








# COVID-19 prognosis in systemic lupus erythematosus compared with rheumatoid arthritis and spondyloarthritis: results from the CONTROL-19 Study by the Italian Society for Rheumatology

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## ABSTRACT

**Introduction** Data concerning SARS-CoV-2 in patients affected by SLE are contradicting.

The aim of this study was to investigate disease-related differences in COVID-19 prognosis of patients affected by rheumatic diseases before vaccination; we tested the hypothesis that patients with SLE may have a different outcome compared with those with rheumatoid arthritis (RA) or spondyloarthritis (SPA).

**Methods** We analysed data from the national CONTROL-19 Database with a retrospective, observational design, including rheumatic patients affected by COVID-19. The principal outcome measure was hospitalisation with death or mechanical ventilation. Differences between SLE, RA and SPA were analysed by univariable and multivariable logistic regression models.

**Results** We included 103 patients with SLE (88.2% female, mean age 48.9 years, 50.4% active disease), 524 patients with RA (74.4% female, mean age 60.6 years, 59.7% active disease) and 486 patients with SPA (58.1% female, mean age 53.2 years, 58% active disease). Outcome prevalence was not different between patients with SLE and those with RA (SLE 24.5%, RA 25.6%), while patients with SPA showed a more favourable outcome compared with those with SLE (SPA 15.9%); data from the multivariable analysis confirmed this result.

In SLE, age >65 years (OR 17.3, CI 5.51 to 63.16,  $p<0.001$ ), hypertension (OR 6.2, CI 2.37 to 17.04,  $p<0.001$ ) and prednisone (PDN) use (OR 3.8, CI 1.43 to 11.39,  $p=0.01$ ) were associated with severe outcomes, whereas hydroxychloroquine use was found to be protective (OR 0.3, CI 0.14 to 0.91,  $p=0.03$ ).

**Conclusion** Our data suggest that patients with SLE and RA do not show a different COVID-19 outcome, while patients with SPA have a more favourable disease course compared with those with SLE. Risk of hospitalisation with ventilation or death was associated with age >65 years, hypertension and PDN use in patients with SLE.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ COVID-19 expression in rheumatic diseases has been largely studied in the last 3 years. Some studies reported an increased risk of severe COVID-19 in these patients, while others did not confirm these data. Concerning patients with SLE, data on COVID-19 incidence and prognosis come mainly from case series, reports, observational and retrospective studies, and evidence is controversial. Moreover, little has been investigated about the comparison between SLE and other rheumatic diseases concerning COVID-19 outcome.

## WHAT THIS STUDY ADDS

⇒ We analysed the national surveillance study's data promoted by the Italian Society for Rheumatology (CONTROL-19 Database) including patients with rheumatic diseases and COVID-19. The principal outcome measure was hospitalisation with death or mechanical ventilation. We included 103 patients with SLE, 524 patients with rheumatoid arthritis (RA) and 486 patients with spondyloarthritis (SPA). According to our results, outcome prevalence was not different between patients with SLE and those with RA, while patients with SPA showed a more favourable outcome compared with those with SLE. Moreover, we analysed the relationship between demographic and clinical features and risk of worse outcomes of patients with SLE. This is one of the first studies to our knowledge to address COVID-19 outcomes in patients with SLE compared with other rheumatic diseases. The availability of new data on the outcome of this infection in patients affected by autoimmune diseases, particularly SLE, is important to improve its management in these conditions.



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**HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY**

⇒ Our study gives more insights into COVID-19 outcomes in SLE and other rheumatic diseases, evidencing in addition demographic and clinical features correlated with a worse prognosis of the infection. This can help physicians to manage such infection in rheumatological patients and to stratify them according to risk factors of a more severe COVID-19 outcome. Our findings are in line with some previous literature data, but further studies are necessary to enrich knowledge on this issue.

