Review

SARS-CoV-2 infection in patients with systemic autoimmune diseases

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ABSTRACT

Systemic autoimmune diseases (SAD) are a heterogeneous group of diseases with a common aetiopathogenic basis affecting all ages characterised by a systemic phenotypic expression with a wide range of severity and outcomes that often require immunosuppressive therapies, leaving patients at high risk of infection. Knowledge of the impact of COVID-19 in patients with SAD is limited because most are included in studies carried out in patients with autoimmune and rheumatic diseases (mainly inflammatory arthritis). Most studies supported an increased risk of SARS-Cov-2 infection in patients with AD and SAD. Although case-control studies reported no significant differences in the rate of poor outcomes between patients with and without AD, large population-based studies analysing baseline risk factors reported a 2–3 times higher rate of poor outcomes in patients with AD, especially in those with SAD. Individual risk factors associated with poor outcomes included gender male, older age, and underlying comorbidities and therapies (glucocorticoids, sulfasalazine, immunosuppressants and rituximab). Patients with SAD had less favourable COVID-19 outcomes than those with inflammatory arthritis, possibly due to a differentiated underlying therapeutic approach (glucocorticoids, immunosuppressants and B-cell depleting agents for most SAD, anti-cytokine therapies and JAK inhibitors for inflammatory arthritis). Despite the limited evidence, most studies suggest that patients with SAD have an increased risk of a worse evolution of SARS-CoV-2 infection, including a greater risk of hospitalisation/ICU admission and worse survival rates and, therefore, should be considered a high-risk group for COVID-19.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the seventh coronavirus known to infect humans after the identification of SARS and Middle East respiratory syndrome viruses (MERS) (1). The lack of prior immunity to the virus has resulted in a rapid increase in infected patients worldwide (2) and by November 27, 2020 there were more than 60 million confirmed cases. The disease caused by SARS-CoV-2 (COVID-19) has a very wide spectrum (2). The most frequent clinical presentation requiring hospitalisation is pneumonia with fever, cough and dyspnoea, that may progress, in some patients, to respiratory and multiorgan failure (3). SARS-CoV-2 appears to preferentially target the respiratory epithelium, where it enters host cells through the angiotensin-converting enzyme 2 (ACE2) receptor, similar to SARS-CoV (4, 5, 6). COVID-19-associated pneumonia is associated with robust interferon suppression with low IFN-γ production by $CD4^+$T-cells (7) and autoantibodies against type I IFNs in 10% of severe patients (8, 9).

The disease course of individuals with COVID-19 is highly diverse, and several studies have identified subgroups of patients with a poor prognosis. Various epidemiological features and pre-existing conditions have been associated with poor outcomes, including male sex, older age, non-White people and those with baseline comorbidities (obesity, diabetes, cancer, and chronic diseases involving internal organs) (10-13). Patients with autoimmune diseases (AD) are also considered to be at increased risk of more severe infection (10). Among AD, systemic autoimmune diseases (SAD) comprise a group of diseases with a common aetiopathogenic

basis, affecting people of all ages, and characterised clinically by a systemic phenotypic expression with a wide range of severity and outcomes. Until now, knowledge of the impact of COVID-19 on these patients is dispersed between dozens of studies. This narrative review summarises current knowledge on how SARS-CoV-2 infection may affect patients with SAD and whether these patients have an enhanced risk of poor outcomes after infection.

SARS-COV-2 infection in systemic autoimmune diseases

Patients with SAD are overwhelmingly included in studies that analyse the frequency and prognosis of COVID-19 in patients with AD and which contain varying proportions of patients with rheumatic diseases (inflammatory arthritis, the subset most frequently represented in more than 60% of patients), SAD (representing around 30%) and organ-specific autoimmune diseases (representing <10%) (14-21). We analysed studies offering specific data for the subset of patients with SAD whenever possible.

Frequency of SARS-Cov-2 infection

It is unclear whether patients with SAD have a higher risk of SARS-Cov-2 infection than the general population (22). Studies have analysed how frequently patients with SARS-Cov-2 infection (overwhelmingly hospitalised patients) have an underlying AD (including SAD). Among 15620 patients hospitalised due to COVID-19 included in 8 studies (23-30), 196 (1.25%) had an underlying AD and 84 (0.54%) an underlying SAD (Supplementary Table S1). Considering that a recent population-based study has estimated a frequency of SAD in the general population of around 0.8% (31), all studies but two have reported lower frequencies of underlying SAD in people with SARS-CoV-2 infection.

Other studies have analysed how prevalent SARS-Cov-2 infection is in cohorts of patients with AD (including SAD). SARS-CoV-2 infection has been investigated in 6502 patients with SAD included in nine studies (32-40), of which 61 (0.94%) had a positive PCR diagnosis (Table I). A recent meta-analysis (41) reported SARS-CoV-2 infection in 58 (3.5%) out of 1641 patients with SAD, although the studies selected were heterogeneous, with some including only patients with a single SAD, such as SLE (42-44), and others including patients without microbiological confirmation of infection (42). Available data on the rate of SARS-CoV-2 infection in individual SAD is summarised in Supplementary Table S2.

No case-control studies have compared the frequency of SARS-Cov-2 in patients with and without SAD. Of studies analysing patients with AD (Table II), one found no significant differences between the frequency of SARS-Cov-2 infection in patients with and without AD (0.25% *vs*. 0.28%) (45), while two studies reported a significantly higher rate of SARS-CoV-2 infection in patients with AD (0.76-1.4%) than in those without (0.5–0.58%), with an estimated odds ratio (OR) that was 1.3–3-times higher in AD patients (32, 40); likewise, an OR of 1.59 was reported in a meta-analysis by Akiyama *et al*. (41).

In population-based studies designed to identify baseline risk factors for SARS-CoV-2 infection, we identified five studies that specifically included AD in the adjusted multivariate analysis (Table II). Two studies reported a lower risk of testing positive for SARS-CoV-2 infection (46, 47), and the remaining three reported that patients with AD had a higher risk of testing positive (OR between 1.3–3.01) (32, 40, 48). Zhong *et al*. (48) analysed 43 patients with AD and 83 of their relatives, and reported that 27 (63%) AD patients developed SARS-CoV-2 infection compared with 28 (34%) family members without AD (adjusted OR 2.68, 95% CI 1.14–6.27); however, if patients without confirmed PCR are excluded from the analysis, the infection rates are lower and the comparison was not significant (46.5% *vs*. 30.1%, $p>0.05$).

