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# Risk and prognosis of SARS-CoV-2 infection and vaccination against SARS-CoV-2 in rheumatic and musculoskeletal diseases: a systematic literature review to inform EULAR recommendations

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## ABSTRACT

**Objectives** Perform a systematic literature review (SLR) on risk and prognosis of SARS-CoV-2 infection and vaccination against SARS-CoV-2 in patients with rheumatic and musculoskeletal diseases (RMDs).

**Methods** Literature was searched up to 31 May 2021, including (randomised) controlled trials and observational studies with patients with RMD. Pending quality assessment, data extraction was performed and risk of bias (RoB) was assessed. Quality assessment required provision of (1) an appropriate COVID-19 case definition, and (2a) a base incidence (for incidence data) or (2b) a comparator, >10 cases with the outcome and risk estimates minimally adjusted for age, sex and comorbidities (for risk factor data).

**Results** Of 5165 records, 208 were included, of which 90 passed quality assessment and data were extracted for incidence (n=42), risk factor (n=42) or vaccination (n=14). Most studies had unclear/high RoB. Generally, patients with RMDs do not face more risk of contracting SARS-CoV-2 (n=26 studies) or worse prognosis of COVID-19 (n=14) than individuals without RMDs. No consistent differences in risk of developing (severe) COVID-19 were found between different RMDs (n=19). Disease activity is associated with worse COVID-19 prognosis (n=2), possibly explaining the increased risk seen for glucocorticoid use (n=13). Rituximab is associated with worse COVID-19 prognosis (n=7) and possibly Janus kinase inhibitors (n=3). Vaccination is generally immunogenic, though antibody responses are lower than in controls. Vaccine immunogenicity is negatively associated with older age, rituximab and mycophenolate.

**Conclusion** This SLR informed the July 2021 update of the European Alliance of Associations for Rheumatology recommendations for the management of RMDs in the context of SARS-CoV-2.

## INTRODUCTION

In April 2020, the European Alliance of Associations for Rheumatology (EULAR) commissioned provisional recommendations for the management of patients with rheumatic and musculoskeletal diseases (RMDs) in the context of SARS-CoV-2, the virus, causing the disease COVID-19, which has gripped the world since December 2019.[1] In the absence of an evidence base to inform those recommendations, those statements were based largely on expert opinion. However, the number of publications in this field has grown exponentially since then. In light of the newly accrued data with the opportunity to provide evidence-based guidance, it was therefore time to update the April 2020 recommendations. This paper presents the systematic literature review (SLR) on risk and prognosis of SARS-CoV-2 infection and vaccination against SARS-CoV-2 in patients with RMDs that accompanies the July 2021 update of the recommendations.

## METHODS

### Research questions

This SLR was used to inform the EULAR task force for the July 2021 update of the recommendations for the management of RMDs in the context of SARS-CoV-2. The task force outlined the scope of the literature search by defining five research questions according to the Participants, Interventions, Comparators, Outcomes format (see online supplemental material)[2]:

1. Do patients with RMDs face more risk of contracting SARS-CoV-2?
2. Do patients with RMDs have a worse prognosis when contracting SARS-CoV-2?
3. In patients with RMDs who contract SARS-CoV-2, is antirheumatic medication associated with a worse outcome?
4. Should patients with RMDs who contract SARS-CoV-2 continue their drug treatment?
5. What evidence informs the use of vaccination against SARS-CoV-2 in patients with RMDs?

Effects of the SARS-CoV-2 pandemic on the referral and monitoring of patients with RMDs (eg, (postponement of) regular blood monitoring and face-to-face consultation) were not included as a separate research question, as this will be investigated by a separate EULAR task force.

### Literature search

A systematic search was conducted in PubMed/MEDLINE, Embase, Cochrane CENTRAL and the WHO COVID-19 databases up to 31 May 2021 by an experienced librarian (JWS). Additionally, conference abstracts of the EULAR 2021 annual conference were screened. No language restrictions were applied. Papers only published on a preprint server were excluded, unless they provided evidence on vaccination (in order not to miss relevant studies on this novel subject). The search strategy can be found in the online supplemental material.



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The review focused on available evidence specifically in patients with RMDs and was not intended to summarise evidence for the prevention, diagnosis, treatment or prognosis of SARS-CoV-2 infection in the general population. While the EULAR recommendations will focus primarily on the management of patients with autoimmune inflammatory rheumatic diseases, studies including patients with other types of ('non-inflammatory') RMD were not excluded. Studies including participants with non-RMD diagnoses were only eligible if the results were presented separately for participants with RMDs or if ≥75% of the study population had an RMD.

Studies with a comparator were viewed higher in the hierarchy of evidence, though studies without a comparator were not a priori excluded. All outcomes relevant for the research questions were extracted without specific hierarchy.

Eligible study types were (randomised and non-randomised) controlled trials (RCT/CCT) and observational studies (cohort, case–control, cross-sectional; prospective or retrospective, including registries). The following hierarchy of study design was adopted: RCT/CCT, prospective observational longitudinal cohort study, retrospective observational longitudinal cohort study, case–control study, cross-sectional study.

Studies were excluded when the number of participants was lower than 75 (arbitrary cut-off), with the exception of studies on vaccination against SARS-CoV-2. Studies that were not published as a full-text manuscript were only eligible if the authors provided sufficient data to extract information on the population, intervention, comparator and study outcomes.

