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PERSPECTIVES IN RHEUMATOLOGY

Different systemic rheumatic diseases as risk factors for COVID-19-related mortality

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Abstract

COVID-19 has been associated with increased morbidity and mortality, globally. Whether COVID-19-related mortality is increased in patients with systemic rheumatic diseases (SRDs) is still debatable. Although results are somewhat conflicting, there are a handful of nationwide studies published indicating that, in individuals with SRD, there is signal for increased adverse COVID-19-related outcomes and higher mortality. It appears that there are differences in COVID-19-related mortality across various SRDs. Besides, certain disease-specific (disease activity, disease duration, medication received) and/or other features (e.g. comorbidities) seem to also affect COVID-19-related mortality in SRD patients. Herein, we wanted to highlight that a more individualized approach taking into consideration the effect of the aforementioned factors into the risk calculation for COVID-19 adverse outcomes, including mortality, in SRD patients is warranted. A multinational study based on nationwide data, examining all common SRDs and stratifying accordingly, would be of interest, toward this direction.

Key Points

- *It is still debatable whether Covid-19-related mortality is increased in patients with sytemic rheumatic diseases (SRD).*
- *Disease-specific risk factors (e.g. type of SRD, disease activity) should be taken into account in risk assessment for Covid-19-releted outcomes in SRD patients.*

Keywords COVID-19 · Mortality · Systemic rheumatic diseases

COVID-19 has been associated with increased morbidity and mortality, globally. Whether patients with systemic rheumatic diseases (SRDs) are more vulnerable to infection, hospitalization, Intensive Care Unit (ICU) admission, or death is still not clear. In the early days of the pandemic, it was highlighted that well-designed studies were needed to assess whether the risk for adverse COVID-19-related outcomes was increased for SRD patients [1]. Currently, more than 2 years after the start of the pandemic, several studies assessing the impact of COVID-19 on SRD patients have been published, but only a handful of them are of high-quality and/or powered enough to address these questions [2, 3]. Along these lines, the need for more robust data about the vulnerability of SRD patients to COVID-19 and its adverse outcomes is still stressed by experts in the field [4, 5]. Notably, waiting for these data, health policy makers in many countries gave priority to vaccination of SRD patients [6].

European Alliance of Associations for Rheumatology (EULAR), one the major rheumatology alliances, recently published its recommendations for the management and vaccination of people with SRD in the context of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). As stated in the first overarching principle: "in general, patients with rheumatic disease do not face higher risk of contracting SARS-CoV-2 compared to individuals without rheumatic disease, and do not have a worse prognosis when they contract it" [7]. The authors mention that the words "In general" have been added to address a few exceptions of severe systemic autoimmune or autoinflammatory diseases that could be at higher risk of death from COVID-19 but are

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not yet adequately studied. Despite this quote, to our view this overarching principle does not capture differences in mortality from COVID-19 among discrete SRD and understates the risk for more severe COVID-19 in many patients.

Below, we present existing evidence about COVID-19-related mortality in SRD patients. In Table 1, we show only high-quality studies included in the Systematic Literature Review (SLR) (up until May 2021) [8] that informed EULAR recommendations for the management and vaccination of people with SRD in the context of SARS-CoV-2 as well as studies published after May 2021 [9–12] (Table 1). Quality of these studies, which include unvaccinated patients only, was assessed with the Newcastle–Ottawa scale for observational studies and AMSTAR (A MeaSurement Tool to Assess systematic Reviews) 2 tools for SLRs [13, 14].