Outcomes of COVID-19 in patients with SAD

No studies have compared the rate of symptomatic (COVID-19) *versus* asymptomatic people according to the presence or absence of an underlying AD. Several case-control studies have analysed the main features of COVID-19 in patients with and without underlying AD (including SAD). One study reported a higher frequency of some symptoms (dyspnoea, myalgia, malaise, anorexia, ageusia and anosmia) in AD patients (26), while two studies found no significant differences (20, 27). The rate of patients with AD who developed pneumonia was 57.7% (15, 18, 20, 21, 25, 40) (Suppl. Table S3), and only one study has compared the rate of pneumonia in patients with and without AD, finding a lower rate of pneumonia in AD patients (40). Some studies have reported a differentiated biological profile in AD patients, including a higher mean WBC count (27) a lower frequency of lymphopenia (26), a lower ferritin peak level (27) and a higher mean creatinine (40) than in patients without AD.

- *Hospitalisation*

The hospitalisation rate due to COVID-19 in patients with AD is 51.09% (14, 15, 18-21, 27, 49) (Suppl. Table S3). Case-control studies have reported a similar rate or risk of hospitalisation between patients with and without underlying AD (16, 26, 27, 50), with a similar duration of hospital stay (20, 27) (Suppl. Table S4). In patients with AD, one study reported that patients with an underlying SAD had an increased risk of hospitalisation compared with patients with other AD, with an adjusted OR of 3.55 (18) (Suppl. Table S5).

Studies have identified some epidemiological and clinical features that increase the risk of hospitalisation in AD patients (Fig. 1) (Suppl. Table S6). Epidemiologically, male sex and older age were associated with an enhanced risk of hospitalisation, with adjusted ORs of 1.08-2.56 for age (14, 18, 19) and 7.4 for male sex (21). All studies but one (20) have reported a higher frequency of baseline comorbidities compared with patients without AD (14, 18, 19, 21), an association confirmed by adjusted multivariate models with an estimated OR of 1.86 in patients with underlying hypertension (14), 2.61 in those with diabetes mellitus (14), 3.02 in those with kidney disease (14) and

Table I. Studies analysing SARS-CoV-2 infection in patients with AD in which the number of cases with SAD are detailed (32-40).

Author (reference)	Country	Patients with AD (n)	Patients with SAD (n)	Individual SAD (n)	Patients with SAD and COVID-19 (n)	Individual SAD with COVID-19 (n)
Benucci (32)*	Italy	295	26	SLE (8), GCA (12), IM (6)	2	GCA (1), IM (1)
Conticini (33)*	Italy	859	103	TA (2), Sarco (8), BD (5), SAPHO (1), SSc (54), AAV (8), IM (5), SLE (6), Sweet (1), GCA (11), Still (1)	1	GCA (1)
Emmi (34)	Italy	458	352	SLE (117), SSj (37), SSc (18), APS (17), GCA/TA (63), BD (41), EGPA/GPA/MPA (40), Cryo (3), HSP (2), FMF (15), Pericarditis (9), Uveitis (14), Retroperitoneal fibrosis (4), Sarco (4)	1	SSj (1)
Favalli (35)	Italy	955	31	SLE (13), SSc (3), SSj (2), BD (6), Sarco (1), Still (3), AIS (4)	1	Sarco (1)
Michaud (36)	CA	530	150	SLE (30), Other (120)	0	0
Quartuccio (37)	Italy	1051	131	AAV (74), SLE (38), Other CID (19)	0	0
Zen (38)	Italy	916	805	SLE (397), AAV (182), SSc (176), IM (50)	2	SLE (1), SSc (1)
Favalli (39)	Italy	123	123	SLE (397), SSc (43), CTD (9), SSj (10)	1	SSc (1)
Pablos (40)	Spain	4781	4781	SLE (2253), AI/IMID: RA, PsA, SpA, SLE, SSj, SSc, PMR-GCA and Others: AAV, BD, Sarco, IM (2528)	53	SLE (14), other SAD (39)
TOTAL		**9968**	**6502**		**61**	

SLE: systemic lupus erythematosus; GCA: giant cell arteritis; IM: inflammatory myopathies; TA: Takayasu arteritis; Sarco: sarcoidosis; BD: Behcet disease; SAPHO: synovitis, acne, pustulosis, hyperostosis, osteitis; SSc: systemic sclerosis; AAV: associated vasculitis; Sweet: Sweet's syndrome; Still: Still disease; SSj: Sjögren syndrome; APS: antiphospholipid syndrome; EGPA: eosinophilic granulomatosis with polyangiitis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; Cryo: cryoglobulinaemia; HSP: Henoch-Schönlein purpura; FMF: familial Mediterranean fever; AIS: autoinflammatory disease; CID: chronic inflammatory diseases; AI/IMID: autoimmune or immune-mediated disease; RA: rheumatoid arthritis; PsA: psoriatic arthritis; SpA: spondyloarthritis; PMR: polymyalgia rheumatica; SAD: systemic autoimmune disease.

Table II. Frequency of SARS-Cov-2 infection and probabilities of being tested and testing positive for SARS-Cov-2 infection in case-control studies comparing patients with and without AD (32, 40, 45-48, 99).

Frequency of SARS-CoV-2 infection (first author, reference)	Patients with AD (%)	Controls (%)	Study design	Results
Aries (45)	0.25%	0.28%	Comparison with general population (regional estimation)	No significant differences
Pablos (40)	0.76%	0.58%	Comparison with general population (regional estimation)	**Higher rate in AD patients**
Benucci (32)	1.4%	0.5%	Comparison with general population (regional estimation)	**Higher rate in AD patients**
Probability of being tested for SARS-Cov-2 infection	OR	95% CI	Study design	Results
Chadeau (46)	1.53	1.42-1.64	Risk factors for infection in population-based study	**Higher probability in AD patients**
Salvarani (99)	1.19	0.8-1.19	Comparison with general population (regional estimation)	No significant differences
Probability of testing positive for SARS-Cov-2 infection	OR	95% CI	Study design	Results
Chadeau (46)	0.83	0.71-0.98	Risk factors for infection in population-based study	**Lower probability in AD patients**
Vila-Corcoles (47)	0.49	0.07-3.61	Comparison with general population (regional estimation)	No significant differences
Benucci (32)	3.01	1.13-8.09	Comparison with general population (regional estimation)	**Higher probability in AD patients**
Pablos (40)	1.3	1.15-1.52	Comparison with general population (regional estimation)	**Higher probability in AD patients**
Zhong (48)	2.68	1.14-6.27	Familial exposure in AD patients and their relatives	**Higher probability in AD patients***

*NS when only PCR+ included.