### Study selection, data extraction and risk of bias (RoB) assessment

Two reviewers (FPBK and AA/AN) independently screened titles and abstracts, and thereafter the full-text for eligibility. The same reviewers performed a quality assessment of included studies, based on predefined criteria set by the steering group as minimal requirements to justify data extraction. All studies were required to have an appropriate case definition of COVID-19, defined as a positive SARS-CoV-2 PCR+ test, serological antibody response, typical imaging abnormalities on X-ray or CT, physician diagnosis, International Classification of Diseases, 10th Revision (ICD)-10 diagnostic code or fulfilment of WHO diagnostic criteria set. Studies with data on incidence of COVID-19 in a RMD population or prevalence of RMDs in a COVID-19 population were required to report a base incidence of the outcome in the base population (ie, population from which the study was sampled) to be able to compare the reported and the base incidence. Studies with data on risk factors for development or worse prognosis of COVID-19 were required to (1) include a comparator, (2) have at least 10 cases with the outcome and (3) provide risk estimates at least adjusted for age, sex and comorbidities.

Data from eligible studies were extracted by one reviewer (FPBK) and verified by a second reviewer (AA/AN) using a standardised data-extraction form.

RoB of all studies was assessed in duplicate by junior (AA/AN/FPBK) and senior (PMM/RBML/VN-C) reviewers using an appropriate tool depending on the study type: Newcastle-Ottawa Scale was used for longitudinal observational cohort and case–control studies,[3] and the AXIS tool was used for cross-sectional studies.[4] For the final RoB judgement, an additional weighting was applied, in which studies were *not* rated low RoB when (1) possible selection bias had not been recognised and somehow adjusted for; (2) selection bias was irreparable by design (eg, voluntary enrolment of SARS-CoV-2-positive cases); or (3) ascertainment of cases, exposure or outcome was uncertain.

For study selection, quality assessment, data extraction and RoB assessment, disagreements were discussed until consensus was reached, and a third reviewer (PMM/RBML/VN-C) was involved whenever necessary.

## RESULTS

Of 5165 records (after deduplication), 501 were selected for full-text review and 208 articles were included (see flowchart in online supplemental figure 1). Of these, 90 articles passed quality assessment and were eligible for data extraction of incidence data (n=42), risk factor data (n=42) or vaccination data (n=14). The most important reasons for a negative quality assessment were lack of a base incidence, having no comparator or presentation of risk estimates with no minimal adjustment for age, sex and comorbidities (see online supplemental tables 1 and 2) for an overview of studies that did not pass quality assessment). The detailed RoB assessment is provided in online supplemental tables 3–5.

### Incidence of (severe) COVID-19 in patients with RMDs

#### Incidence of COVID-19

In total, 26 studies reported on the incidence of COVID-19 in patients with RMDs (online supplemental table 6). Most (n=17) were cross-sectional studies; 8 were retrospective; and 1 was a prospective study. The number of patients varied from 25[5] to 39 835[6] patients with RMD with 1[7]–199[8] COVID-19 cases. All but two studies were performed in the first wave of the pandemic.[9 10] Most studies included multiple inflammatory RMDs (n=13) or any type of RMD (n=5). COVID-19 diagnosis was defined as PCR+ (n=18), a combination of laboratory testing, imaging or symptoms (n=6) or through diagnostic criteria (n=2). RoB was high (n=15) or unclear (n=10) in most studies. The reported incidence of COVID-19 in patients with RMDs varied substantially (0.16%–0.36%), with a similar variation in the base population. Compared with the general population, most studies reported an equal incidence (n=19); six reported a higher incidence (n=5 with patients with various RMDs, n=1 with patient with systemic lupus erythematosus (SLE)) and one a lower incidence. Three studies assessed age-adjusted and sex-adjusted incidence rates,[11–13] of which one was at low RoB, reporting an equal incidence of COVID-19 in patients with RMD and the general population.

#### Incidence of severe COVID-19

Eleven studies investigated the incidence of COVID-19-related hospitalisation (table 1). All were retrospective studies, from the first wave of the pandemic. Study size varied from 8[14] to 110 567[15] patients with RMD with 1[16]–581[15] hospitalisations. Four studies had a high or unclear RoB, while three were at low RoB. The reported hospitalisation rate in patients with RMDs varied substantially (0.11%–44%), as did the hospitalisation rate in the general population. Compared with the general population, six studies found a higher hospitalisation rate, while four studies reported an equal and one a lower incidence of hospitalisation. Only three studies (low RoB) investigated age-adjusted and sex-adjusted hospitalisation rates[11 15 17]; among these, Bower *et al* found that the increased risk of hospitalisation for COVID-19 was comparable to the increased risk of all-cause hospitalisation in patients with RMD.[15]

Six studies, five of which were retrospective and all were conducted during the first wave of the pandemic, assessed the



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**Table 1** Studies with data on the incidence of severe COVID-19 in patients with RMDs compared with persons without RMDs

