lupus: key points from the COVID-19 era

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ABSTRACT

The purpose of this work was to analyse published data on rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and multiple sclerosis (MS) and SARS-CoV-2 infection: susceptibility, post-infection autoimmune disease (AD) exacerbation, immunosuppressive therapies and long COVID. Supported by PICO strategy, two independent reviewers conducted the research in the PubMed/Medline database from January 2020 to June 2022 and included 16 articles on RA, 25 on MS and 12 on SLE. The quality assessment of the studies was performed using criteria from the National Institute of Health. Patients with RA or SLE had increased susceptibility to contracting SARS-CoV-2. It was higher in RA and increased with the patients' comorbidities. For MS, susceptibility to SARS-CoV-2 was similar to the general population. Post-infection AD exacerbation occurred in AR, SLE and MS with an increased number of hospitalisations and deaths. Regarding therapies, in RA the use of glucocorticoids (GC) was associated with a worsening of the infection. A more severe clinical picture was associated with anti-CD20 in SLE and with anti-CD20 and methylprednisolone in MS. Considering long COVID, RA and SLE patients had a higher risk of complications opposite to MS patients. There was a higher susceptibility to SARS-CoV-2 infection in rheumatological diseases AR and SLE, exacerbated by age and comorbidities. For RA and MS, GC aggravated the infection and for SLE and MS anti-CD20 antibodies use. In all AD there was exacerbation and worsening of the clinical picture translated in long COVID, the latter with MS exception.

Keywords: SARS-CoV-2, Multiple sclerosis, Rheumatoid arthritis, Systemic lupus erythematosus, Immunosuppressors

INTRODUCTION

COVID-19 is a respiratory disease caused by SARS-CoV-2 coronavirus, and was first identified in the city of Wuhan, China in January 2020. On 16 August 2022, there were 588,757,628 cases of SARS-CoV-2 infection and 6,433,794 deaths caused by COVID -19 confirmed worldwide.[1]

Patients with chronic AD, such as RA, SLE and MS, have been strongly affected not only by the severity of the pandemic but also by the constraints imposed by public health protection measures in most countries.[2] It is thought that these patients are more likely to be infected by SARS-CoV2, and also that their immune response, when in contact with the virus, may be exacerbated and potentiated by both the pre-existing immune status to this

infection and the immunosuppressive therapy associated to AD.[3,4]

Given the lack of solid results from ongoing clinical trials and considering the urgency for scientific information, we conducted a systematic review to assess the impact of SARS-CoV-2 infection on patients with RA, SLE and MS. We had 4 aims: to determine whether patients with RA, SLE or MS are more susceptible to infection by SARS-CoV-2; to understand whether viral infection is related to periods of exacerbation of the AD; to understand whether immunosuppressive therapies for these diseases worsen the infection; and to understand whether there is any association between these diseases and COVID-19 sequelae, the so-called long COVID.

METHODS

Search strategy

This review followed the preferred reporting items for systematic reviews guidelines (PRISMA) for articles that revealed the relationship between infection by SARS-CoV-2 and the AD diseases: RA, SLE and MS.[5] In accordance with the objective of this systematic review, a question was formulated using the PICO (population, intervention, comparison, outcome) strategy: Is SAR-CoV-2 infection (I) aggravated (O) in patients with autoimmune disease (P) compared to infection in healthy people (C)?

A literature search was conducted in the PubMed/Medline electronic database between January 2020 and June 2022 in Portuguese and English. The search strategy was carried out according to the keywords and medical descriptor terms (MeSH-medical subject headings): SARS-CoV-2, complications, sequelaes, multiple sclerosis, lupus erythematosus systemic rheumatoid arthritis and infections combined through the Boolean markers AND and OR.

Selection criteria

Inclusion criteria included observational studies (case series, cross-sectional, case-control and cohort studies); randomized clinical trials were also included. All studies were conducted in humans with one of the autoimmune diseases, RA, SLE or MS, and SARS-CoV-2 infection. The included studies focused on the RA, SLE or MS population's susceptibility to infection and outcomes, including autoimmune disease exacerbation, COVID-19 worsened cases, impact of the immunosuppressive therapies on the infection, and association of RA, SLE or MS and sequelae of COVID-19, the so-called long COVID.

Excluded articles were systematic reviews, meta-analyses, case-reports, in vitro and animal studies, commentaries or conference papers, and unpublished studies. Studies where the full text of the article was not available were also excluded. This systematic review was duly registered in PROSPERO (International Prospective Register of Systematic Reviews) under the number CRD42022365576, following PRISMA recommendations.

Study and data extraction

Data extraction from selected publications was done independently by the authors, JS and SS, after screening, eligibility and inclusion; any doubts and disagreements were solved by negotiation. The main characteristics of the included studies were grouped in tables, one for each autoimmune disease: RA, SLE or MS. The data of each study were synthesized according to: author, year of publication, country, type of study, N (patients and controls), mean age of patients, how data were obtained, results and limitations of the study.

The main topics identified in the results were immunosuppressive therapies of patients at the time of SARS-CoV-2 infection, comorbidities, method of infection confirmation, outcome of infection (hospitalization, type of complications and need for intensive care admission), duration of post-infection signs/symptoms (weeks/months), and exacerbation of pre-existing AD. The authors then examined the outcome results in detail to identify potential patterns.

The quality assessment of the studies was performed using criteria adapted by the National Institute of Health-NIH.[6] As there is no standardized method to classify the quality of studies, in the case of qualitative systematic reviews, the quality assessment of each study involves a clear description of the process used, following the initial PICO criteria. Five quality criteria were established: value of N (patients with RA, SLE or MS) greater than 20, presence of healthy controls, outcome assessment (whether clinical parameters, signs or symptoms, or hospital conditions such as assisted ventilation), clear methodology (study design) and appropriate data collection (direct method: laboratory, in hospital or clinic setting, through databases and through online questionnaires). Telephone collection data was considered a cause for concern. If all criteria were met, the study was labelled as "good". If one criterion was not met, the study was labelled as "fair", and if two or more criteria were not met, the study was labelled as "poor".

RESULTS

Study selection process

For MS, from 118 articles obtained, following the scanning of titles, abstracts, and full texts, a total of 25 studies were considered for analysis in this systematic review (Figure 1). For SLE, from 72 articles obtained, following the scanning of titles, abstracts, and full texts, a total of 12 studies were considered for analysis in this systematic review (Figure 2). For RA, from 63 articles

obtained, following the scanning of titles, abstracts, and full texts, a total of 12 studies were considered for analysis in this systematic review (Figure 3).