2.48–8.93 in patients with chronic lung diseases (14, 21). With respect to underlying therapies, adjusted multivariate models confirmed a lower risk of hospitalisation in patients receiving only DMARDs (OR 0.46) (14), while those receiving glucocorticoids had a higher risk of hospitalisation due to COVID-19 (OR 2.05–5.0) (14, 21) (Fig. 1).

- ICU admission

Of 796 patients with AD infected by SARS-Cov-2 included in 10 studies (15, 16, 18, 23, 25-27, 29, 45, 49), 60 (7.5%) required ICU admission. When the rate is calculated only in hospitalised patients, 57 (9.8%) of 584 patients required ICU admission, with rates ranging from 0% to 48% (Suppl. Table S3). All studies but one reported a similar rate of ICU admission in patients with and without AD (16, 26, 45) (Suppl. Table S4). D'Silva *et al*. (27) in the US reported a higher frequency of ICU admission in AD patients (48% *vs*. 18% p=0.01, adjusted OR 3.11) (Suppl. Table S5), and this was the highest rate reported among all studies; the high rate of non-white patients included in this study may explain the significantly

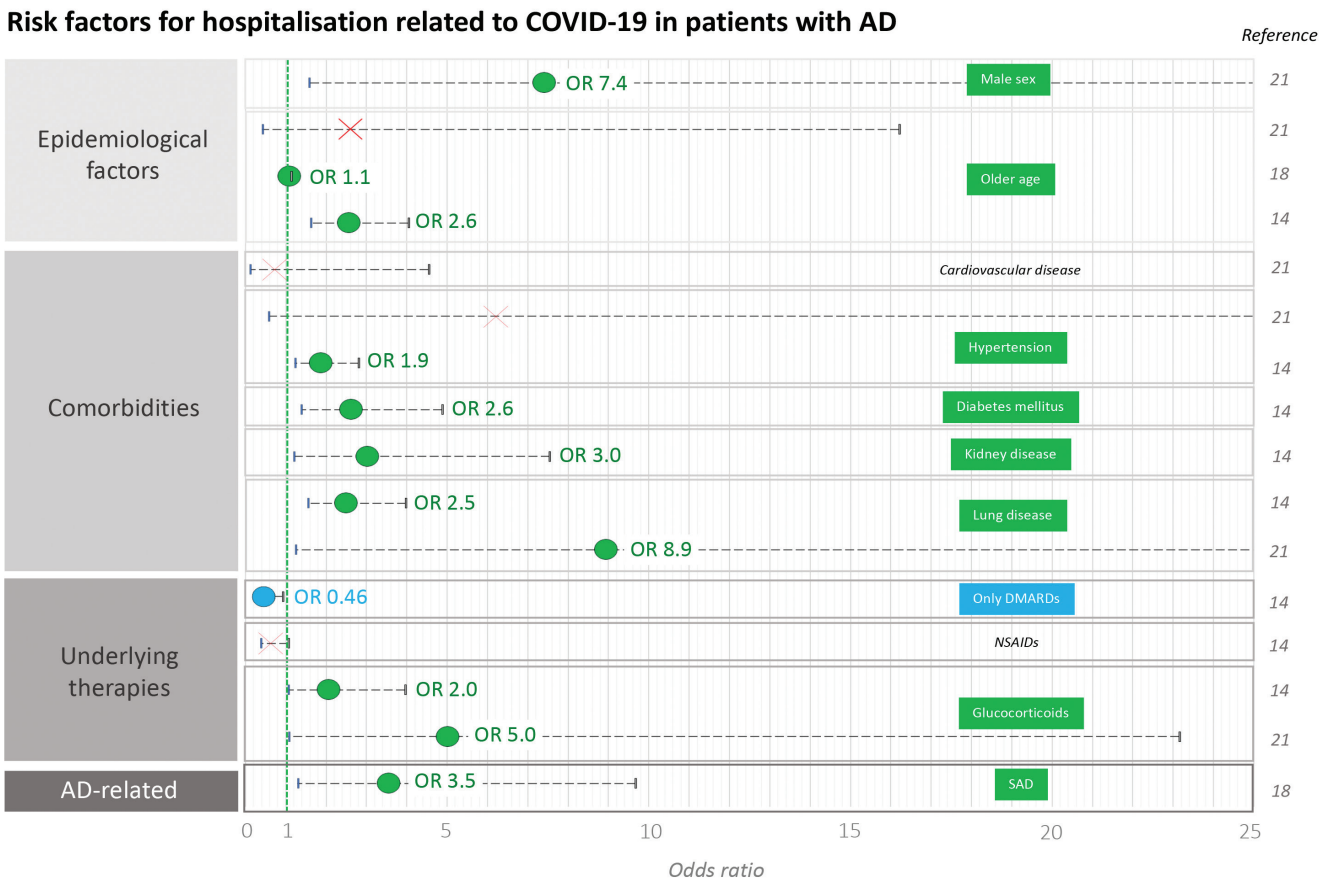

Fig. 1. Epidemiological features, comorbidities, autoimmune-related factors and underlying therapies that increase the risk of hospitalisation related to COVID-19 in patients with autoimmune diseases: estimated odds ratio (OR) and 95% confidence intervals in multivariate analysis (green box: risk factor; blue box: protective factor; X red mark: no statistical association)
DMARDs: disease-modifying anti-rheumatic drugs; NSAIDs: non steroidal anti-inflammatory drugs; SAD: systemic autoimmune diseases.

higher rate found in comparison with European studies. No studies have identified specific individual risk factors for ICU admission, since this is often included in a composite variable often reported as "poor outcomes" (together with the risk of mechanical ventilation and/or death).