| First author | Country | Cohort | Study period | Study type | Setting | Study population, recruitment | Case definition RMD | Case definition COVID-19 | Source population of base incidence | Total (N) | Incidence in patients with RMD | Base incidence | Incidence in patients with RMD versus base population (higher, equal, lower) | RoB |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (A) Outcome: Hospitalisation for COVID-19 | | | | | | | | | | | | | | |
| Bachiller-Corral[72] | Spain | – | 1 March–30 April 2020 | Retrospective | Secondary care | Patients with inflammatory RMD in hospital area of care, hospital records | Physician diagnosis | PCR+ or typical imaging | Non-RMD population in hospital area of care | 4592 | 41/4592 (0.89%) (all), 16/1708 (0.94%) (RA), 3/862 (0.35%) (SpA), 4/515 (0.78%) (PsA), 4/254 (1.57%) (SLE), 4/175 (2.29%) (SjS), 3/165 (1.82%) (vasculitis), 1/88 (1.14%) (IM), 6/474 (1.27%) (PMR) | 2274/488 153 (0.47%) | Higher for all (OR 1.91, 95% CI 1.41 to 2.61), RA (OR 2.01, 95% CI 1.23 to 3.28), SLE (OR 3.38, 95% CI 1.28 to 8.95), SjS (OR 4.90, 95% CI 1.86 to 12.94), vasculitis (OR 3.90, 95% CI 1.27 to 11.99), PMR (OR 2.71, 95% CI 1.23 to 6.02); equal for SpA (OR 0.74, 95% CI 0.24 to 2.31), PsA (OR 1.66, 95% CI 0.63 to 4.43), IM (OR 2.43, 95% CI 0.35 to 17.13) | |
| Bjornsson[11] | Iceland | ICEBIO | Until 3 June 2020 | Retrospective, registry, matched | Population-based | tsDMARD/bDMARD-treated patients with RMD and MTX-treated patients with RMD; data from national registries | Physician diagnosis | PCR+ | General population registries, matched (age, sex, location) | 39 961 | 3/9 (33%)(tsDMARD/bDMARD), 1/5 (20%) (MTX) | 3/84 (3.6%)(tsDMARD/bDMARD controls), 13/134 (9.7%) (MTX controls) | Higher for tsDMARD/bDMARD (RR 9.33, 95% CI 2.20 to 39.6) and MTX (RR 6.22, 95% CI 1.19 to 32.46) | |
| Bower[15] | Sweden | – | May–September 2020 | Retrospective, registry, matched | Population-based | Patients with inflammatory arthritis, data from national registries | Physician diagnosis | ICD-10 | General population registries, matched (age, sex, location) | 110 567 | 581/110 567 (0.5%) (all), 379/53 455 (0.7%) (RA), 202/57 112 (0.4%) (other IJD) | 1443/484 277 (0.3%) (all controls), 784/484 277 (0.4%) (RA controls), 659/484 277 (0.3%) (other IJD controls) | Higher for all (fully adjusted HR 1.32, 95% CI 1.19 to 1.46), RA (HR 1.40, 95% CI 1.22 to 1.60), other IJD (HR 1.20, 95% CI 1.02 to 1.41) Comparable to increased all-cause hospitalisation risk | |
| Comarmond[14] | France | – | 4–20 May 2020 | Retrospective | Secondary care | Patients with TAK or GCA, followed up at outpatient clinic | Physician diagnosis | PCR+ or typical CT imaging or serology+ | Modelled risk in country | 148 | 3/8 (37.5%) | 9.6% (age 70–79), 21% (age>80) | Higher | |
| Cordtz[17] | Denmark | DANBIO | 1 March–12 August 2020 | Retrospective, registry | Population-based | tsDMARD/bDMARD-treated patients with RA, SpA, CTD or vasculitis; data from national registries | Physician diagnosis | ICD-10 | General population registries | 58 052 | 69/58 052 (age-adjusted and sex-adjusted IR per 1000 py 1.73, 95% CI 1.34 to 2.23) | 2536/4.5 mln (age- and sex-adjusted IR per 1000 py 1.26, 95% CI 1.21 to 1.31) | Higher (HR 1.46, 95% CI 1.15 to 1.86) | |
| Fernandez-Gutierrez[26] | Spain | – | 1 March–15 Apr 2020 | Retrospective | Secondary care | Patients with Inflammatory RMD with COVID-19; all patients followed up at outpatient clinic from March 2019 to March 2020 | ICD-10 | PCR+or physician diagnosis | General population in region | 3951 (5896 patient-months) | 54/3,951 (1.36%; cumulative incidence 15 per 1000 patients; IR 9.15 (7–11.9) per 1000 patient-months) | 1059/325 900 (cumulative incidence 3.2 per 1000 persons; IR 4.6 (3.4–6.1) per 1000 person-months) | Higher (p<0.001) | |