A higher risk of COVID-19-associated death in patients with SRD was reported in a nationwide study from South Korea examining data from about 8.300 SRD patients (Table 1) [12]. Along the same lines, a Swedish, nationwide cohort study [8] showed that COVID-19-associated mortality was higher in patients with rheumatoid arthritis (RA) compared to the general population, whereas no difference was found for patients with other forms of inflammatory arthritis (including psoriatic arthritis, ankylosing spondylitis, other spondyloarthropathies, or juvenile idiopathic arthritis) (Table 1). Additionally, 12-month data from our center, derived from the interlinkage of electronic databases covering nearly 99% of the Greek population of about 11 million individuals, indicate that COVID-19-associated mortality was higher in patients with RA and systemic sclerosis (SSc) compared to matched referents from the general population; no difference in mortality was found for systemic lupus erythematosus, ankylosing spondylitis, and psoriatic arthritis (Table 1) [9]. Increased mortality (odds ratio (OR) 2.08 (95% confidence intervals (CI): 1.55–2.73)) is also reported for SRD patients, in a smaller Italian study enrolling 668 individuals [15]. Along the same lines, a population-based study from Canada reported higher complicated (admission to intensive care unit/ventilation or death) COVID-19 hospitalizations in patients with SRD (including also patients with multiple sclerosis, iritis, and inflammatory bowel disease) compared to those without (OR 1.21 (95% CI 1.02, 1.43)), but this was attenuated when adjustments were made for comorbidities as well as for demographic and socioeconomic factors (OR 1.09 (95% CI 0.91, 1.29)) [16]. Results from a nationwide cohort study from Denmark [17] suggest that RA patients admitted with COVID-19 had 43% increased hazard rate for a severe outcome (intensive care, acute respiratory distress syndrome, or death), compared with COVID-19 patients without systemic rheumatic disease (hazard ratio (HR):1.43 (95% CI 0.80 to 2.53)). On the other hand, an American multicenter study (Table 1) and a smaller study from France reported equal mortality risk in individuals with or without SRD [11, 18]. Of note, a SLR and meta-analysis of observational or case–control studies, published in November 2021, reported an odds ratio for COVID-19-associated mortality of 1.74 (95% CI 1.08, 2.80) for SRD patients [10].

Drawing the main strands together, one could say that results are still somewhat conflicting. However, an increased signal for mortality in some SRD patient groups is observed in most high-quality meta-analyses and studies performed on a national level. Ethnic disparities, including variations in the geoepidemiology and preventive measures taken for SARS-Cov2 as well as differences in methodology, could partially be blamed for the discordance between studies. Of note, a recent meta-analysis has shown that there were significantly different COVID-19-related outcomes reported, across different regions [19]. Additionally, data from the COVID-19 Global Rheumatology Alliance Physician Registry have shown that race/ethnicity could also be associated with different COVID-19-realted outcomes [20]. However, we feel that some other parameters that are under-recognized thus far could better explain the observed differences.

Firstly, mortality differs among distinct SRDs. This is evident in the Swedish study, in which fully adjusted mortality is higher in patients with RA but not with other forms of arthritis [8], and also in the study conducted in South Korea [12], in which mortality is presented to be higher in patients with inflammatory arthritis, but not in those with connective tissue diseases, compared to matched individuals without SRD (Table 1). Similarly, in our study, we found higher mortality rates for RA and SSc, but not for other SRDs [9]. Currently, it is difficult to explain variations observed among distinct SRDs. Higher age (for RA compared to other SRDs) could partially be blamed. Also, as discussed below, one could speculate that this may owe to different treatment regimes administered [8, 21, 22] and/or to different comorbidities/extra-articular manifestations (e.g., interstitial lung disease) [23]. It should be noted that adjustments for immunosuppressive/immunomodulatory treatment received were not conducted in most of these studies [2]. Besides, rituximab and JAK inhibitors have been associated with higher risk of COVID-19-related death [8, 21, 22], while some data also link use of some immunosuppressives and/or glucocorticoids, above certain doses, with mortality risk [2, 18, 21, 24]. Along the same lines, disease activity (for which it is extremely difficult to control in nationwide studies using electronic records) has also been suggested as an adverse prognostic factor for COVID-19-related mortality [21].