The detailed characteristics of the included studies are presented in Tables 1-3, with G- study rated as "Good", F- study rated as "Fair"; and P- study rated as "Poor".

Autoimmune diseases and susceptibility to SARS-CoV-2 infection

According to the study by Pablos et al a higher prevalence of hospitalisations with COVID-19 was found for patients with rheumatic AD compared to patients with no history of rheumatic AD in a ratio of 31.6% to 28.1%, respectively. The same group also found that advanced age, and a history of comorbidities are very common in rheumatic patients and were noted as risk factors.[57] This study, classified as "good" is in line with all studies, is in line with results by other authors.[48,58,59]

Wang et al also found that patients with RA had a higher risk of contracting SARS-CoV-2 than the general population. In this study, the number of patients with RA was relatively high, 17268 individuals, mostly females and a mean age of 65 years, with a ratio of 0.9% of RA infected to 0.3% of cases in the control population.[9] This study classified as "good" was also in agreement with results obtained previously.[10,15,18]

On the other hand, in countries where the prevalence of RA was lower, such as South Korea, no differences in susceptibility to SAR-CoV-2 infection were found. There was a slight, but not significant, increase in mortality in patients with RA and COVID-19 infection This study was classified as "fair" in the totality of the studies included in this work.[11] Another study also found the same risk of infection for both RA and healthy populations but was classified as "poor".[17]

Zucchi et al in a study conducted in Tuscany, Italy, observed an infection rate of 1.8% in SLE patients and 0.4% in the general population: a higher susceptibility to SARS-CoV-2 in SLE patients However, there were different results in northern Italy where 7.2% of the general population was infected. It is important to refer that Italy was the first region in Europe to be heavily affected by SARS-CoV-2 and a high number of asymptomatic people were not tested. Thus, this study was classified as "fair".[56] There were 2 studies in which the results were different showing a similar incidence of COVID-19 in SLE and the general population. Thus, in both ones there was lack of data regarding infection confirmation and one was classified as "fair" and the other one as "poor".[52,55]

The observational study by Alroughani et al conducted in three Arabian clinics, observed an average of 3.7% MS patients infected with SARS-CoV-2. The number of SARS-CoV-2 infected cases with MS was actually lower than the general population in Kuwait, 5.3%, Dubai, 4.75% and Oman, 4.07%. These patients with MS had a higher severity and outcome of infection only if they had associated comorbidities or if MS was progressive.[25] Saharian et al conducted their study at the MS Clinic of Sinai Hospital, through a questionnaire survey of a population and found that 1.46% of MS patients were infected, a number identical to the infection rate in the general population41. This study was classified as "fair" and supported the results obtained by Alroughani.[25] In addition, MS patients and the general population were found equally susceptible to SARS-CoV-2 infection.[26,28,30,35,42] Of notice, all these studies were recent and classified as "good" and "fair" but the study from Mantero was classified as "poor".[42]

COVID-19 and autoimmune exacerbation

In addition to age, the comorbidities to which these patients are more vulnerable, such as sedentarism, diabetes, hypertension, dyslipidemia, and other neurological pathologies, are the main factors of imbalance and disease exacerbation, being the cause of early death in patients with RA and SLE.[58] These are the main causes of long hospitalisations, more severe health states and death.[8] In the study rated as "good", Nørgård monitored patients infected with SARS-CoV-2 and with RA or inflammatory bowel disease, for 6.5 months compared with healthy controls. They found an increase in overall hospitalisation, cardiovascular, respiratory and blood system complications, and infections in the patients with AD.[10]

Mahdavi et al observed exacerbations of the pre-existing RA in SARS-CoV-2 infected patients. They noted that these exacerbations could have been triggered by the comorbidities present as well as by pharmacological treatment-prednisolone, methotrexate and hydroxy-chloroquine (HCQ).[15] The study by Mahdavi et al was rated as "good" and the results obtained are partly supported by Hasseli et al also in a "good" study: they found that age, comorbidities, and the use of GC were associated with a higher risk of hospitalisation for patients with RA.[18]

Mageau et al studied a COHORT, from a French hospital, of SLE with a diagnosis of COVID-19. In this study, rated "good", the most common comorbidities were hypertension, cardiovascular disease, chronic renal disease, history of solid organ transplantation, obesity and chronic lung disease.[48] Advanced age and presence of comorbidities was dramatically increased in patients with SLE who were infected when compared with controls.[53] The number of deaths in the SLE-infected group was 25.3% and in the non-SLE-infected group 15.4%, which the authors associated with exacerbation of pre-existing disease with organ failure. They also found that SLE infected patients were more prone to co-infections.[48] Raiker also found that the patients had more frequent

exacerbations of the AD, such as venous thromboembolism and septic shock, the main causes of death in this group.[51]

Concerning SARS-CoV-2 infected patients with MS the severity of the infection and autoimmune exacerbation was related to advanced age and comorbidities like obesity and type 1 diabetes.[5,36,43]

Immunosuppressive therapy and SARS-CoV-2 infection

According to some authors, the use of GC along with advanced age and comorbidities caused a significant increase in COVID-19 hospitalisations among RA patients.[22]

This use was associated with RA patients' loss of functionality during the pandemic time and to the increased susceptibility to infection.[12] However, the use of non-steroidal anti-inflammatory drugs (NSAIDs) showed no impact on infection, in a study with a large number of patients and classified as "good".[19] Along the same lines, Raiker observed that RA patients medicated with glucocorticoids had a significant increase in mortality, hospitalisations, inpatient admissions, severe COVID-19 cases, septicaemia and thromboembolism to the detriment of the control group (RA patients without GC therapy).

They also found that therapy with rituximab and IL-6 inhibitors led to increased hospitalisations compared to treatment with anti-TNFs.[14] This study was rated "good". In the same year, Sparks et al studied patients with RA and COVID-19.