**INTRODUCTION**

The COVID-19 pandemic spread all over the world at the end of March 2020.<sup>1-4</sup>

The clinical course of the disease, in the early phase, was extremely variable, from asymptomatic or mild forms to severe and life-threatening ones, characterised by pneumonia, acute respiratory distress syndrome (ARDS) and/or multiorgan failure, requiring critical care.<sup>5,6</sup>

Patients' features can partly explain this huge clinical heterogeneity; particularly, in the general population, more severe cases and high mortality rates were described in elderly patients and in those affected by comorbidities such as obesity, cardiovascular or respiratory diseases, and diabetes.<sup>7</sup>

An underlying autoimmune inflammatory rheumatic disease (AIIRD) was described, since the start of the pandemic, as a factor that could increase both the risk of COVID-19 and the probability of a worse outcome of the disease, because of the well-known susceptibility to infections of these patients due to autoimmune dysregulation, presence of organ damage and concomitant use of immunosuppressive drugs.<sup>8</sup>

Rheumatological drugs seemed to increase the risk of infections. On the other side, some of these medications were initially used for the prevention and/or treatment of COVID-19 and its consequences, such as cytokine storm and hyperinflammation.<sup>9,10</sup>

Particularly, patients with SLE have a general higher risk of infection because of an altered intrinsic innate and adaptive immune response, the potential presence of organ damage, and chronic use of steroids and immunosuppressants. Therefore, they are considered a vulnerable population for coronavirus infection and COVID-19; however, some aspects of this disease, such as female predominance, could be protective against this viral infection.<sup>11-14</sup>

Hyperactive immunity, a typical feature of SLE, has been linked to cytokine storm and tissue damage in patients with COVID-19. Moreover, both the connective tissue and the viral disease share some pathogenetic and clinical aspects such as cytopenia, arthralgia, multiorgan complications of interstitial pneumonia, myocarditis and haemophagocytic lymphohistiocytosis.<sup>11</sup> Data concerning both the incidence and the prognosis of COVID-19 in patients affected by SLE emerged during the last 2 years, but they appear not uniform.<sup>10,15-23</sup>

One of the reasons for this scarce evidence is represented by the relatively small number of patients affected by SLE that limits sample size and the research in this field.

Italy was suddenly seriously affected by COVID-19; therefore, the Italian Society for Rheumatology (SIR) timely launched the CONTROL-19 Database, a retrospective, anonymised data collection registry to monitor this infection in AIIRDs, which was part of the COVID-19 Global Rheumatology Alliance Registry.<sup>24,25</sup>

Results from CONTROL-19 reporting incidence and clinical manifestations of COVID-19 infection and mortality data among rheumatic patients have been published.<sup>26</sup>

The aim of this study was to investigate disease-related differences in COVID-19 prognosis of patients with AIIRD, analysing data of the CONTROL-19 registry, before SARS-CoV-2 vaccination. We particularly tested the hypothesis that patients affected by SLE may have a different outcome from patients with rheumatoid arthritis (RA) or spondyloarthritis (SPA).

**MATERIALS AND METHODS**

We analysed data from the CONTROL-19 registry, a national, retrospective, multicentre, non-profit design that included patients affected by AIIRDs and COVID-19 infection.

Anonymised data were collected by rheumatologists based on patients' medical records and manually entered in an online database on the REDCap platform and hosted on SIR servers; collection started on 26 March 2020 and ended on 1 March 2021.

The CONTROL-19 inclusion criteria were as follows: a previous clinical diagnosis of any AIIRDs, an established molecular diagnosis for SARS-CoV-2 infection (real-time PCR) and the availability of the COVID-19 outcome data.

Patients were informed to contact their rheumatologists in case of COVID-19 test positivity, considering that the Italian protocol at that time was to test also in case of close contacts with an infected subject.

Patients' demographic and clinical data, both related to the rheumatic disease and COVID-19 infection, were collected.

Age, sex, smoking habits, presence of comorbidities, such as obesity (defined as a body mass index >30), pulmonary disease, including chronic obstructive pulmonary disease (COPD), interstitial disease or others, diabetes and hypertension, were assessed.

Rheumatic disease activity (remission, low, moderate or high) was defined according to the clinician's judgement.

Data concerning ongoing antirheumatic treatment prior to COVID-19 diagnosis were also reported: hydroxychloroquine (HCQ), prednisone (PDN), conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (methotrexate, sulfasalazine, leflunomide, ciclosporin), immunosuppressants (azathioprine, cyclophosphamide, mycophenolate mofetil), biological