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**Table 1** Continued

| First author | Country | Cohort | Study period | Study type | Setting | Study population, recruitment | Case definition RMD | Case definition COVID-19 | Source population of base incidence | Total (N) | Incidence in patients with RMD | Base incidence | Incidence in patients with RMD versus base population (higher, equal, lower) | RoB |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Flood[73] | Ireland | – | Until 3 June 2020 | Retrospective | Secondary care | Patients with RMD, all patients followed up at outpatient clinic | Physician diagnosis | PCR+ or physician diagnosis | General population in city | 7500 | 15% (Inflammatory RMD) | 13% | Equal | |
| Jovani[74] | Spain | – | Until 2 May 2020 | Retrospective | Secondary care | tsDMARD/bDMARD-treated patients with RMD, followed up at outpatient clinic | Physician diagnosis | PCR+ | General population in city | 1037 | 3/1037 (0.29%) | 306/274 122 (0.11%) | Equal (OR 2.61, 95% CI 0.84 to 8.16) | |
| Ramirez[16] (*COVID-19 in*) | Italy | – | 17 April to 27 April 2020 | Retrospective | Secondary care | Patients with SLE, all patients followed up at three outpatient clinics | Physician diagnosis | Self-reported PCR+ | General population in region | 417 | 1/417 (0.24%) | 42 889 hospitalised (0.43%) | Equal | |
| Salvarani[5] (*Susceptibility and*) | Italy | – | Until 24 April 2020 | Retrospective | Secondary care | tsDMARD/bDMARD-treated patients with RMD, treated since December 2019 (pharmacy data) | Physician diagnosis | PCR+ | General population in region | 1195 | 4/9 (44.4%) | 1342/3746 (35.8%) | Equal (p=0.73) | |
| Santos[75] (*Biological agents*) | Spain | – | NR | Retrospective | Secondary care | bDMARD-treated patients with RMD, treated between December 2019 and December 2020 (hospital records) | Physician diagnosis | PCR+ | General population in region | 820 | 4/820 (0.48%) | 4464 hospitalised (3.6%) | Lower | |
| (B) Outcome: COVID-19-related death | | | | | | | | | | | | | | |
| Aries[18] | Germany | Hamburg COVID-19 registry | Until 9 June 2020 | Cross-sectional, registry | Secondary care | DMARD-treated patients with RMD with COVID-19, cases reported by rheumatologists | Physician diagnosis | Symptoms and PCR+ or IgG+ | General population in region | 11 771 | 0/30 (0%) | 226/5120 (4.4%) | Lower | |
| Bower[15] | Sweden | – | May–September 2020 | Retrospective, registry, matched | Population-based | Patients with inflammatory arthritis, data from national registries | Physician diagnosis | ICD-10 | General population registries, matched (age, sex, location) | 110 567 | 161/110 567 (0.1%) (all), 134/53 455 (0.3%) (RA), 27/57 112 (0.05%) (other IJD) | 338/484 277 (0.07%) (all controls), 245/484 277 (0.11%) (RA controls), 93/484 277 (0.04%) (other IJD controls) | Higher for RA (fully adjusted HR 1.27, 95% CI 1.02 to 1.59)<br>Equal for all (fully adjusted HR 1.18, 95% CI 0.97 to 1.44), other IJD (0.83, 95% CI 0.54 to 1.28)<br>Comparable to increased all-cause mortality risk and not different from 2015 to 2019 | |
| Cleaton[76] | UK | – | 1 Febuary–1 May 2020 | Retrospective | Secondary care | Patients with RMD, followed up at outpatient clinic | Physician diagnosis | PCR+ | General population in region | 10 387 | 12/10 387 (0.12%) | 4131/7 415 149 (0.12%) | Equal | |
| Comarmond[14] | France | – | 4 May–20 May 2020 | Retrospective | Secondary care | Patients with TAK or GCA, followed up at outpatient clinic | Physician diagnosis | PCR+ or typical CT imaging or serology+ | Modelled risk in country | 148 | 1/8 (12.5%) | 2.2% (age 70–79), 8% (age >80) | Lower | |

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**Table 1** Continued

| First author | Country | Cohort | Study period | Study type | Setting | Study population, recruitment | Case definition RMD | Case definition COVID-19 | Source population of base incidence | Total (N) | Incidence in patients with RMD | Base incidence | Incidence in patients with RMD versus base population (higher, equal, lower) | RoB |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FAI Consortium[19] | France | French COVID-19 registry | Until 18 May 2020 | Retrospective, matched (age, sex, comorbidities) | Secondary care | Patients with inflammatory RMD and COVID-19; cases reported by rheumatologists | Physician diagnosis | PCR+ or serology+ or typical CT imaging or highly suspected based on clinical symptoms | Patients with COVID-19 from the Lille University Hospital COVID-19 Research Network | 694 | 58/256 hospitalised subgroup (22.6%); death rate in matched subgroup (n=175) 25.1% (95% CI 18.7% to 31.6%) | Death rate 18.9% (95% CI 13.1% to 24.7%) | Equal (OR 1.45, 95% CI 0.87 to 2.42) | |
| Salvarani[5] (*Susceptibility and*) | Italy | – | Until 24 April 2020 | Retrospective | Secondary care | tsDMARD/bDMARD-treated patients with RMD, treated since Dec 2019 (pharmacy data) | Physician diagnosis | PCR+ | General population in region | 1195 | 1/9 (11.1%) | 383/3746 (10.2%) | Equal (p=1.0) | |
| (C) Outcome: Other (ICU or 'severe COVID-19') | | | | | | | | | | | | | | |
| Aries[18] | Germany | Hamburg COVID-19 registry | Until 9 June 2020 | Cross-sectional, registry | Secondary care | DMARD-treated patients with RMD with COVID-19, cases reported by rheumatologists | Physician diagnosis | Symptoms and PCR+ or IgG+ | General population in region | 11 771 | ICU admission 3/30 (10%) | 227/5120 (4.4%) | Lower | |
| Bower[15] | Sweden | – | May–September 2020 | Retrospective, registry, matched | Population-based | Patients with inflammatory arthritis, data from national registries | Physician diagnosis | ICD-10 | General population registries, matched (age, sex, location) | 110 567 | ICU admission 45/110 567 (0.04%) (all), 31/53 455 (0.06%) (RA), 14/57 112 (0.6%) (other IJD) | 162/484 277 (0.01%) (all controls), 79/484 277 (0.02%) (RA controls), 83/484 277 (0.03%) (other IJD controls) | Equal for all (fully adjusted HR 1.18, 95% CI 0.97 to 1.44), RA (1.53, 95% CI 0.98 to 2.40), other IJD (0.83, 95% CI 0.54 to 1.28) | |
| Cordtz[17] | Denmark | DANBIO | 1 March–12 August 2020 | Retrospective, registry | Population-based | tsDMARD/bDMARD-treated patients with RA, SpA, CTD or vasculitis, data from national registries | Physician diagnosis | ICD-10 | General population registries | 29 440 | 'Severe COVID-19'* 22/47 (age-djusted and sex-adjusted IR per 1000 py 35.2, 95% CI 20.8 to 59.4) | 945/2536 (age-adjusted and sex-adjusted IR per 1000 py 32.7, 95% CI 30.7 to 34.9) | Higher (HR 1.43, 95% CI 0.80 to 2.53) | |

*Severe COVID-19 was only assessed in patients with RA and defined as need for mechanical ventilation (procedure code), ICD-10 code of acute respiratory distress syndrome due to COVID-19 or death following COVID-19. Colours denote overall RoB assessment of each study (green denotes low RoB; orange denotes unclear RoB; and red denotes high RoB).
bDMARD, biological disease-modifying antirheumatic drug; CTD, connective tissue disease; DMARD, disease-modifying antirheumatic drug; FAI, Filière des Maladies Autoimmunes et Autoinflammatoires Rares; GCA, giant cell arteritis; ICD-10, International Classification of Diseases, 10th Revision; ICU, intensive care unit; IJD, inflammatory joint disease; IM, inflammatory myopathy; IR, incidence rate; mln, million; MTX, methotrexate; NR, not reported; PMR, polymyalgia rheumatica; PsA, psoriatic arthritis; py, person years; RA, rheumatoid arthritis; RMD, rheumatic and musculoskeletal disease; RoB, risk of bias; SjS, Sjögren syndrome; SLE, systemic lupus erythematosus; SpA, spondyloarthritis; TAK, Takayasu arteritis; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.