They found that patients treated with rituximab, abatacept and JAK inhibitors experienced higher disease exacerbation states with greater need for hospitalisation, hospitalisation with the aid of oxygen therapy, and greater number of deaths. Patients treated with rituximab had a higher incidence of all these outcomes.[16] This study was classified as "good" and the results are supported others.[8,14,20]

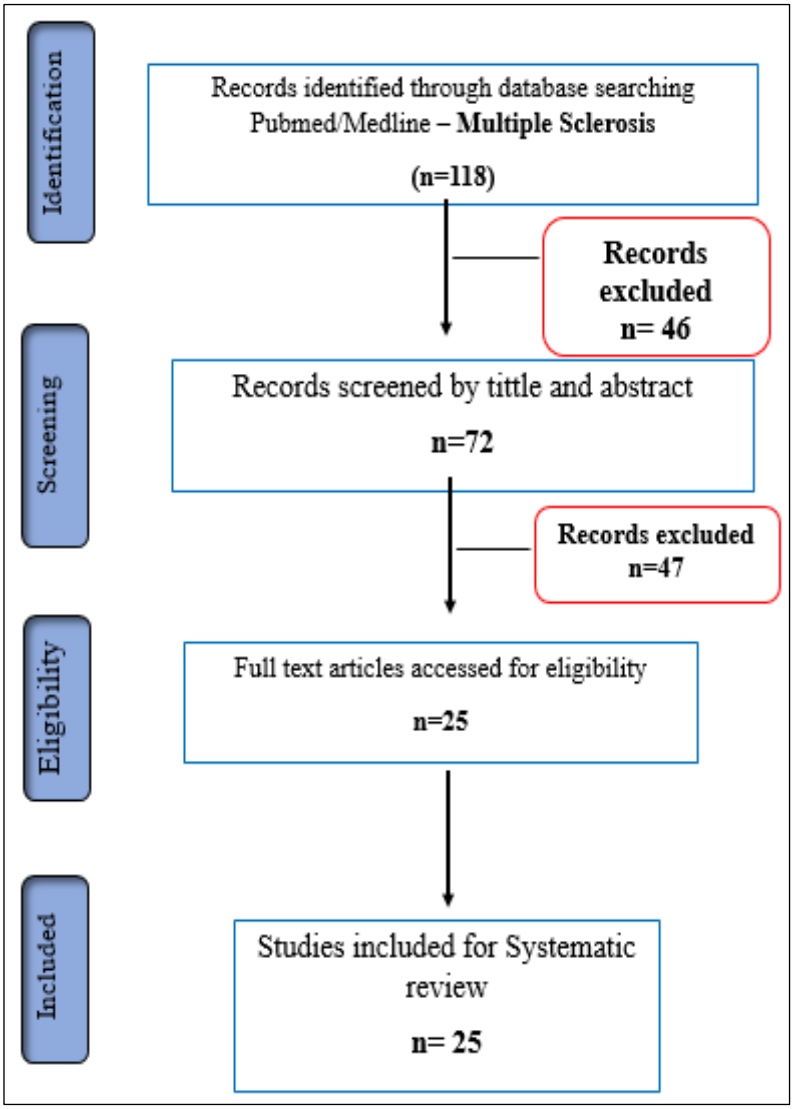

Figure 1: Study selection flow diagram (MS).

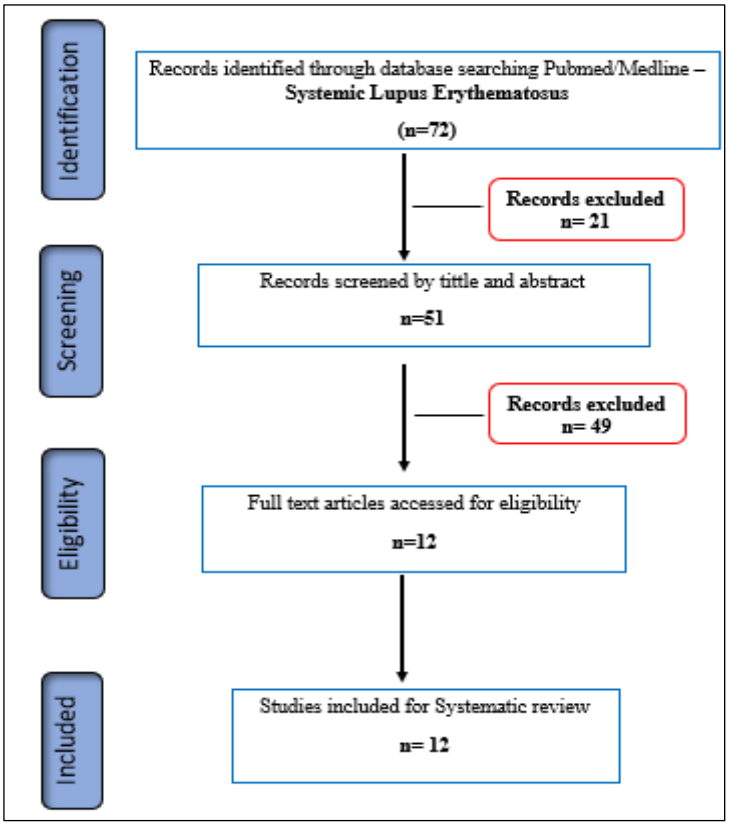

Figure 2: Study selection flow diagram (SLE).

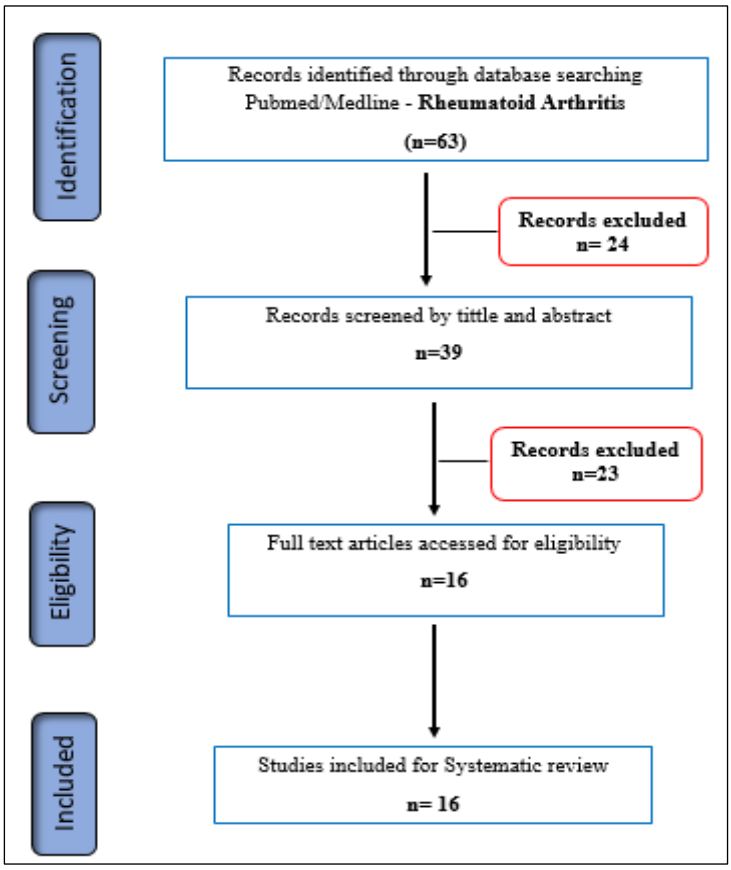

Figure 3: Study selection flow diagram (RA).