- *Mortality*

The mortality rate among AD patients with COVID-19 is 12% (227 of the 1874 patients included in 17 studies died) (14–21,23–27,29,45,49) (Suppl. Table S3), with a wide range between countries, ranging from 0% in Germany to 15-16% in Italy and Spain and up to 27% in Turkey. For studies reporting specific information about patients with SAD, the specific mortality rate disease by disease is summarised in Supplementary Table S7.

Case-control studies have reported no significant differences in the survival rate of patients with and without AD (26, 40, 45) (Suppl. Table S3). In contrast, population-based studies have reported that people with underlying AD are at higher risk for COVID-19-related death. Siso *et al*. (40) found patients with AD had an adjusted OR of 2.82 for a poor outcome, while the OpenSAFELY study (10) found patients with underlying rheumatoid arthritis, SLE or psoriasis had a fully-adjusted OR of 1.19 for COVID-19-related death (those with other immunosuppressive conditions had a fully-adjusted OR of 2.21) (Suppl. Table S5).

Table III summarises the risk factors associated with poor outcomes in patients with AD included in five studies that analysed the risk of death (19, 25, 51) or a composite variable of poor outcomes (ICU admission, IT requirement and/or death) (15, 16). Figure 2 summarises the risk factors associated with poor outcomes identified in multivariate analysis. Epidemiological features such as male sex and older age were associated with poor outcomes, with estimated adjusted ORs of 4.8–6.2 for older age and 1.5–1.9 for male sex (16, 51). Adjusted multivariate models identified several baseline comorbidities associated with poor outcomes, including hypertension and/or cardiovascular disease (25, 51), dyslipidaemia (25) and chronic lung diseases (25, 51). In addition, patients with moderate/high disease activity (25) had a greater risk of poor outcomes in the multivariate adjusted models; one study found a higher risk in patients with SAD (16), while Strangfeld *et al*. (51) reported a lower risk in patients with SAD excluding those with SLE and vasculitis. With respect to active therapies at the time of COVID-19 diagnosis, adjusted multivariate models confirmed a higher risk of poor outcomes in patients receiving glucocorticoids, sulfasalazine, immunosuppressants and rituximab (15, 16, 51) (Fig. 3).

Table III. Studies evaluating baseline features associated with an increased risk of poor outcomes (ICU admission, IT requirement and/or death) in patients with AD and COVID-19. (15,16,19,25,51). In **bold**, statistically significant associations in multivariate analysis.

		First author (reference)	Univariate OR	95% CI	Multivariate OR	95% CI
Epidemiological	Male gender	Pablos (16)	2.34	1.55-3.53	**1.93**	**1.21-3.07**
		Strangfeld (51)	NA	NA	**1.46**	**1.11-1.91**
	Mean age	Pablos (16)	6.06	3.65-10.06	**4.83**	**2.78-8.37**
		Nuño (19)	1.6	1.20-2.01	NA	NA
		Strangfeld (>75yrs) (51)	NA	NA	**6.18**	**4.47-8.53**
Comorbidities	Hypertension	Sieiro (25)	NA	NA	**9**	**1.0-80.8**
		Pablos(16)	2.6	1.72-3.94	NA	NA
		Nuño (19)	12.17	2.58-57.38	NA	NA
		Starngfeld (HTA+CDV) (51)	NA	NA	**1.89**	**1.31-2.73**
	Diabetes	Sieiro (25)	NA	NA	**33**	**3.46-314.55**
		Pablos (16)	1.81	1.11-2.95	0.82	0.46-1.46
	Cardiovascular disease	Sieiro (25)	NA	NA	**6,18**	**1.10-34.7**
	Dyslipidaemia	Sieiro (25)	NA	NA	**12**	**1.33-108**
	Chronic lung disease	Sieiro (25)	NA	NA	**5.5**	**1.16-26**
		Pablos(16)	2.15	1.34-3.45	NA	NA
		Nuño (19)	5.36	1.60-17.94	NA	NA
		Strangfeld (51)	NA	NA	**1.68**	**1.26-2.25**
	Obesity	Pablos (16)	1.78	1.13-2.81	1.47	0.86-2.51
	Heart failure	Pablos (16)	3.49	2.21-5.51	1.57	0.93-2.66
SAD-related	Moderate/high activity of AD	Sieiro (25)	NA	NA	**41,4**	**4.23-405.23**
		Strangfeld (51)	NA	NA	**1.87**	**1.27-2.77**
	SAD	Pablos (16)	1.64	1.02-2.66	**1.82**	**1-3.3**
		Strangfeld (51)	NA	NA	**0.75**	**0.58-0.97**
Therapies	Hydroxychloroquine	Pablos (16)	2.26	1.35-3.79	NA	NA
	Sulfasalazine	Strangfeld (51)	NA	NA	**3.6**	**1.66-7.78**
	Glucocorticoids	Pablos (16)	2.2	1.36-3.54	1.1	0.6-2.01
		Scirè (15)	2.45	0.78-7.06	1.6	0.4-5.86
		Nuño (19)	5.7	1.63-19.92	NA	NA
		Strangfeld (51)	NA	NA	**1.69**	**1.18-2.41**
	No DMARD	Strangfeld (51)	NA	NA	**2.11**	**1.48-3.01**
	Immunosuppressants	Strangfeld (51)	NA	NA	**2.22**	**1.43-3.46**
	b/ts DMARDs only	Scirè (15)	0.29	0.09-0.87	0,5	0.13-1.81
		Pablos (16)	0.45	0.21-0.96	NA	NA
	Rituximab	Strangfeld (51)	NA	NA	**4.04**	**2.32-7.03**
	Antivirals	Pablos (16)	2,. 7	1.58-3.59	**2.05**	**1.30-3.23**

COVID-19 in individual systemic autoimmune diseases

Systemic lupus erythematosus

Several intrinsic features that characterise systemic lupus erythematosus (SLE) can drive a differentiated SARS-Cov-2 infection. On the one hand, most SLE patients are young women, an epidemiological profile associated with better outcomes. On the other hand, the high frequency of cardiovascular disease and renal involvement, together with the frequent use of glucocorticoids and B-cell depleting therapies, may be risk factors for a worse outcome. Of all SAD, SLE has the large number of reported patients with COVID-19, with 639 cases included in both disease-specific and general cohorts (Suppl.Table S8). A recent review found that 41/4307 (0.9%) patients with SLE had a PCR-confirmed diagnosis of COVID-19 (52), while a Spanish study by Pablos *et al*. (40) found the infection rate was lower (14/2253, 0.62%) and did not differ from that of the reference population.