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incidence of COVID-19-related death, including 8[14]–110 567[15] patients with RMD with 0[18]–161[15] deaths (table 1). Reported mortality rates in patients with RMDs varied considerably (0%–22.6%), with similar variation observed in the general population. Studies demonstrated an equal (n=4) or lower (n=2) risk of COVID-19-related death in patients with RMD compared with the general population. Two studies with age-matched and sex-matched analyses reported an equal incidence rate, of which one was at low RoB.[15 19] Of note, although Bower *et al* did report an increased risk of COVID-19-related death in the rheumatoid arthritis (RA) subgroup, they also demonstrated that this increased risk was comparable to the increased all-cause mortality risk in patients with RA and that the increased mortality risk in 2020 in patients with RA was not different from that in 2015 to 2019.

Finally, two studies reported on the risk of intensive care unit (ICU) admission and found an equal[15] or lower[18] risk of ICU admission for COVID-19 in patients with RMD compared with the general population (table 1). A large Danish registry study (low RoB) found that the risk of severe COVID-19 (a composite outcome including several COVID-19 complications) was higher in patients with RA compared with the general population, although the reported (non-significant) risk estimate did not seem to have a clinically relevant impact on a population-level (table 1).[17]

### Prevalence of RMDs in patients with COVID-19

Five studies (high RoB) investigated the prevalence of different RMDs in a COVID-19 population. Most reported an equal prevalence of RMDs compared with the general population, though some found a higher prevalence (online supplemental table 7).

## Risk factors for developing (severe) COVID-19

### Demographics

In total, 13 studies investigated the association between a variety of demographic factors and different COVID-19-related outcomes (online supplemental table 8). Generally, these studies found that evidence for well-known risk factors for developing (severe) COVID-19 in the general population, such as increased age, male gender and high body mass index (BMI), also applied to patients with RMDs. One USA-based study reported that the risk of hospitalisation, COVID-19-related death and severe COVID-19 is elevated in people from Afro-American, Latin–American, Asian or other/mixed race compared with people from the white race.[20]

### Comorbidities

The risk of various common comorbidities for developing (severe) COVID-19 in patients with RMDs was investigated in 14 studies (online supplemental table 9). Associations are similar to those known from the general population, such as cardiovascular disease, diabetes mellitus, chronic lung disease and chronic kidney disease.

### RMD type

In total, 19 studies assessed the association between type of RMD and the risk of contracting SARS-CoV-2 (n=4), COVID-19-related hospitalisation (n=9), COVID-19-related death (n=7) and severe COVID-19 (n=7) (online supplemental table 10). A wide range of RMD types and comparisons were studied. Most studies were at unclear or high RoB. The majority did not adequately adjust for important confounders, such as antirheumatic medication or disease activity. Overall, no consistent difference in risk between different RMDs was found. Some studies reported a signal for an increased risk of hospitalisation in patients with autoinflammatory diseases or systemic autoimmune diseases, and for developing 'severe COVID-19' in patients with connective tissue disease (CTD), compared with patients with inflammatory arthritis. However, these results were not consistent across all studies that compared these patient groups.

## Risk associated with antirheumatic medication and disease activity

A total of 26 studies assessed the association between a variety of antirheumatic medication and the risk of contracting SARS-CoV-2 (n=4), COVID-19-related hospitalisation (n=13), COVID-19-related death (n=9) and severe COVID-19 (n=10) (online supplemental table 11).

### Disease activity

Two studies, both from the Global Rheumatology Alliance (GRA)-COVID-19 registry, reported moderate or high disease activity as a risk factor for COVID-19-related death in patients with RMD (OR 1.87, 95% CI 1.27 to 2.77)[21] and for severe COVID-19 in patients with SLE (OR 2.24, 1.46–3.43),[22] even after extensive adjustment including the use of antirheumatic medication.

### Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs were not associated with the risk of contracting SARS-CoV-2 (n=2, 1 low RoB),[12 23] COVID-19-related hospitalisation (n=1)[24] or COVID-19-related death (n=2, 1 low RoB).[23 25]

### Glucocorticoids

Glucocorticoid use was associated with an increased risk of COVID-19 hospitalisation in seven studies (one low RoB), although not all analyses reached statistical significance.[17 19 24 26–29] Two studies showed that this increased risk was particularly present in those using a daily dosage of 10 mg or more.[24 27] Similar results were found in studies assessing the association between glucocorticoid use and COVID-19-related death (n=2)[21 30] or severe COVID-19 (n=5).[19 22 31–33] Again, a dose–response effect was found.[21 22 31] Strangfeld *et al* performed subgroup analyses of patients with inflammatory arthritis and CTD/vasculitis separately, and reported that the increased risk of COVID-19-related death associated with glucocorticoid use remained only in the CTD/vasculitis subgroup.[21] A post hoc analysis of the same study, using data from the GRA-COVID-19 registry, strongly suggested that the association with glucocorticoids mainly results from confounding by disease activity.

### Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs)

Antimalarial drugs were not associated with the risk of contracting SARS-CoV-2 (n=2),[34 35] COVID-19-related death (n=4)[21 36–38] or severe COVID-19 (n=3).[31 38 39] Five studies (one low RoB) also found no association with COVID-19-related hospitalisation,[17 27 36 38 39] though a small study by Haberman *et al* reported an increased risk.[29]

Single studies investigated the risk associated with the use of various other csDMARDs, including methotrexate (COVID-19 hospitalisation, no association; n=2),[29 36] sulfasalazine (COVID-19-related death, higher risk (OR 3.6, 95% CI 1.66 to 7.78); n=1)[21] and leflunomide (COVID-19-related death, no association; n=1).[21]



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### Biological disease-modifying antirheumatic drug (bDMARDs)/targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs)

Tumour necrosis factor alpha inhibitors (TNFis) were not associated with COVID-19-related hospitalisation in four studies (two low RoBs),[15 17 26 29] while two studies suggested a 'protective' effect.[19 27] TNFi use was not associated with COVID-19-related death (n=2, 1 low RoB)[15 21] or severe COVID-19 (n=1, low RoB).[15]

One study suggested that rituximab was associated with an increased risk of contracting SARS-CoV-2,[40] though two other studies (one low RoB) did not confirm this association.[15 27] Multiple studies found a higher risk of COVID-19-related death (n=4, 1 low RoB)[15 21 30 40] and severe COVID-19 (n=4),[19 31 40 41] although not all analyses reached statistical significance. Several of these studies are separate analyses of (parts of) the GRA-COVID-19 registry.

Fewer studies investigated Janus kinase inhibitors (JAKis), of which most found a higher risk of COVID-19-related hospitalisation (n=2, 1 low RoB),[15 29] COVID-19-related death (n=1, low RoB)[15] and severe COVID-19 (n=1).[41] Strangfeld *et al* reported no association between JAKi use and COVID-19-related death.[21]

Single studies investigated other bDMARDs/tsDMARDs, including abatacept, belimumab, interleukin-6 inhibitors (IL-6i), IL-17i and IL-23i, but no association was observed with any of the COVID-19 outcomes.

Studies (n=3, 1 low RoB)[15 26 29] found no association with COVID-19-related hospitalisation, COVID-19-related death (n=1, low RoB)[15] or severe COVID-19 (n=2, 1 low RoB)[15] for any bDMARD users versus non-bDMARD/tsDMARD users.

### Immunosuppressive medication

Few studies investigated the risk associated with use of immunosuppressive medication. One study found a higher risk of COVID-19-related death in users of immunosuppressive medication (a heterogeneous group composed of azathioprine, cyclosporine, cyclophosphamide, mycophenolate or tacrolimus users), compared with methotrexate users (OR 2.22, 95% CI 1.43 to 3.46).[21] One study also reported a higher risk of severe COVID-19 in mycophenolate mofetil users (OR 6.60, 95% CI 1.47 to 29.62),[19] while another found no association with this outcome in users of immunosuppressive medication.[31] These studies were all conducted in the GRA-COVID-19 registry.

## Vaccination against SARS-CoV-2

In total, 14 articles, two of which were preprints, with data on vaccination against SARS-CoV-2 in patients with RMDs, were identified (online supplemental table 12).

### Efficacy

Nine out of 14 studies reported on the efficacy of vaccination against SARS-CoV-2, measured as (presence or level of) antibody response (online supplemental table 12). Four studies had a prospective design; three were cross-sectional; and one was retrospective. The studies consisted of patients with (inflammatory) RMDs (n=5) or patients with various chronic inflammatory/autoimmune diseases including RMDs (n=3). Five studies also included a healthy control group. The number of patients with RMD ranged from 68[42] to 807.[43] All participants received an mRNA vaccine. Responsiveness was measured after the second dose in most studies (n=6). RoB was high (n=6) or unclear (n=2) in most studies.

The percentage of cases with a detectable antibody response ranged from 62% to 100% (median 88%, n=8 studies), while this was 96%–100% (median 100%, n=5 studies) in controls. Five studies measured the level of antibody response, all demonstrating lower IgG antibody titres or neutralising titres in cases versus controls.

One study assessed T-cell response using flow cytometry in a subset of participants, reporting a significant increase in spike-specific B cells, T-follicular helper cells, activated CD4+ T cells and HLA-DR+CD8+ T cells in cases and controls, though activated CD8+ T cells and granzyme-B-producing CD8+ T cells were only induced in patients with RMD not using methotrexate and healthy controls.[44]

Factors that were negatively associated with antibody response in more than one study were increased age (3/4 studies) and use of rituximab or anti-CD20 (6/6), mycophenolate (4/4) and glucocorticoids (3/3). Two studies showed that a longer interval between vaccination and rituximab infusion was associated with a positive antibody response.[43 45] Ruddy *et al* detailed that 86% of negative responders on glucocorticoids concurrently used rituximab or mycophenolate.[46] Less convincing results were seen for methotrexate (negative association in 2/5 studies), abatacept (2/3) and JAKi (1/2). Use of anticytokine therapy was not, or even positively, associated with antibody response. Furer *et al* (low RoB) found detectable antibodies in 86% of cases versus 100% of controls, lower antibody titres in cases, and a negative association with vaccine responsiveness for increased age, rituximab, mycophenolate, glucocorticoids and abatacept (but not methotrexate or JAKi).[43]

In total, 19/2989 (0.6%, n=5 studies) patients with RMD developed postvaccination COVID-19.[43 46–49] One study reported a post-vaccination COVID-19 case in a control subject (1/807, 0.1%).[43]

### Safety

Ten studies (one low RoB) reported safety data (online supplemental table 12). In all but one study, all patients received an mRNA vaccine. Generally, vaccination was well tolerated. Reported adverse events, though common, were mild and similar in type and severity/seriousness between patients with RMD and controls. Most reported were local symptoms, such as pain at the injection site, and less frequently systemic symptoms such as fatigue, myalgia and fever.