Table 1: Characterization of the included studies for RA and SARS-CoV-2 infection.

Authors	N	Type of study	Results	Strengths/limitations	Quality assessment
Wang et al[7]	70	Clinical study - after vaccination, adverse reactions were monitored and presence of IgM and IgG	Patients react similarly to controls - either in adverse effects or IgM and IgG concentrations. The majority, 61%, were on immunosuppressive medication	IgGs were tested at one time point only	G
El-Malky et al[8]	419	Retrospective study - patients in a state of renal failure and reaction to COVID	Higher mortality in patients with renal failure; longer hospitalisation time for older patients with respiratory support, lymphopenia, high urea values and low ferritin values	Large number of patients; did not study medication, only comorbidity	G
Wang et al[9]	17.258	Observational cohort study - risk of COVID-19 infection in patients with RA compared with controls (healthy or osteoarthritis)	Patients with RA at higher risk of infection	N very good; presence of controls; study of comorbidity	G
Nørgår et al[10]	417	Observational cohort study - risk of hospitalisation; cardiovascular, respiratory, blood, and nervous complications; infections; sequelae and death	Higher risk of successive hospitalisations compared to controls (9248)	Follow up - 18 months; considered comorbidities and period of disease activity	G
Jung et al[11]	35	Cross-section study - risk of infection and severity of the disease	Found no association between RA and COVID infection or mortality (121 Controls)	Did not include those taking biological drugs and DMARD	F
Tuna et al[12]	119	Descriptive study - describes symptoms, pain and loss of functions during the pandemic	Patients during the pandemic required more pain medication and injections, and lost functionality	Questions for patients in the hospital itself	G
Bartels et al[13]	154	Descriptive study - reactions to vaccine use such as fever, fatigue, muscle and/or joint pain	Most patients had adverse reactions compared to controls, but the severity level was similar	Other types of adverse effects were not taken into account; no reports of the number of controls	F
Raiker et al[14]	9.730	Cohort retrospective, comparative study	Patients with greater risk of infection and greater severity of 2	No mention of the state of the disease	G

Continued.

Authors	N	Type of study	Results	Strengths/limitations	Quality assessment
		- risk and severity of infection, hospitalisation, ICU, mechanical ventilation, urinary, respiratory and septic problems, and/or mortality	outcomes: venous thromboembolism and sepsis; patients taking GCs had increased risk of adverse effects and taking RTX or IL-6i had increased risk of hospitalisation		
Mahdavi et al[15]	128	Cross-section study – risk of infection and severity of outcomes in COVID, measured in terms of need of ICU and of mortality	Risk of infection was higher in the patients taking TNFi or with complications: obesity, diabetes, lung or urinary problems (RA controls without infection, 760, and healthy, 92). The prognosis is not worse despite the increased number of hospitalisations.	Very good descriptive analysis of patients' comorbidity and disease status	G
Sparks et al[16]	2869	Descriptive study - relationship of DMARds, ABT, RTX, JAKi, IL-6i and TNFi with severity of infection: hospitalisation, ventilation and death	Patients treated with RTX and JAKi with a more severe prognosis compared to those treated with TNFi (Controls-1388)	Limitation - some patients may not have registered in the study database.	G
Migkos et al[17]	17	Observational study - patients with different treatments: conventional, DMARDs or biological - risk of infection and severity	Similar risk compared to the normal population, even on different immunosuppressant therapies	No controls; very small sample	P
Hasseli et al[18]	225	Observational study - severity of infection and risk factors for hospitalisation: age, renal, respiratory and cardiovascular comorbidities; use of GCs	More severe infection in older patients, with comorbidities and taking GCs; disease activity was not related to severity (Controls were non-hospitalised patients RA-146)	N good; there are no healthy controls	F
Wong et al[19]	175.495	Cohort study - relate NSAIDs to the number of deaths from COVID	There is no difference in terms of the number of deaths whether patients with RA were taking NSAIDs or not	N large; good methodological quality of the study (8 parameters measured)	G
Loarce-Martos et al[20]	6	Descriptive study - severity of	Worse prognosis with higher risk of	N small; no control group	P

Continued.

Authors	N	Type of study	Results	Strengths/limitations	Quality assessment
		infection and patients on RTX in the last 12 months	hospitalisations in patients on RTX		
Pablos et al[21]	228	Retrospective observational study - association of RA risk factors such as age, comorbidities and COVID severity therapy	Patients with associated comorbidity or connective tissue diseases had more hospitalisations, contrary to patients with immunosuppressive therapies (Controls - without rheumatic diseases)	Covers not only RA but other rheumatic diseases	G
Montero et al[22]	20	Retrospective descriptive study - severity of infection and association with age, comorbidities and therapy	Having RA is not related to disease severity, nor is taking DMARDs, except in patients with previous lung disease or taking GCs	Study includes not only RA but also various rheumatic diseases; the controls were people with other rheumatic diseases	F

RA-rheumatoid arthritis; ICU-intensive care unit; GCs-glucocorticoids; DMARDs-disease-modifying antirheumatic drugs; TNFi-TNF inhibitors; JAKi-JAK inhibitors; IL-6i-IL-6 inhibitors; ABT-abatacept; NSAIDs-non-steroidal anti-inflammatory drugs; RTX-rituximab, G- study rated as "Good", F- study rated as "Fair"; and P- study rated as "Poor.

Table 2: Characterization of the included studies for MS and SARS-CoV-2 infection.

Authors	N	Type of study	Results	Strengths /limitations	Quality assessment
Manzano et al[23]	23	Observational study - use of monoclonal antibodies in the treatment of COVID-19 in patients with MS	+ 50% recovered in less than 7 days; use of monoclonal antibodies in patients with MS and acute COVID-19 is unlikely to be harmful	N small; 91% of patients vaccinated before infection; lack of healthy controls	F
Smith et al[24]	1439	Prospective monocentric study - assess the risks of COVID-19 in MS patients taking DMDs	SARS-CoV-2 infection was more frequent in MS patients treated with RTX; DMDs does not imply ↑ number of patients infected with SARS-CoV-2; RTX may imply ↑ severe infection	Lack of consistency in identification of DMDs; lack of systematic evaluation of the incidence of SARS-CoV-2 infection	F
Alroughani et al[25]	134	Cross-sectional observational study - evaluates prevalence, severity, outcomes, demographic and clinical risk factors of COVID-19 in patients with MS from 3 different countries	Comorbidities are the main factor in severe cases of COVID-19; duration of MS does not imply severity of COVID-19;	Study conducted in Italy and Spain reported similar prevalence of COVID-19 in	F

Continued.