Secondly, an important parameter that should be considered is that comorbidities are linked with increased mortality in patients with or without SRD [25]. Some of the published studies have controlled for comorbidities, although it should be noted that their recording was based on retrospective data obtained from electronic records, with all the limitations that this may have. Importantly, comorbidities are closely linked with SRD [23, 26]. In fact, it has been argued by

Table 1 COVID-19-related mortality in unvaccinated patients with systemic rheumatic diseases (SRDs) compared to the general population in high-quality studies (assessed by the Newcastle–Ottawa scale and AMSTAR2 tool). *RA* rheumatoid arthritis, *IA* inflammatory arthritis, *HR* hazard ratio, *RR* relative risk, *BMI* body mass index, *OR* odds ratio, *CTD* connective tissue diseases

Author/Date/Country (REF)	Study type, duration, control population	SRD	Adjustments	Mortality	Limitations
Bower/2021/Sweden (8)	Nationwide, 6 months, matched comparators ($n=484,277$)	RA ($n=53,455$) IA ($n=57,112$)	Age, sex, geographical region, comorbidities, socioeconomic factors	HR = 1.27 (1.02 to 1.59) [RA] HR = 0.83 (0.54 to 1.28) [IA]	- Included only RA and IA patients
D'Silva/2021/USA (11)	Multicenter, limited to SARS-CoV2 infected, 7 months, matched comparators ($n=2379$)	SRD ($n=2379$)	Age, sex, race, ethnicity, BMI, comorbidities, and health care utilization	RR = 1.18 (0.88 to 1.58)	- SRD were examined as one group - No adjustment for geographical region
Shin/2021/South Korea (12)	Nationwide, limited to those tested for SARS-CoV2, 5 months, matched comparators ($n=133,609$)	SRD ($n=8297$)	Age, sex, geographical region, comorbidities, socioeconomic factors, smoking alcohol, BMI, aerobic activity	OR = 1.69 (1.01 to 2.84) [SRD] OR = 1.81 (1.02 to 3.18) [IA] OR = 1.87 (0.71 to 4.85) [CTD]	- Not examined per specific SRD (grouped as IA and CTD)
Bournia/2022/Greece (9)	Nationwide, 12 months, matched comparators ($n=374,850$)	RA ($n=40,014$) PsA ($n=13,405$) SLE ($n=9960$) AS ($n=9566$) SSc ($n=2025$)	Age, sex, use of bDMARDs, geographical region	OR = 1.86 (1.37 to 2.52) [RA] OR = 1.23 (0.52 to3.23) [PsA] OR = 1.60 (0.73 to 3.50) [SLE] OR = 0.33 (0.1 to 8.54) [AS] OR = 2.90 (0.97 to 8.67) [SSc]	- Not adjusted for comorbidities
Conway/2021 (10)	SLR-meta-analysis	13 studies	Unadjusted	OR = 1.74 (1.08 to 2.80) [SRD]	- Substantial heterogeneity, I^2 83% (95% CI 71 to 89%)

some investigators that in some cases like in RA, some comorbidities like excessive cardiovascular risk could not be seen as conditions unrelated to the underlying rheumatic disease [27]. To add another level of complexity, other studies have shown that comorbidities are accumulating earlier than expected in patients with some SRD [28].

To conclude, the small number of studies available so far, some of which are of low quality, currently precludes firm conclusions regarding the impact of COVID-19 on patients with SRD. The complex nature of this issue, given the various confounders as outlined above, directs toward a more individualized approach into the risk calculation for COVID-19 adverse outcomes in SRD patients, taking into consideration the effect of disease-specific risk factors (type of SRD, disease activity, disease duration, medication received). Vaccination against SARS-CoV2 will also affect favorably the COVID-19-related mortality in SRD patients [6, 29], as it has been shown in the general population as well [30]. We propose that a multinational study based on nationwide data, examining all common SRDs and stratifying accordingly, taking also into account confounders, will help us to identify the characteristics of SRD patients who are more vulnerable to COVID-19.

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Data interpretation: all authors
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Critically revising the manuscript: PPS
Final approval: all authors

Declarations

Disclosures None.

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