Data on COVID-19 outcomes in SLE patients have been detailed in 26 studies (Suppl. Table S9) (18-21, 23-25, 29, 30, 38, 43, 51, 53-65): the rates for the main outcomes were 70.6% for pneumonia, 50.8% for hospital admission, 13.5% for ICU admission and 10% for mortality. Some studies have reported a high frequency of comorbidities in SLE patients with COVID-19 (66), but without including a control group of non-SLE COVID-19 patients. A recent study identified non-white ethnicity (adjusted OR=7.78), ≥1 comorbidities (OR=4.66) and BMI (OR=1.08 per increase in kg/m^2) as risk factors for hospitalisation in SLE patients with COVID-19 (55). Several studies have reported no influence of the underlying use of hydroxychloroquine on COVID-19 outcomes (67-69), while others found a correlation between the glucocorticoid dose and a positive PCR result (43) or a higher risk of hospitalisation (43); belimumab has also been reported to be associated

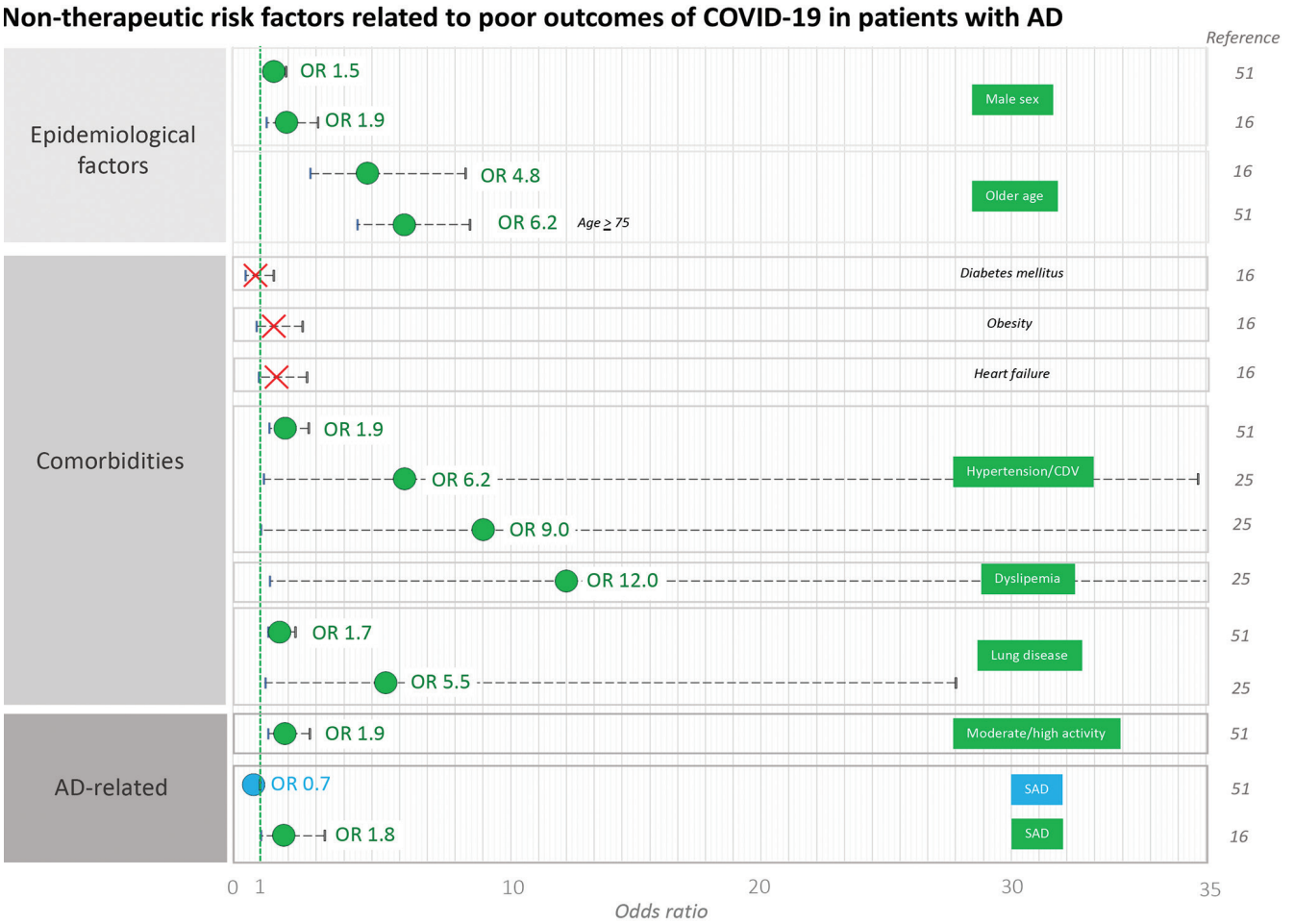

Fig. 2. Epidemiological features, comorbidities and autoimmune-related factors associated with poor outcomes of COVID-19 in patients with autoimmune diseases: estimated odds ratio (OR) and 95% confidence intervals in multivariate analysis (green box: risk factor; blue box: protective factor; X red mark: no statistical association)
CDV: cardiovascular disease; AD: autoimmune diseases; SAD: systemic autoimmune diseases.

a higher risk of hospitalisation (43), and a case series from Malaysia reported one patient receiving belimumab who required ICU admission (63).

COVID-19 has also been associated with SLE relapse in some patients. Kondo *et al*. (59) reported a severe exacerbation of underlying thrombocytopenia in an SLE patient, which may be reminiscent of reports of patients with underlying ITP who relapsed after SARS-CoV-2 infection (70, 71) (72). Mathian *et al*. (60) found no manifestations of lupus activity during the course of COVID-19 in a cohort of SLE patients, except for one patient who had tenosynovitis at the onset of SARS-CoV-2 infection.