Authors	N	Type of study	Results	Strengths /limitations	Quality assessment
			94.0% of patients report mild COVID-19; 91.0% of patients recovered	patients with MS; voluntary notification	
Paybast et al[26]	202	Cross-sectional observational study - evaluating MS patients with one year follow-up, COVID incidence and complications with different DMDs	Lower incidence of COVID-19 infection in MS patients; DMDs were not associated with COVID-19 infection; vaccination reduced the risk of developing COVID-19	Serological tests for Anti-SARS-CoV-2 IgG antibodies; the study did not evaluate the seroprevalence of SARS-CoV-2 at the end	F
Madelon et al[27]	20	UNIGE cohort prospective study - determine T-cell responses to the Omicron variant in MS patients, before and after a third vaccination	CD4 and CD8 specific T-cell memory against all variants was maintained in 9 to 12 patients, 6 months after their second vaccination; the third dose increased response for all variants	N small; blood sampling before and 1 month after the third dose of the vaccine; comparison with other studies for healthy controls	F
Ghadiri et al[28]	692	Retrospective-comparative cohort study - assess the impact of vaccination against COVID-19 and the frequency of the disease	91.9% received 2 doses of the vaccine; lowered the frequency of COVID-19; little difference in the decrease in the frequency of COVID-19 when comparing vaccinated MS patients and the general population; some severe allergic reactions	No data on mortality; population at lower risk of SARS-CoV-2 infection; prevalence of COVID-19 infection was observed before vaccination and after complete vaccination	F
Zabalza et al[29]	145	Retrospective cohort study - MS patients performed at the Centre for Multiple Sclerosis of Catalonia	83.45% of the HIV-positive sample; 59.5% had cellular response up to 13.1 months after COVID-19; humoral response decreases under anti-CD20 treatment even in the absence of	Strengths include the phenotypic cohort with serological confirmation	G

Continued.

Authors	N	Type of study	Results	Strengths /limitations	Quality assessment
			antibodies; T-cell response profile against SARS-CoV-2 is heterogeneous		
Solomon et al[30]	7000	Descriptive, retrospective study - patients with MS from a single clinic and COVID-19 infection confirmed by PCR	Patients with MS did not have a higher prevalence of COVID-19 compared to the general population	COVID-19 infection confirmed by PCR; underestimation of the total number of COVID-19 cases in one single clinic	F
Briggs et al[31]	719	Retrospective cohort study - reaction of MS patients to anti-COVID-19 vaccine	64% reported having had at least one reaction after the first vaccine; 17% report severe reaction: injection site pain (54%), fatigue (34%), headache (28%) and malaise (21%); more reactions to the second dose; SARS-CoV-2 vaccine is highly recommended for MS patients; vaccination reaction profiles seem similar to those reported for the general population	Able to examine the relationships between the reactions of the SARS-CoV-2 vaccine and specific DMTs; attributes of the population studied representative of the population with MS; absence of control group	F
Zakaria et al[32]	119	Cohort study - impact of DMD and risk factors for severe COVID-19	DMDs have a safe profile for patients with MS and COVID-19; headache was the most frequent symptom in cases of death; only 9% of cases presented severe outcome	Only 28% of the cases of infection are confirmed-in all the people tested between May and September 2020	F
Simpson-Yap et al[33]	2340	Cohort cross-sectional observational study - DMD therapies and COVID-19 severity in MS patients	RTX increases the risk of hospitalisation, need for artificial ventilation; associated therapy with OCR to hospitalisation.	Data from 12 sources from 28 different countries on different continents; only 61.9% of confirmed cases	F

Continued.

Authors	N	Type of study	Results	Strengths /limitations	Quality assessment
Alshamrani et al[34]	70	Prospective cohort study - aimed to determine the prevalence, severity, and possible complications of COVID-19 infection in patients with MS in Saudi Arabia (SA)	MS patients infected with SARS-CoV-2 have a similar clinical picture to controls; in 75.7% of patients who received DMDs during COVID-19, only 13% of patients with MS relapsed	The most commonly used DMDs was FG (25%) and antibodies IFN-β (25%); positive PCR test in severe cases	G
Kempen et al[35]	546	Prospective cohort study - tested SARS-CoV-2 antibodies to assess asymptomatic infections and immunological responses to COVID-19 in MS patients	Fewer cases of SARS-CoV-2 in 71.1% of patients with anti-CD20 therapy; patients with MS and neuromyelitis + Anti-CD20 and positive PCR SARS-CoV-2 had no antibodies; 14% of patients with asymptomatic MS are similar to the general population	11.7% of patients with MS, with antibodies to SARS-CoV-2; few patients with MS and SARS-CoV-2+	G
Salter et al[36]	1626	Cross-sectional cohort study - CoViMS Registry database - intend to test whether MS patients have characteristics associated with more severe outcomes	82.7% with positive laboratory test; 3.3% mortality rate; advanced age is a risk factor in all severity levels of SARS-CoV-2; RTX associated with greater severity of infection	82.7% with laboratory test positive; data reported	F
Khedr et al[37]	2	Observational study - neurological manifestations of COVID-19 in 439 hospitalised patients	222 patients demonstrated neurological manifestations: 117 with acute neurological disease; 105 patients with non-specific symptoms; cerebrovascular stroke was the most common CNS disease; only the 2 patients with MS relapsed	N very small; 439 patients had COVID-19 confirmed or probable; non-random population; lack of controls	P
Mallucci et al[38]	140	Observational study - description of symptoms of COVID-19 and	13.4% of MS patients had	100% of sample	G

Continued.

Authors	N	Type of study	Results	Strengths /limitations	Quality assessment
		disease severity in MS patients treated with FG, HCL and NTZ	asymptomatic anti-SARS-CoV-2; 2 MS patients were symptomatic; no one with severe hospitalisation or COVID-19; it is safe to maintain continuous treatment with DMDs	tested; questionnaire; supported by several previous studies	
Sormani et al[39]	844	Retrospective Observational study - impact of immunosuppressive/immunomodulatory therapies on the severity of COVID-19	Duration of MS disease, body mass index, comorbidities, recent use of methylprednisolone and anti-CD20 agent therapy were associated with ↑ prevalence of cases of COVID-19; mPRED associated with increased deaths; demonstrates the safety of immune-modulatory and immunosup-pressive therapies in patients with MS	N good; all patients had complete follow-up until death or recovery; data obtained from 85 Italian centres of MS	F
Maillart et al[40]	13	Retrospective study - evaluation of the effect of anti-CD20 therapies with the development of antibodies	Serology for anti-COVID-19 antibodies was negative for all patients treated with monoclonal anti-CD20 antibodies; Rituximab is associated with rapid and almost complete depletion of CD19+ peripheral B lymphocytes	N small; results obtained from French medical registration platform; no controls	P
Sahraian et al[41]	4647	Observational study - incidence of COVID-19 in patients with MS, the rate of hospitalisation or death and DMDs risk	The mean age of patients infected with SARS-CoV-2 is identical to the general population (with or without MS); more cases of COVID-19 in	N large; healthy controls and good study methodology; data not recorded in the computer base were	F

Continued.