**Table 1** Demographic and clinical characteristics of patients with SLE, RA and SPA

	SLE (N=103)	RA (N=524)	P value SLE vs RA	SPA (N=486)	P value SLE vs SPA
Age, mean (SD)	48.9 (16.9)	60.6 (13.1)	<b>&lt;0.001</b>	53.2 (14.4)	<b>0.004</b>
Sex—female, n (%)	90 (88.2)	389 (74.4)	<b>&lt;0.001</b>	282 (58.1)	<b>&lt;0.001</b>
Smoking habit, n (%)	10 (9.9)	52 (10.4)	0.15	59 (12.6)	<b>0.087</b>
Comorbidities					
Obesity (BMI >30), n (%)	8 (8)	73 (14.5)	<b>0.107</b>	77 (16.4)	<b>0.031</b>
Hypertension (%)	22 (21.6)	204 (39.8)	<b>&lt;0.001</b>	172 (35.8)	<b>0.005</b>
CVD, n (%)	17 (16.7)	89 (17.2)	1	51 (10.6)	0.091
Diabetes, n (%)	4 (3.9)	60 (11.7)	<b>0.02</b>	50 (10.3)	<b>0.039</b>
Pulmonary disease (COPD), n (%)	1 (1)	31 (6)	<b>0.046</b>	20 (4.2)	0.149
Pulmonary disease (interstitial), n (%)	2 (2)	20 (3.9)	0.557	2 (0.4)	<b>0.141</b>
Pulmonary disease (other), n (%)	6 (5.9)	48 (9.4)	0.338	27 (5.7)	1
Disease activity			0.336		0.321
Remission, n (%)	50 (49)	205 (39.6)	–	200 (41.5)	–
Low, n (%)	42 (41.2)	238 (45.9)	–	207 (42.9)	–
Moderate, n (%)	9 (8.8)	66 (12.7)	–	70 (14.5)	–
High, n (%)	1 (1)	9 (1.7)	–	5 (1)	–
Antirheumatic drugs prior to COVID-19 diagnosis					
HCQ, n (%)	71 (69.6)	112 (21.4)	<b>&lt;0.001</b>	10 (2.1)	<b>&lt;0.001</b>
PDN, n (%)	54 (52.9)	233 (44.6)	0.148	86 (17.7)	<b>&lt;0.001</b>
csDMARDs, n (%)	7 (6.9)	309 (59.1)	<b>&lt;0.001</b>	194 (40)	<b>&lt;0.001</b>
Immunosuppressant, n (%)	40 (39.2)	5 (1)	<b>&lt;0.001</b>	4 (0.8)	<b>&lt;0.001</b>
b/tsDMARDs, n (%)	21 (20.3)	263 (50.1)	<b>&lt;0.001</b>	294 (60.4)	<b>&lt;0.001</b>

The values in bold are statistically significant.

BMI, body mass index; b/tsDMARDs, biological/targeted synthetic disease-modifying antirheumatic drugs; COPD, chronic obstructive pulmonary disease; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; CVD, cardiovascular disease; HCQ, hydroxychloroquine; PDN, prednisone; RA, rheumatoid arthritis; SPA, spondyloarthritis.

DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs).

Evaluated COVID-19 clinical features were: fever, dyspnoea, myalgia, chest pain, abdominal pain, joint pain, asthenia/fatigue, nasal congestion, irritability, diarrhoea, cough, nausea/vomiting, sore throat, headache, anosmia, dysgeusia, conjunctivitis, tachypnoea, pneumonia, serious acute respiratory failure, ARDS, sepsis, secondary infection and macrophage activation syndrome (table 1).

The primary study outcome was defined as hospitalisation with death or mechanical ventilation (severe) versus hospitalisation (either yes or no) without both these conditions (not severe).

The secondary objective was to evaluate the relationship between patients' clinical variables and the final COVID-19 outcome.

### Patient and public involvement

Patients were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

### Statistical analysis

Categorical and continuous variables were described in terms of frequency and percentage or mean and SD as appropriate.

To evaluate the differences between SLE, RA and SPA, categorical variables were analysed using either the Pearson's  $\chi^2$  test or the Fisher's exact test, while quantitative variables were examined using Mann-Whitney test or the Student's t-test.

The association between clinical and treatment variables with clinical outcome was assessed by univariable logistic regression models; age was considered as a dichotomous variable using 65 years as a cut-off, according to previous literature data reporting a worse outcome in this population.

Either crude or adjusted multivariable logistic regression for prespecified confounders, such as age, sex, comorbidities and disease activity, was employed to model the groups' prognoses and test differences; results are presented as ORs and 95% CIs.