Primary Sjögren syndrome

Primary Sjögren syndrome (SjS) has specific features that could favour an increased risk for severe COVID-19 (pulmonary autoimmune damage, use of immunosuppressive agents, high frequency of lymphoma). Until now, there are 118 reported patients with primary SjS and COVID-19 included in global series and case reports (Suppl. Table S8).

Two studies have estimated the rate of infection in primary SjS patients. We recently estimated a frequency of confirmed and probable COVID-19 of 0.62% (95%CI 0.44–0.80), although this should be treated with caution due to the significant risk of bias associated with the very different approaches used to diagnose and follow COVID-19 around the world (73). The other study is a Spanish population-based study that estimated the prevalence of PCR-confirmed COVID-19 in SjS, and found a prevalence of 1.85%, higher than that found in patients with other SAD and in the reference population (40). Analysis of the frequency of PCR+ patients from the Spanish centres included in our study (73) showed a similarly high prevalence of 2.3% (33/1438). The reasons why patients with primary SjS may have one of the highest rates of COVID-19 (at least in Spain) compared with other systemic and rheumatic autoimmune diseases are unknown.

Only one study has analysed COVID-19 outcomes in primary SjS patients (73). Of the 51 patients included, all but two presented with symptoms suggestive of COVID-19. The infection was managed at home in 26 (51%) cases and 25 (49%) required hospitalisation (five required ICU admission and four died). Patients with comorbidities were older (adjusted OR 1.05) and had a six-fold higher risk of hospital admission than those without comorbidities (adjusted OR 6.0). We

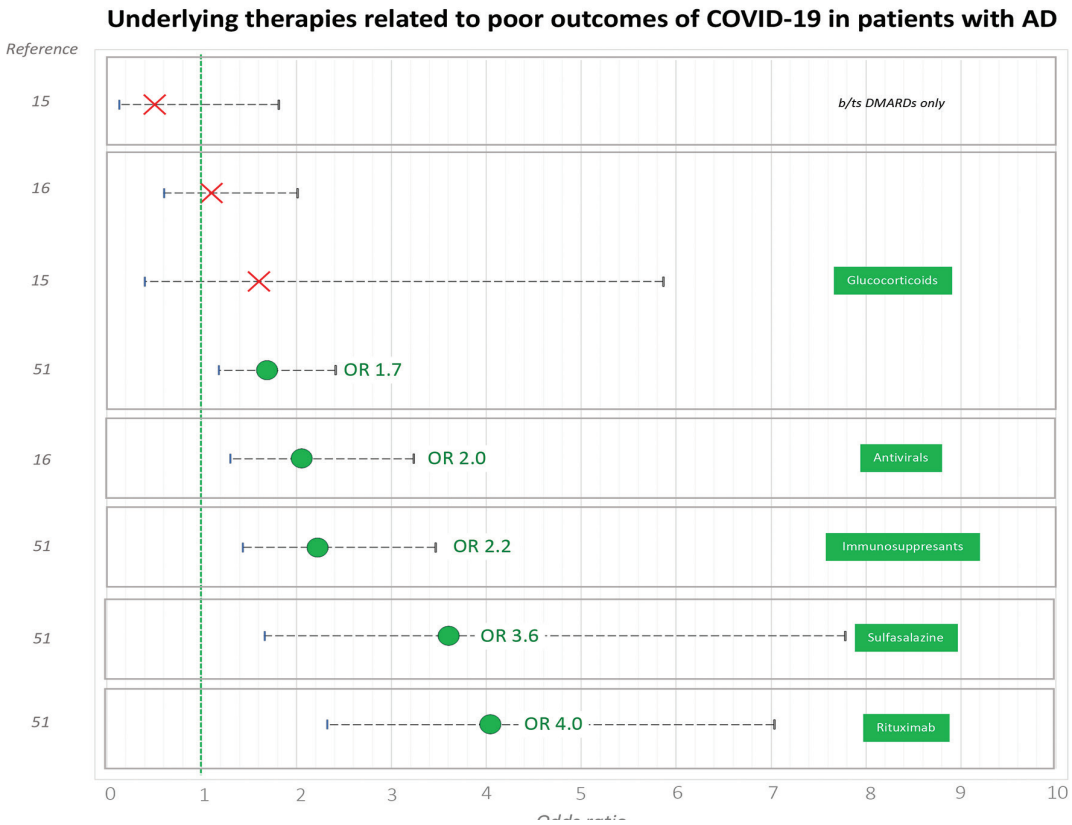

Fig. 3. Underlying therapies associated with poor outcomes of COVID-19 in patients with autoimmune diseases: estimated odds ratio (OR) and 95% confidence intervals in multivariate analysis (green box: risk factor; blue box: protective factor; X red mark: no statistical association)
b/ts DMARDs: biologic or targeted synthetic disease-modifying anti-rheumatic drugs.

found a non-significant influence of underlying immunosuppressive therapies on COVID-19 outcomes, probably related to the low frequency of the use of these therapies in SjS patients. There is only one additional report detailing the outcome of COVID-19 in one patient with overlapping SjS and polymyositis receiving maintenance treatment with methotrexate, prednisone and rituximab who was diagnosed with COVID-19 and required ICU admission for invasive ventilation (74).

Systemic sclerosis

Patients with systemic sclerosis (SSc) with baseline cardiopulmonary damage and COVID-19 could have an increased risk of poor outcomes (75). There are 48 reported cases of COVID-19 in SSc patients (Suppl. Table S8). The infection rate of COVID-19 in patients with SSc from seven Spanish centres was 1.14% (40), while an Italian study found only 1/168 (0.6%) patients was diagnosed with COVID-19 (76). Outcomes were detailed in six patients with SSc and COVID-19 and included hospitalisation in 83% of cases, ICU admission in 50% and death in 17% (35, 76-78). Most patients had no underlying lung involvement or pulmonary hypertension, and all but one were receiving biologic therapies (four with rituximab, one with tocilizumab); of the four receiving rituximab, the ICU was required in three and one died (a 32-year-old woman with SSc and pulmonary involvement) (35). In contrast, the patient receiving tocilizumab had a mild form of COVID-19 despite having insulin-dependent type 2 diabetes mellitus (78).