Authors	N	Type of study	Results	Strengths /limitations	Quality assessment
			patients taking RTX but no increase in hospitalisation time; COVID-19 duration identical for patients with and without MS	collected by telephone	
Mantero et al[42]	275	Cross-sectional observational study - demonstrate susceptibility of patients with MS to develop COVID-19; relationship with first-line drugs for the treatment of MS	Prevalence of COVID-19 identical for the general population and patients with MS	15 of 275 patients had suggestive symptoms and only 1 had a positive diagnosis by PCR; patient database of 2 neurologists; telephone interview	P
Parrotta et al[43]	76	Observational study - MS patients from a medical centre on DMD therapy and COVID severity	The relationship between DMD therapy and the outcome of COVID-19; high hospitalisation rate; more frequent comorbidities - obesity and type I diabetes; hospitalised patients are older; one patient with thromboembolism died	COVID-19 diagnosis confirmed by laboratory; anti-CD20 therapy (RTX) in 50% of the sample	G
Costa et al[44]	399	Multicentre European study - prevalence and impact of COVID-19 among patients with MS	Higher risk of COVID-19 symptoms under treatments with ALZ and CDA compared to injections; no worse disease progression for MS patients compared to the general population; DMDs do not significantly alter disease progression	N large; remote monitoring, description of symptoms may vary between patients	G
Mecca-Lallana et al[45]	7	Observational study - 7 patients with SARS-CoV-2 infection and treated with anti-CD2+	Incidence of low severe infection for patients treated with OCR, RTX and placebo; B	N very small; it may be conclusive for patients treated with	Y

Continued.

Authors	N	Type of study	Results	Strengths /limitations	Quality assessment
			cells may not be necessary to eliminate viral load; absence of CD19+ B cells and negative serologies in 2 patients with symptoms	RTX and OCR	
Safavi et al[46]	712	Retrospective cross-sectional observational study - incidence of COVID-19 in patients with MS; testing the risk of contracting SARS-CoV-2 during treatment with DMDs	Most MS patients are women treated with DMDs and 40% with RTX; use of anti-CD20 therapy implied 2.6x increased risk of COVID-19; contact with symptomatic person increased 6.2x risk of being in the suspected COVID-19 group	Only 34 met criteria for suspected COVID-19; healthy controls, appropriate outcome assessment, as well as data collected and study	G
Sormani[47]	232	Cross-sectional observational study - conducted by the Italian Multiple Sclerosis Society (AISM), the Italian Multiple Sclerosis Foundation (FISM) and the Multiple Sclerosis Study Group of the Italian Neurological Society	232 cases of COVID-19 classified as mild and 222 as severe; 6 patients in critical condition, leading to 5 deaths; of the 232 patients, 57 confirmed COVID-19 and 175 suspected with symptoms. Preliminary results showed no impact on DMDs in COVID-19 infection	No healthy controls, but assessment is adequate - parameters collected in databases; study design is adequate	F

MS-multiple sclerosis; DMDs-disease-modifying drugs; RTX-rituximab; PCR-polymerase chain reaction; DMTs-disease -modifying therapies; CNS-central nervous system; OCR-ocrelizumab; FG-fingolimod; HCL-hydrochloride; NTZ-natalizumab; ALZ-alemtuzumab; CDA-cladribine; mPRED-methilprednisolone, G- study rated as "Good", F- study rated as "Fair"; and P- study rated as "Poor.

Table 3: Characterization of the included studies for SLE and SARS-CoV-2 infection.

Authors	N	Type of study	Results	Strengths /limitations	Quality assessment
Mageau[48]	127380	Cohort study - hospital database; analyse the factors associated with OSF and COVID-19 in SLE patients	196 patients with SLE versus 908 patients with COVID-19 controls; about 190 patients with SLE and COVID-19 had OSF; COVID-19-OSF is associated with a severe late-onset	N large with healthy controls; gathers exhaustive data from all French hospitals; original 'Wuhan' SARS-CoV-2 variant; presence of confounding factors that the authors addressed	G

Continued.

Authors	N	Type of study	Results	Strengths /limitations	Quality assessment
			prognosis among patients with SLE: increased late mortality (between 30 and 90 days)		
Zavala-Flores[49]	130	Descriptive observational study - identify side effects after SARS-CoV-2 vaccine BNT162b2	100 received the 1st dose and 90% had symptoms within 10 days; 90 patients received the 2nd dose and 92.2% had symptoms within 10 days; 87% with pain at the injection site and 69% systemic symptoms; 27% of SLE patients immunized had episodes of reactivation of the disease	No healthy controls; SLE patients assessed prior to immunization; not all patients had immunological tests	F
Barbhaiya[50]	183	Observational study - SLE disease flares post-SARS-CoV-2 vaccination	74.3% reported vaccination SARs-CoV-2 and 72 in 129 received both doses: 100 reported adverse effects on the 1st dose; 71% reported adverse effects on the 2nd dose: pain at the injection site (54%), fatigue (45%), headache (36%), shoulder pain (34%) and muscle pain (26%), anaphylactic (0%)	No healthy controls; absence of laboratory studies and measurement of outcome in terms of signs/symptoms described by patients	F
Raiker[51]	2140	Retrospective study - association of risk factors: sex, race, presence of nephritis and immunomodulatory therapy	Comparing SLE patients with and without COVID-19: more severe clinical picture and higher risk of hospitalisation in the latter; identical death % in the 2 groups	International study proved results; lack of information on duration and activity of disease	G
Sjöwall[52]	100	Observational study - SARS-CoV-2 antibodies in SLE patients and autoimmune disease impact	In patients with SLE, 4% had confirmed PCR infection; 36% had SARS-CoV-2 isotype ≥1 → IgA (30%), IgM (9%) and IgG (8%); antibodies with neutralization capacity; Swedish SLE patients had serological signs of SARS-CoV-2	Lack of actual knowledge of people infected at the beginning of the pandemic due to absence of tests; no healthy controls	F

Continued.