**Table 2** Results from univariable analysis of the study outcome in patients with SLE, RA and SPA according to demographic and clinical data

	Outcome prevalence N (%)			SLE OR (95% CI)			Outcome prevalence N (%)			RA OR (95% CI)			Outcome prevalence N (%)			SPA OR (95% CI)			P value		
	prevalence N (%)	SLE OR (95% CI)	P value	prevalence N (%)	RA OR (95% CI)	P value	prevalence N (%)	RA OR (95% CI)	P value	prevalence N (%)	SPA OR (95% CI)	P value	prevalence N (%)	SPA OR (95% CI)	P value						
Sex—female	22 (24.4)	Ref	Ref	73 (19.2)	Ref	Ref	29 (10.5)	Ref	Ref	2.6 (1.59 to 4.39)	<0.001	Ref	Ref	<0.001							
Sex—male	3 (25)	1.03 (0.21 to 3.81)	0.966	58 (44.3)	3.3 (2.18 to 5.15)	<0.001	47 (23.5)	3.3 (2.18 to 5.15)	<0.001	2.6 (1.59 to 4.39)	<0.001	Ref	Ref	<0.001							
Age <65 years	11 (13.9)	Ref	Ref	51 (16.8)	Ref	Ref	41 (11.2)	Ref	Ref	Ref	Ref	Ref	Ref	Ref							
Age >65 years	14 (73.7)	17.3 (5.51 to 63.16)	<0.001	80 (38.5)	3.1 (2.05 to 4.67)	<0.001	35 (34)	3.1 (2.05 to 4.67)	<0.001	4.1 (2.41 to 6.88)	<0.001	Ref	Ref	<0.001							
Obesity (BMI >30)	3 (37.5)	2.0 (0.39 to 8.98)	0.359	30 (41)	1.6 (0.94 to 2.83)	0.076	18 (23.3)	1.6 (0.94 to 2.83)	0.076	1.3 (0.70 to 2.46)	0.361	Ref	Ref	0.361							
Hypertension (yes)	15 (50)	6.2 (2.37 to 17.04)	<0.001	85 (37.4)	3.2 (2.1 to 4.87)	<0.001	47 (25.3)	3.2 (2.1 to 4.87)	<0.001	3 (1.82 to 5.03)	<0.001	Ref	Ref	<0.001							
Pulmonary disease (yes)	6 (66.7)	8.1 (1.95 to 41.45)	0.006	36 (48)	3.4 (2.04 to 5.69)	<0.001	18 (41.9)	3.4 (2.04 to 5.69)	<0.001	4.9 (2.48 to 9.56)	<0.001	Ref	Ref	<0.001							
Diabetes (yes)	2 (50)	3.3 (0.37 to 28.43)	0.25	25 (43.1)	2.5 (1.42 to 4.42)	0.001	17 (34.7)	2.5 (1.42 to 4.42)	0.001	3.3 (1.7 to 6.28)	<0.001	Ref	Ref	<0.001							
Remission	10 (20)	Ref	Ref	29 (14.4)	Ref	Ref	32 (16.3)	Ref	Ref	Ref	Ref	Ref	Ref	Ref							
Low/moderate/severe disease activity	15 (28.8)	1.6 (0.65 to 4.16)	0.301	99 (32.2)	2.8 (1.8 to 4.53)	<0.001	43 (15.5)	2.8 (1.8 to 4.53)	<0.001	0.9 (0.57 to 1.55)	0.801	Ref	Ref	0.801							
No DMARD, no PDN	3 (12)	Ref	Ref	9 (25)	Ref	Ref	6 (10.5)	Ref	Ref	Ref	Ref	Ref	Ref	Ref							
b/tsDMARD only	2 (16.7)	1.5 (0.17 to 10.25)	0.699	20 (15)	0.5 (0.22 to 1.34)	0.164	18 (8.8)	0.5 (0.22 to 1.34)	0.164	0.8 (0.32 to 2.35)	0.686	Ref	Ref	0.686							
csDMARD only	11 (28.9)	3 (0.81 to 14.43)	0.124	69 (38.1)	1.8 (0.84 to 4.37)	0.138	29 (25.7)	1.8 (0.84 to 4.37)	0.138	2.9 (1.21 to 8.26)	0.026	Ref	Ref	0.026							
b/tsDMARD+csDMARD	1 (11.1)	0.9 (0.04 to 8.43)	0.943	20 (16)	0.5 (0.23 to 1.44)	0.219	21 (25.3)	0.5 (0.23 to 1.44)	0.219	2.9 (1.13 to 8.33)	0.034	Ref	Ref	0.034							
PDN only	8 (44.4)	5.9 (1.38 to 31.42)	0.023	13 (35.1)	1.6 (0.59 to 4.58)	0.347	2 (10.5)	1.6 (0.59 to 4.58)	0.347	1 (0.13 to 4.83)	0.46	Ref	Ref	0.46							
PDN (yes)	19 (35.2)	3.8 (1.43 to 11.39)	0.01	83 (36.2)	2.7 (1.85 to 4.22)	<0.001	19 (22.4)	2.7 (1.85 to 4.22)	<0.001	1.7 (0.92 to 2.98)	0.077	Ref	Ref	0.077							
HCCQ (yes)	13 (18.3)	0.35 (0.14 to 0.91)	0.031	28 (25)	1 (0.58 to 1.54)	0.872	0 (0)	1 (0.58 to 1.54)	0.872	--	--	Ref	Ref	--							