Systemic vasculitis

Data on COVID-19 in patients with systemic vasculitis are dispersed between several reports, and include 133 reported cases (Suppl. Table S8). In patients with large-vessel vasculitides, the estimated incidence of COVID-19 in patients with giant-cell arteritis (GCA) from seven Spanish centres was 1.45% (40), while in a single-centre Italian study, 2/95 (2.1%) patients with GCA and 2/67 (2.99%) with Takayasu arteritis were diagnosed with COVID-19 (79). The two GCA patients were older men treated only with corticosteroids who were hospitalised and recovered, and the two patients with Takayasu arteritis were young women with intense immunosuppression (anti-TNF) who did not require hospitalisation (79). There are three reported cases with detailed information on COVID-19 outcomes in patients with ANCA vasculitis, all of whom were receiving maintenance therapy with rituximab (of the two patients hospitalised, one required mechanical ventilation (80) (81) (82).

Sarcoidosis

We identified 62 reported patients with sarcoidosis and COVID-19 (Supplementary Table 8), but only three had information on outcomes available, including one patient with COVID-19 pneumonia superimposed on pulmonary sarcoid lesions who required hospitalisation (83), another with an underlying Löfgren syndrome who presented with pneumonia and pain and swelling in both ankles (84) and a third patient receiving intense immunosuppression (including anti-TNF) in whom the ICU was required and who had a good outcome after treatment with tocilizumab (85). With respect to underlying therapies, data from the International Registry (86) reported that 18 (44%) out of

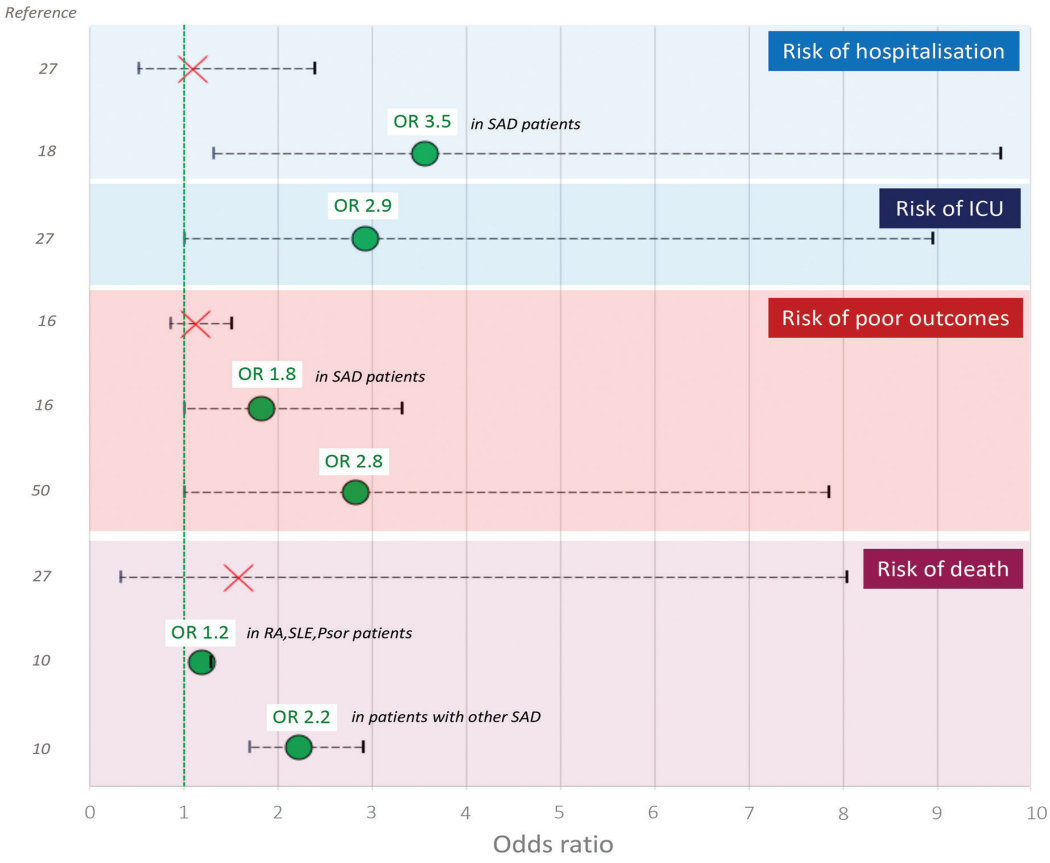

Fig. 4. Risk for poor outcomes of COVID-19 patients with autoimmune diseases in comparison with those without autoimmune diseases in large population-based studies: estimated odds ratio (OR) and 95% confidence intervals in multivariate analysis (X red mark: no statistical association)
ICU: intensive care unit; SAD: systemic autoimmune diseases; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; Psor: psoriasis.

41 patients with sarcoidosis included in the registry were receiving corticosteroids, and there were no significant differences in hospitalisation rates compared with those who were not.

Other diseases

There are 19 reported cases of COVID-19 in patients with Behçet disease (87,88) (79% required hospitalisation, 14% ICU admission and 7% died). Supplementary Table S8 shows patients with other SAD in whom COVID-19 was diagnosed.

Overview

Patients often ask whether they might have a greater risk of SARS-Cov-2 infection, considering the underlying SAD they have and/or the underlying therapies they receive. Most studies have no separate information on the risk of infection in SAD patients, and we have extrapolated the data from studies of patients with AD (which include a variable proportion of SAD patients). One meta-analysis and three case-control studies have reported a 1.3-3 times higher risk of SARS-Cov-2 infection in AD patients than in patients without AD (32, 40, 41, 48), one study reported no significant differences (47) and one reported a lower risk (46). Therefore, most studies support an increased risk of SARS-Cov-2 infection in patients with AD and SAD, although the high degree of heterogeneity between studies precludes solid confirmation of these results, and other unanalysed factors may influence the infection positivity rate. Only one study has evaluated the risk of infection according to the type of AD. Patients with SAD had a 1.32-fold higher prevalence of hospital PCR+ COVID-19 than the reference population (0.76% *vs.* 0.58%), especially patients with SAD other than SLE, whereas patients with inflammatory arthritis or SLE did not (40).