Authors	N	Type of study	Results	Strengths /limitations	Quality assessment
			infection with no impact on SLE		
Ramirez[53]	334	Observational cohort study and questionnaire - impact of COVID-19 on SLE patients	In 334 patients with SLE, 28 had COVID-19: 90% female sex, 63% + 40years; patients with SLE - only 31% with infected relatives, developed COVID-19; SARS-CoV-2 with moderate impact on this population; public health protection measures were beneficial.	Online anonymous questionnaire; excludes mortality or severely ill; unable to compare questionnaire data with health reports	F
Schioppo[54]	51	Multicentre observational study - cohort and case report - COVID-19 impact on SLE	17.6% asymptomatic infection; ↑ organ involvement (66,7%) in asymptomatic infected patients: renal, CNS, lungs; 5.9% of patients with exacerbation of the disease post-infection	Limitation of retrospective study design; no healthy controls	F
Espinosa[55]	400	Retrospective observational study - evaluate the incidence of COVID-19 among SLE patients	Incidence of COVID-19 confirmed in patients with SLE similar to the general population (recorded data)	No healthy controls; access to laboratory data only in hospitalised patients; telephone questionnaire	P
Zucchi[56]	332	Observational cohort study - patients with SLE - incidence and clinical presentation of Infections by SARS-CoV-2 and therapy	DMARDs or GCs imply ↑of SARS-CoV-2+ in patients with SLE, most of whom were undergoing DMARDs therapy; 11.1% of patients with SLE discontinued therapy; ↑rash with discontinuation of therapy; consider maintaining therapy even with SARS-CoV-2	N good; not all patients were tested with PCR; no healthy controls	F
Pablos[57]	456	Comparative cohort study - patients with rheumatic diseases with a control cohort	Rheumatic diseases - 60%, connective tissue diseases - 40%, 74% hospitalised: 31.6% severe risk of COVID-19 in rheumatic cohort and	N large; In agreement with results of another study	G

Continued.

Authors	N	Type of study	Results	Strengths /limitations	Quality assessment
			28.1% in non-rheumatic cohort; advanced age, male sex and history of comorbidities = ↑risk in rheumatic cohort		
Montero[58]	62	Retrospective observational study - describe clinical characteristics (includes any rheumatic or inflammatory autoimmune disease)	62 patients with COVID-19 and rheumatic disease; 42% men, 62% with COVID-19; hospitalised elderly men with more comorbidities; deaths -16%: lung disease, sex and use of glucocorticoids therapies = ↑hospitalisation	Results supported by the literature; retrospective study of a single centre; short analysis period and no healthy controls.	F
Gianfrancesco[59]	600	Retrospective observational cohort study - from international database; patients with rheumatic diseases: determination of demographic and clinical risk factors	46% of hospitalised, deaths = 9%; PDN therapy ≥10 mg/day = ↑probability of hospitalisation; therapy with DMARDs, NSAIDs or HCQ without influence on hospitalisations; TNFi therapies associated with the probability of hospitalisation; recovery from COVID-19 of the majority of the sample	Cases from 40 different countries; 1st major analysis of patients with rheumatic diseases and COVID-19; voluntary registration of patients with rheumatic diseases	F

SLE-systemic lupus erythematosus; OSF-organ system failure; PCR-polymerase chain reaction; GCs-glucocorticoids; DMARDs-disease-modifying antirheumatic drugs; HCQ-hydroxychloroquine; TNFi- inhibitors of TNF; NSAIDs-non-steroidal anti-inflammatory drugs; PDN-prednisone, G- study rated as "Good", F- study rated as "Fair"; and P- study rated as "Poor".

Corticosteroid therapy in SLE patients may also be the cause of a significant number of asymptomatic SARS-CoV-2 infected patients. However, if these patients developed symptoms, they were at greater risk of further complications, as mentioned above, increased risk of admission to intensive care units and use of oxygen therapy.[53,54]

The paper by Zucchi et al demonstrated that patients with SLE on GC or disease-modifying antirheumatic drugs (DMARDs) were also at increased risk of contracting COVID-19, but the use of HCQ appeared to have no influence on the course of SARS-CoV-2 infection.[56] This study was classified as "fair". According to Pablo et al DMARDs and anti-TNF-α were not associated with increased risk of serious hospitalisations for COVID-19 and SLE patients opposite to GC.[57]

Sormani observed that elderly MS patients treated with IFN, glatiramer acetate or teriflunomide had more clinical complications of the infection: 1.54% confirmed deaths, 4.5% admitted to intensive care, 11.4% hospitalised and 11.7% with pneumonia.[39] Other studies showed that the use of methylprednisolone and ocrilizumab or rituximab, both anti-CD20 antibodies, were associated with a worsened clinical picture of SARS-CoV-2 infection in MS patients.[24,33,34,36]

Regarding disease-modifying drugs (DMDs) several good and reasonable studies showed no impact of their use in the susceptibility to SARS-Cov-2 infection.[24,26,32,38] Interestingly, older studies from 2020 showed the same preliminary results despite lack of confirmation of SARS-Cov-2 infection.[47]

Association between autoimmune disease and long COVID

Long COVID refers to the presence of symptoms or consequences after the usual period of resolution of COVID-19. Most authors consider it from the 3rd or 4th week of infection with persistence of at least one symptom.[60]

In the study by Nørgård as mentioned before, patients infected with SARS-CoV-2 and with RA or inflammatory bowel disease, were monitored for 6.5 months in order to evaluate the recurrence of readmissions and thus try to interpret long COVID. The study consistently showed that the main causes of readmission were respiratory diseases and several infections (respiratory tract, gastrointestinal tract), but also cardiovascular diseases, in this case with a lower incidence.[10] Mageau et al conducted a study in SLE patients and analysed the consequences of SARS-CoV-2 infection for a period between 30 and 90 days. They found that SLE patients infected with SARS-CoV-2 show a significant increase in co-infections, 9.09% in this group versus 7.6% in the control group, and also found an increased late mortality with 25.3% for SLE patients with COVID-19 versus 15.4% without SLE but with COVID-1918. Supporting these results, Raiker found that, after 30 days, SLE patients infected with SARS-CoV-2 had a higher risk of acute renal injury, higher rate of venous thromboembolism, sepsis and stroke compared to SLE patients without COVID-19 and COVID-19 patients in the general population. Venous thromboembolism may be driven by Virchow's triad dysfunction, common to SLE patients and antiphospholipid antibodies.[51]