Three studies found no postvaccination disease flare of the underlying RMD in 868 patients with RMD,[42 43 50] while a report from the EULAR COVAX registry describes a disease flare in 73 out of 1375 (5%) patients, of whom 17 experienced a severe flare (mean±SD) 5±5 days postvaccination.[48]

No RMD-specific factors (eg, disease type or medication) were consistently associated with the development of adverse events

## Other outcomes

One USA-based, prospective study assessed the association of SARS-CoV-2 infection with development of a disease flare in Latin-American patients with RMDs, reporting an increased risk (OR 4.57, 95% CI 1.2 to 17.4).[9]

One US-based, retrospective study in the TriNetX database compared outcomes of matched patients with inflammatory RMDs and COVID-19 in the early (January–April 2020) and late (April–July 2020) phases of the pandemic.[51] The study showed that patients with COVID-19 in the late cohort fared better than those in the early cohort, based on lower risk of COVID-19-related hospitalisation (RR 0.71, 95% CI 0.67 to



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0.76), ICU admission (RR 0.56, 95% CI 0.47 to 0.65), mechanical ventilation (RR 0.39, 95% CI 0.31 to 0.49), death (RR 0.48, 95% CI 0.39 to 0.60) and severe COVID-19 (composite of ICU admission, mechanical ventilation and death; RR 0.51, 95% CI 0.45 to 0.58). Results from several sensitivity analyses were similar. The results of this study are confirmed in studies from the GRA-COVID-19 database, where adjustment for time period was also significant.[22]

### Post hoc data

As this SLR covers a highly dynamic field in which new studies emerge on a weekly basis, particularly regarding vaccination against SARS-CoV-2, during the review process of the manuscript, a partial literature search update was done for vaccination studies only, in order to provide a more up-to-date overview of these data. Importantly, these data were not available for the task force at the time of deciding on the recommendations. We searched PubMed up to 11 October 2021 using previously described search terms (see online supplemental material), with the addition of specific terms for vaccination. The search retrieved 189 new hits, of which 23 were eligible (online supplemental table 13). Three reports concerned different outcomes and/or follow-up moments of a study already included in the main search,[52–54] and two reports concerned different outcomes and/or follow-up moments of the same study.[55 56] RoB was not assessed for this post hoc analysis.

Twelve studies, primarily concerning mRNA vaccines, provided efficacy data. Most studies confirmed a lower seroconversion rate or antibody titre in patients with RMD.[57–62] One large study by Boekel *et al* showed that after double exposure (ie, first dose after previous SARS-CoV-2 infection or second dose of a two-dose vaccination scheme), seroconversion rates became similar in cases and controls, except among those treated with anti-CD20 therapies.[57] Seven studies confirmed the negative association between anti-CD20 therapy and antibody response,[52 53 55 57 58 60 63] though studies assessing T-cell response (all based on interferon-γ release assays) showed signs of a present T-cell response, independent of antibody response.[58 63] Other antirheumatic medications reported to be associated with impaired antibody response include methotrexate (3/3 studies), mycophenolate (3/3 studies) and glucocorticoid use (3/6 studies). One study reported lower immunogenicity of the Ad26.COV2.S vaccine (Johnson & Johnson) compared with mRNA vaccines,[52] but other studies did not report differences between vaccine types. It should be noted that such analyses are hampered by low patient numbers. One small study reported a beneficial effect of withholding mycophenolate in the perivaccination period on antibody response, but at the cost of a disease flare in 2/24 patients.[53]

Seventeen studies assessed vaccine safety, but no new safety signals were reported. Nine studies assessed postvaccination RMD disease flares, which occurred in 0.6%–15.0% of patients, were generally mild to moderate and not leading to treatment changes (except in one study on patients with SLE)[64] and resolved quickly.[54 59 61 64–69] Disease flare within 6–12 months prior to vaccination appeared a risk factor for postvaccination flare.[54 64] Two case studies described characteristics and outcomes of 26 patients with RMD with SARS-CoV-2 infection after complete vaccination.[70 71] The most commonly used antirheumatic medication among these patients were glucocorticoids (n=8, 31%), methotrexate (n=6, 23%), rituximab (n=6, 23%) and mycophenolate (n=5, 19%). Three of the four patients who died were on rituximab. We did not find studies investigating the yield of an additional vaccine dose after an initial primary vaccine series in patients with RMD.

## DISCUSSION

Current literature provides no evidence that patients with RMDs face more risk of contracting SARS-CoV-2 than individuals without RMDs. While some studies suggest a higher rate of COVID-19-related hospitalisation in patients with RMDs compared with the general population, there is no evidence that patients with RMDs suffer from higher rates of COVID-19-related mortality or ICU admission. This apparent contradiction may be explained by other factors that influence hospitalisation than COVID-19 severity, such as concern of a worse prognosis by the treating physician and consequently a lower threshold for hospital admission. A large Swedish registry study, judged as being at low RoB, provided convincing evidence for this conclusion by demonstrating that the increased risk of hospitalisation and mortality observed in patients with RMD, particularly patients with RA, during the COVID-19 pandemic was similar to the increase reported in previous years.[15] Notably, results of a Danish registry study, which seem to point towards a higher incidence of severe COVID-19 in patients with RA, may be explained by the same mechanism as the Swedish study, but this was not investigated by the authors.[17] Still, if true, the impact of the reported risk estimate from that study is not clinically relevant at the population level.