There is little information on the interpretation of SARS-Cov-2 tests in patients with SAD. Diagnostic tests may give false negative and false positive results (89), and RT-PCR may be negative at the initial presentation (90, 91). In SAD patients, there is a report of a false negative result in an 80-year-old patient diagnosed with GPA (receiving rituximab) who was admitted for pneumonia with swab PCR SARS-Cov-2 negative twice, in whom a further tracheal aspirate confirmed COVID-19 (92). There are also some worries about false positive results when COVID-19 serological tests are used in SAD patients. However, no studies have demonstrated a potential cross-reaction between circulating autoantibodies and anti-COVID-19 antibodies, although two patients with SAD were reported as having false positive serological results (93, 94), although a better explanation may be that these patients had an asymptomatic or pauci-symptomatic infection and that, at admission, PCR was becoming negative. The maximum sensitivity for IgM tests (75%) is reached at days 15–21 after symptom onset (95, 96), while the sensitivity of PCR in the same period is much greater (25–60%) (97) and, therefore, 15–50% of patients with positive IgM may have negative PCR results (as reported in the two above-mentioned cases).

Another frequent question raised by patients with SAD is whether they could have a worse outcome if infected by the virus. Studies focused on the outcomes

related to COVID-19 mainly included the need for hospitalisation, the requirement for intensive care, and survival as the three main parameters to be evaluated, but this can be measured using different methodological approaches. The first is comparing the ratio of these outcomes between patients with and without AD (case-control studies): all studies except one (27) reported no significant differences. In contrast, studies that analysed baseline risk factors in large population-based studies reported a 1.8–2.8 times higher risk of poor outcomes in patients with underlying AD, especially in those with SAD (10, 16, 50) (Fig. 4). Two additional studies (16, 18) have reported that the risk of hospitalisation/poor outcomes was 1.8–3.5 times higher in patients with SAD. Therefore, current data mostly point to an increased risk of poor outcomes in AD patients (especially in patients with SAD), although the heterogeneity of the studies does not allow robust conclusions.

The main studies in AD patients have reported a higher risk of hospitalisation/poor outcome in males, elderly patients, and patients with underlying comorbidities at the time of infection, especially in those with cardiovascular, pulmonary and renal chronic diseases. In patients with SAD, comorbidities may be more frequent than in the general population, mainly as a result of immune-mediated organ-specific damage (*e.g.* lupus nephritis, interstitial lung disease, vasculitis) or as a treatment complication (*e.g.* glucocorticoid-induced cardiovascular features). In addition, one study linked a moderate/high degree of SAD activity at COVID-19 diagnosis with a trend to lower survival (25). With respect to underlying treatments of patients with AD, several studies have shown a greater risk of hospitalisation in patients receiving corticosteroids (21, 98) while the risk was lower in those who were on DMARDs alone (14, 41). Akiyama *et al*. (41) reported that studies with a higher proportion of glucocorticoid use had a higher prevalence of COVID-19. Similar results were obtained with respect to the risk of a poor outcome of the infection, although the adjusted multivariate studies did not confirm the risk. Once again, these findings should be interpreted with caution because of the risk of bias in most studies.

With respect to the influence of underlying AD therapies in COVID-19 outcomes, several studies have analysed the potential benefit or harm of receiving these therapies at the time of diagnosis of infection. No study has confirmed that patients receiving hydroxychloroquine have a lower risk of infection or better outcomes compared with those who do not, while the use of glucocorticoids, sulfasalazine, immunosuppressants and rituximab was associated with poor outcomes (Fig. 3). In addition, some findings concerning the evolution of anecdotal cases under specific biological treatments merit comment. Some authors have studied the specific, long-lasting effects of B-cell depleting therapies, especially rituximab, on the impact of COVID-19 in SAD patients (80). Among the six reported patients with SAD and COVID-19 receiving rituximab (4 with SSc and 2 with ANCA-vasculitis), four required the ICU and one died, while in SLE patients, Gendebien *et al*. (43) reported an increased risk of hospitalisation in patients treated with belimumab, and Teh *et al*. (63) reported a patient receiving belimumab who required invasive ventilation. These isolated observations suggest that caution about the use of B-cell depleting agents in patients with COVID-19 is necessary until there is data on large patient cohorts. In contrast, the results reported in some patients with SAD under treatment with anti-cytokine agents show that one SSs patient receiving tocilizumab and two patients with Takayasu disease receiving anti-TNF treatment developed mild infections not requiring hospitalisation (78, 79).

Conclusions

The current evidence on the impact of COVID-19 in patients with SAD is limited and overwhelmingly based on subanalyses of studies in patients with AD, small case series and individual reports. Despite the limitations of the current evidence, most studies suggest that patients with SAD have an increased risk of a worse evolution of SARS-CoV-2 infection, including a greater risk of hospitalisation/requiring ICU admission, together with worse survival and, therefore, these patients should be considered as a high-risk group for COVID-19. However, not all the studies confirm this worse prognosis, and this is probably related to the great heterogeneity in study designs and in the population analysed (wide variety of diseases and their relative frequencies). In addition, various factors that modify the prognosis of COVID-19 differed widely across the different studies, mainly the epidemiological profile (age, sex, ethnicity), the frequency and type of associated comorbidities, and the underlying active therapies at the time of diagnosis of infection. Despite this heterogeneity, most studies identified an older age at diagnosis, male sex, chronic diseases affecting vital organs, treatment with corticosteroids or B-cell depleting agents, presenting moderate/high AD activity, and having an SAD as the main risk factors for a worse evolution of COVID-19 in patients with AD. In contrast, some studies identified the use of b/ts DMARDs, especially anti-cytokine therapies, as a protective factor. This suggests there is a differentiated risk profile for COVID-19 between patients with SAD and those with inflammatory arthritis and, therefore, providing separate results for the two groups of AD patients in future studies is recommended whenever possible, since some studies have reported that patients with SAD seem to have less favourable COVID-19 outcomes than those with inflammatory arthritis.

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Key messages

- Patients with systemic autoimmune diseases have an increased risk of a worse evolution of COVID-19
- The key factors that modify the COVID-19 prognosis include the epidemiological profile, comorbidities, and underlying therapies.
- Glucocorticoids, sulfasalazine, immunosuppressants and rituximab were associated with poor outcomes
- These patients should be considered as a high-risk group for severe COVID-19.

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