For patients with MS, the study by Alroughani et al found out that COVID-19 severity and sequelae were dependent on two factors - the duration and type of MS. Patients with more than 10 years of established disease or with a progressive MS phenotype had longer outcomes from infection, as did patients with comorbidities and anti-CD20 therapies.[25] On the other hand, in the same year, Safavi study observed exactly the opposite, for instance, late complications in these patients were similar to those in the general population regardless of the type and duration of MS but were still dependent on risk factors: comorbidities and anti-CD20 therapy. This study is more robust than the previous one.[46] It is interesting to observe that humoral and cellular responses to SARS-CoV-2 infection in MS patients still can be detected one year after COVID-19 diagnosis, before any vaccination, which can help to explain the lack of complications from long COVID. This study was classified as "good".[29]

DISCUSSION

In the beginning of the pandemic, the unavailability of rapid and specific diagnostic tests for SARS-CoV-2 was a challenge for healthcare professionals. A high number of authors, in their study methodology, included individuals considered infected because they were symptomatic positives, especially in the year 2020. These studies were classified as "fair" or even "poor".[22,32,42] On the other hand, public health protection measures influenced people's behaviour, with different results for similar studies in similar cohorts. The importance of the public health measures in the context of COVID-19 was mentioned by Ramirez et al associating them with the lower number of COVID-19 cases in patients with AD.[53] This can also explain the results in MS patients where susceptibility to infection was similar to the general population.[29] Individuals with MS adhered earlier to vaccination and therefore had fewer complications after SARS-Cov-2 infection. Furthermore, this group of patients was considered a priority in 2021 for vaccination due to SARS-Cov-2 tropism of the CNS associating it with neurological sequela.[61] Still concerning susceptibility several authors agree that AD patients are more likely to contract COVID-1962-64 as showed by our results for RA and SLE patients.[56] Nevertheless, the previous AD and its stage, comorbidities, age, gender, pharmacological therapy and regional context are variables that can change the outcome of the AD.[65-67]

Regarding the severity of COVID-19 and exacerbations of AD, the presence of comorbidities, neurological pathologies, advanced age, male gender and/or the number of ACE-receptors will lead to AD flares. These translates in hospitalisation and admission to long-term care with or without oxygen therapy with future negative consequences. Overall our results reflect this observation in agreement with other authors.[68,69]

According to the results RA patients were more susceptible to SARS-CoV-2 infection and also disease flares.[12,14,18] It can be due to the social change induced by the pandemic, imposing limited movement and contributing to the lack of functionality. Thus, RA patients where overmedicated with GC suggesting that this induced not also, higher susceptibility to infection but also to AD flares, as other authors agreed.[70] Concerning SLE, it was observed a higher percentage of patients requiring readmission to the intensive care unit and oxygen therapy with no increased risk of death.[14] There was an increased risk of thromboembolism and septic shock that may be associated with the overexpression of the ACE2 gene facilitating viral entry and increasing viraemia.[71]

Regarding the maintenance of immunosuppressive therapies our studies supported the scientific community, even with associated risks, weighing the benefit against the risk of the therapy in line with other authors.[72] Our results reflected a worsened clinical picture in RA patients on GC, but not other DMARDs, more severe hospitalisations and also increased death numbers, in agreement with other authors.[73,74] Methylprednisolone a commonly used medication in MS flares was associated with increased COVID-19 and death cases 39 in line with studies by other authors.[75] HCQ and anti-TNF antibodies

did not have a major impact in infected AD patients. Furthermore, some studies with these two immunossupressors found protection against more severe stages of COVID-19 as seen more recently by other authors.[43,56,59,76] Rituximab and other anti-CD20 antibodies that cause B-lymphocyte depletion, impairing humoral immunity, were associated, in LES and MS patients, with an aggravated clinical picture as seen by other authors.[77,78] As for IL-6 inhibitors, only in one study, they were associated with an increased number of hospitalisations in RA patients.[14] Nevertheless on 21 December 2022, the NIH approved the use of IL-6i for the treatment of COVID-19 in hospitalized adults on systemic corticosteroids that required supplemental oxygen. Further controlled clinical trials were still needed to determine the efficacy, dosage and duration of IL-6 inhibitors intervention for the treatment of COVID-19 patients, especially those with rheumatic diseases.[79]

Long-COVID was seen in patients with RA10 and SLE concordingly with other authors.[48,51,55,70,74] These results were opposite to the ones involving MS patients. Despite the lack of evidence, it is not surprising that MS patients may develop more sequelae after COVID-19 infection due to cognitive dysfunction.[80]

Limitations

Regarding the limitations of this review, we must first address the choice of narrative textual synthesis, an approach that organizes the studies into more homogeneous groups. Although the study design, search strategy and data extraction were standardized, the focus of each study could be totally different. Furthermore, the heterogeneity of the populations evaluated as well as changes in management of COVID that have occurred since the pandemic began, limits the ability to draw significant conclusions. In addition, we have to consider the heterogeneity of studies resulting from lack of randomisation, study adherence, missing outcome data or even due to lack of methodological description of the study. To address this heterogeneity, each study was assessed in terms of its reliability and the usefulness of its findings using the quality assessment, which is always subject to variables that may not be comparable and, as such, should be meticulously analysed.

CONCLUSION

Patients with autoimmune rheumatic diseases like RA or SLE are more susceptible to infection by SARS-CoV-2, especially if they have associated comorbidities such as hypertension, diabetes mellitus, respiratory, cardiac or renal diseases (in the case of SLE). In MS this was not found to be the case and early vaccination could have reduced the number of late deaths/complications of COVID-19. Post-viral infection results in an exacerbation of RA, SLE or MS associated with more hospitalisations, intensive care admissions, oxygen therapy and even death. Specific immunosuppressive therapies reflect a worsened clinical picture: in RA, GC and IL-6 inhibitors, in SLE, anti-CD20 antibodies and in MS anti-CD20 antibodies and methylprednisolone. Other immunosuppressors like DMARDs, didn't have a negative impact in all the diseases, by the contrary HCQ and anti-TNF antibodies, were considered protective to severe COVID-19 infection. Long-COVID was detected in RA and SLE patients and affected, mainly, pulmonary, cardiovascular and renal systems with severe co-infections. Some studies state that AD doesn`t increase the risk of having COVID-19 and that poor outcomes are only associated with comorbidities. The authors think that the specific pre-existing AD and medication are directly associated with poor outcomes to SARS-CoV-2 infection and long-COVID sequalae. The concept that all AD patients react to the viral infection similarly should not be generalised. Each AD pathophysiology is different and can have different outcomes in the SARS-CoV-2 infected. Also, drug-disease interactions are characteristic of the specific AD and need special attention.

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