The values in bold are statistically significant.

BMI, body mass index; b/tsDMARD, biological/targeted synthetic DMARD; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; HCCQ, hydroxychloroquine; PDN, prednisone; RA, rheumatoid arthritis; SPA, spondyloarthritis.

**Table 3** Results from multivariable regression model adjusted for the selected covariates (age >65 years, male sex, pulmonary disease, disease activity)

	OR	95% CI	P value
RA vs SLE	0.591	0.344 to 1.03	0.061
SPA vs SLE	0.377	0.214 to 0.677	<b>0.001</b>
Age >65 years	3.353	2.398 to 4.703	<b>&lt;0.001</b>
Sex—male	2.313	1.638 to 3.268	<b>&lt;0.001</b>
Pulmonary disease	2.797	1.836 to 4.249	<b>&lt;0.001</b>
Low/moderate/severe disease activity	1.83	1.299 to 2.601	<b>0.001</b>

The values in bold are statistically significant.

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SPA, spondyloarthritis.

In the multivariable regression model, disease type was considered as a categorical variable.

All data were processed and analysed with the statistical analysis software R V.4.0 (Foundation for Statistical Computing, Vienna, Austria).

In order to have a numerically more treatable outcome and to make all the analyses clearer, the final outcome was dichotomised into two classes, as previously described.

With the aim of reducing the overfitting problem, only four variables were included in the final multivariable model, chosen among the most clinically relevant of the statistically significant at the univariate step. We tried to balance the trade-off between overfitting and residual confounding given the distribution of the outcome in the SLE cohort by referring to the suggested 5–10 rule-of-thumb factor.

## RESULTS

### Demographic and clinical characteristics of the study population

We included 103 patients with SLE, 524 patients with RA and 486 patients with SPA; [table 1](#) shows patients' demographic and clinical characteristics.

The mean age of patients with SLE was significantly lower than the age of patients with RA and SPA. Patients with SLE presented with a lower frequency of obesity compared with the SPA group and they had a significant lower rate of arterial hypertension and diabetes compared with those with RA and SPA. With regard to pulmonary diseases, the RA group had a higher proportion of patients with COPD compared with those with SLE.

Concerning rheumatic disease, active disease was reported in 50.4% of patients with SLE, 59.7% of patients with RA and 58% of patients with SPA with no significant difference between the three groups.

In terms of ongoing antirheumatic treatments, PDN therapy was found to be prevalent in patients with SLE and RA compared with those with SPA. Patients with SLE were mostly under HCQ and/or immunosuppressants, while patients with RA and SPA were using csDMARDs and b/tsDMARDs more frequently.

Conversely, among the different biological therapies, rituximab use was comparable between SLE and RA groups (SLE 2.9%, RA 2.3%).

Finally, concerning COVID-19 clinical manifestations, patients with RA and SPA had a higher prevalence of joint pain compared with the SLE group (SLE 26.7% vs RA 42.7%,  $p=0.004$ ; vs SPA 48.8%,  $p<0.001$ ), with patients with SPA showing higher frequency of chest pain (SLE 13% vs SPA 22.5%,  $p=0.04$ ), myalgia (SLE 34.7% vs SPA 53.6%,  $p=0.001$ ) and anosmia (SLE 33% vs SPA 45%,  $p=0.04$ ), while no significant differences in prevalence of other COVID-19 clinical manifestations between the three groups were detected.