Several risk factors for developing (severe) COVID-19 in patients with RMDs were assessed in this systematic review. Generally, demographic risk factors (increased age, male gender and high BMI) and comorbidities (cardiovascular disease, diabetes mellitus, chronic lung disease and chronic kidney disease), known to be associated with a worse prognosis of COVID-19 in the general population, are also applicable to patients with RMDs. Few studies investigated the role of ethnicity, but they found that patients with RMD from most non-white ethnicities, compared with individuals from the white race, likely suffer from a worse prognosis. No consistent difference in risk of developing (severe) COVID-19 was found between different RMDs. While single studies reported a worse prognosis in patients with RA compared with non-RA controls as well as in patients with autoinflammatory or systemic autoimmune diseases or CTD compared with those with inflammatory arthritis, these results were not consistent across all studies. In addition, adequate adjustment for factors known to affect prognosis, such as RMD medication and disease activity, was rarely assessed. Only few studies assessed disease activity as a risk factor for worse COVID-19 prognosis, but studies that did so found compelling evidence that moderate or high disease activity is a negative prognostic factor, even after extensive adjustment for RMD medication, including glucocorticoid use. At the start of the pandemic, a potentially negative effect of NSAIDs and a potentially positive effect of antimalarial drugs in COVID-19 were widely discussed, also outside the rheumatology field, but we did not find an increased or decreased risk of developing (severe) COVID-19 related to either type of medication. Similarly, potential positive effects of IL-6i or TNFi were not evident from the literature. On the other hand, current literature provides evidence for concerns regarding a few other drugs. This particularly pertains to rituximab, the use of which seems to be associated with an increased risk of COVID-19-related complications and death. While glucocorticoid users, in particular those receiving a daily dose above 10 mg of prednisone or equivalent, seem to be at an increased risk of hospitalisation, COVID-19-related complications and death,



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there is evidence that this may be largely due to confounding by disease activity. Some studies also provide a signal for worse prognosis of COVID-19 in patients on JAKi. However, in many countries, these drugs are prescribed in patients who have failed (multiple) other therapies, and therefore, patients on JAKi generally suffer from more severe disease, providing ample room for confounding by indication as an alternative explanation for the observed increased risk, which may be too large to adjust for, even in well-designed observational studies. No other consistent associations between various RMD medication and developing (severe) COVID-19 were found in the current literature.

The first studies assessing efficacy and safety of vaccination against SARS-CoV-2 have been published, with many more expected to come since vaccination in many Western countries has taken flight. Current data show that, in general, SARS-CoV-2 vaccines are immunogenic in patients with RMDs, although the antibody response is lower compared with healthy controls. Still, the reported number of postvaccination COVID-19 cases in patients with RMDs remains low, and no information is available on the severity of these cases. Particularly older patients, as well as rituximab and mycophenolate users, appear to be at risk of lower antibody response. The (negative) effect of methotrexate on antibody response is uncertain. Patients on anticytokine therapy do not seem to exhibit lower antibody responses. Notably, the relation between measured antibody response and immune protection of the vaccines is unknown, and the extent and impact of T-cell response to SARS-CoV-2 vaccination remain unclear, as it was only reported in a subgroup of patients from one study. Adverse event profiles were comparable to the general population regarding the type and severity/seriousness. There was no literature to inform risk–benefit ratios of additional dose after an initial primary vaccine series in (subgroups of) patients with RMDs. None of the studies investigated the usefulness of stopping or postponing (specific) RMD medication in light of vaccination, although two studies showed that in patients in whom a longer period between rituximab infusion and vaccination existed, the antibody response was higher.[43 45]

Since the end of 2019, a large number of publications on COVID-19 have appeared. However, as is often the case, quantity is not necessarily a measure for quality. This becomes clear from the large number of included studies that were not considered eligible for data extraction after quality assessment and from the judgement of high RoB among those that passed the quality filter. A critical caveat relevant for (cohort) studies on COVID-19 in patients with RMDs is 'selection bias', which, even in well-established registries or large cohorts with extensive correction for confounders, can hardly be eliminated and may lead to spurious associations, particularly in studies with voluntary enrolment of COVID-19 cases. Studies at lowest risk of selection bias, and therefore most informative in this context, are population-based studies using, for example, national registries in which all patients from a country are included irrespective of patient characteristics. Examples of such studies are those from Bower *et al* and Cordtz *et al*.[15 17] Another problem in many studies is 'confounding by indication' stemming from selective testing for SARS-CoV-2, particularly at the beginning of the pandemic, when testing was not yet widely available.

When interpreting the data presented in this review, it is important to take into account that almost all studies were done during the first wave of the pandemic. This has some advantages for data interpretation, such as the presence of a lower number of different strains and therefore more homogeneous SARS-CoV-2 infection, and less confounding by indication by suspected risk factors of which at the time knowledge about their association with prognosis was lacking. However, this was also the time at which, for example, SARS-CoV-2 testing was not done ubiquitously, introducing bias as discussed previously. The association between risk factors discussed earlier or efficacy of vaccination in different strains of SARS-CoV-2 is unknown. Furthermore, patients included in studies at a later stage of the pandemic appear to have a better prognosis than those included in the beginning, so it may be true that in general, the studies from the first months of the pandemic paint a more negative picture than is currently justifiable.

In conclusion, this SLR presents an overview of currently available literature on risk and prognosis of SARS-CoV-2 infection and vaccination against SARS-CoV-2 in patients with RMDs, and provided evidence to inform the EULAR task force and formulate the July 2021 update of the recommendations for the management of RMDs in the context of SARS-CoV-2.

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