### COVID-19 study outcome in SLE, RA and SPA and its relationship with comorbidities, disease activity and antirheumatic treatment

Outcome prevalence was not different between patients with SLE (25 cases, 24.5%) and RA (131 cases, 25.6%) (OR 1.06, CI 0.65 to 1.76,  $p=0.82$ ), while patients with SPA (76 cases, 15.9%) showed a more favourable outcome compared with those with SLE (OR 0.58, CI 0.35 to 0.99,  $p=0.04$ ).

Results from the univariable analysis of the study outcome in patients with SLE evidenced a higher rate of hospitalisation with death or ventilation (severe outcome) in patients aged >65 years, with hypertension and on PDN therapy; on the other hand, a lower prevalence was detected among patients under HCQ ([table 2](#)).

The univariable analysis of RA data showed a worse outcome in males, elderly patients (age >65 years), patients with active disease, hypertension, pulmonary disease and diabetes, and those with ongoing PDN treatment.

The univariable analysis of SPA data showed a worse outcome in males, elderly patients (age >65 years), and patients with hypertension, pulmonary disease and diabetes ([table 2](#)).

The most clinically relevant and statistically significant variables were included in a multivariable regression model, including four covariates, to test if there were differences in the prognosis of the three groups, adjusting for potential confounding factors: age >65

years, male sex, disease activity and pulmonary disease (table 3).

Results confirmed that SLE was an independent risk factor for a worse outcome compared with SPA, while no statistically significant difference in COVID-19 prognosis emerged between SLE and RA.

Age >65 years, male sex, disease activity and pulmonary disease confirmed to be independent risk factors for hospitalisation with death or ventilation (table 3).

## DISCUSSION

In the present study, we examined disease-related differences concerning COVID-19 prognosis of patients affected by SLE, RA and SPA; particularly, we investigated if patients with SLE may have a different outcome compared with the other groups. In addition, we evaluated correlations between COVID-19 outcome and demographic and clinical aspects of the three cohorts.

Patients with SLE presented with typical COVID-19 manifestations compared with the general population and those with other rheumatic diseases, in line with literature data.<sup>15–23</sup>

According to the COVID-19 outcome, patients with SLE showed a higher rate of hospitalisation with death or mechanical ventilation compared with patients with SPA, while no significant differences were evidenced between patients with SLE and RA.

Factors associated with higher risk of severe outcomes in SLE were older age, hypertension and glucocorticoid (GC) therapy; on the other hand, a better outcome was detected among patients under HCQ. Similarly to RA, a worse outcome was observed in males, elderly patients, patients with active disease, hypertension, pulmonary disease and diabetes, and those with ongoing GC treatment. Finally, male sex, older age, hypertension, pulmonary disease and diabetes were associated with severe outcomes in SPA.

Age >65 years, male sex, disease activity and pulmonary disease were confirmed to be independent risk factors for a severe outcome in rheumatic patients.

There are not many studies examining COVID-19 manifestations in SLE, neither comparing, particularly, COVID-19 outcomes with other autoimmune/inflammatory rheumatic diseases. In a preliminary paper published by Scirè *et al.*,<sup>27</sup> based on first data from the CONTROL-19 registry including 232 patients with AIIRD, clinical COVID-19 presentation was typical, the overall outcome was severe and males presented a worse prognosis, while immunomodulatory treatments were not associated with a more severe infection.

Most of literature data on COVID-19 in patients with SLE come mainly from case series, reports, observational and retrospective studies.<sup>15–23 28–30</sup>

Previous studies reported that the impact of COVID-19 on patients with SLE was low and not different from the general population; on the other side, some authors

described a worse outcome and systemic GC therapy was mainly identified as a risk factor for hospitalisation.<sup>30–34</sup>

One of the first articles on this issue was published by Mathian *et al.*<sup>16</sup> in June 2020. It described the clinical course of COVID-19 infection in 17 patients under long-term HCQ treatment. Subsequently, an observational study on the impact of COVID-19 and SLE was conducted by Ramirez *et al.*,<sup>19</sup> based on a web survey that was administered to patients from three Italian referral centres during 2020.

Fourteen cases of COVID-19 among 417 patients with SLE were reported with a prevalence of 3.4%. COVID-19 clinical manifestations were typical and heterogeneous; one hospitalisation was reported and a moderate increase in morbidity among patients with SLE was described compared with the general population.<sup>19</sup>

One year later, a web-based survey was conducted by the same authors collecting information from the entire year 2020. A total of 334 patients responded to the survey; 28 reported a diagnosis of COVID-19. Older age and contact with COVID-19 cases within the family setting emerged as the major risk factors to develop the infection, together with unstable disease and treatment escalation.<sup>35</sup>

Another paper was published in 2020 by Fernandez-Ruiz *et al.*, describing data from different sources (web-based questionnaire, medical records and hospital registries). They reported the outcome of 41 patients with SLE with a confirmed COVID-19 diagnosis and 42 suspected cases; among the 41 patients with SLE with confirmed infection, 24 required hospitalisation. No SLE-specific risk factors were correlated with the higher rate of hospitalisation. Moreover, non-white race, presence of one or more comorbidities, such as asthma, COPD, congestive heart failure, current active malignancy, diabetes mellitus not controlled with current medications and hypertension, organ transplantation, pregnancy and body mass index were identified as independent predictors of hospitalisation, as observed in the general population and in line with literature data on patients with SLE.<sup>21</sup> The relationship between comorbidities and more severe outcomes in patients with SLE and other rheumatic diseases was confirmed by our results.

A systematic review and pooled analysis of studies addressing SLE and COVID-19 was then published by Sakthiswary *et al.*<sup>36</sup> The authors aimed mainly to determine the predictors of severe infection in patients with lupus, comparing mild to moderate cases with severe to critical ones. Extracted data showed no significant differences in median age or disease duration among the different clinical presentations of COVID-19. Moreover, only lupus nephritis resulted to be associated with severe to critical clinical manifestations. There was a correlation, but not statistically significant, between PDN and worse outcome.<sup>37</sup>

CONTROL-19 was part of the COVID-19 Global Rheumatology Alliance Registry, including 600 patients from 40 countries, with 85 patients affected by SLE. The majority of patients with AIIRD recovered from COVID-19; the

worse outcome was presented by patients with older age, affected by other comorbidities or those using higher doses of GCs. Use of antimalarials or DMARDs confirmed no correlation with higher rate of hospitalisation.<sup>24</sup>

Ugarte-Gil *et al* published more consistent data focusing on features associated with poor COVID-19 outcomes in individuals with SLE, based on data from the COVID-19 Global Rheumatology Alliance. A total of 1606 people with SLE and COVID-19 reported in the registry from March 2020 to June 2021 were included. The ordinal outcomes were defined as: (1) not hospitalised, (2) hospitalised with no oxygenation, (3) hospitalised with any ventilation or oxygenation and (4) death. In the multivariable model, older age, male sex, comorbidities such as kidney disease and cardiovascular disease/hypertension and moderate/high SLE disease activity were associated with a more severe outcome. Particularly, PDN use, even at lower doses, was found to be related to a poorer prognosis. Mycophenolate, rituximab and cyclophosphamide were associated with a more severe disease course compared with HCQ; outcomes were more favourable with methotrexate and belimumab.<sup>38</sup>

These results were confirmed by a retrospective study published in 2022, comparing data on COVID-19 outcomes of patients with SLE with that of the general population prior to vaccination. A significant worse outcome was evidenced among patients with SLE compared with the general population. Major risk factors linked to a more severe infection were disease activity and GC use, together with use of mycophenolate and tacrolimus.<sup>28</sup>

Another study conducted by Cordtz *et al* aimed to assess the impact of SLE disease on the incidence of hospitalisation, in case of COVID-19 infection, compared with the general population; secondarily, it investigated the potential association between treatment with HCQ or GCs and the risk of being hospitalised in patients with SLE. It was based on the nationwide register in Denmark. It was found that there was an approximately threefold increased incidence of hospitalisation for patients with SLE with COVID-19 compared with age-matched and sex-matched controls from the general population. There was no obvious impact on the risk of hospitalisation associated with GC nor HCQ treatment in this cohort, but authors concluded that the number of hospital admissions was too low to draw any definite conclusion, encouraging further studies.<sup>29</sup>

In conclusion, different studies concerning population with SLE showed that chronic use of GC was linked to a higher risk of hospitalisation and worse outcome,<sup>24 27 38</sup> while contrasting results emerged regarding immunosuppressive treatment, particularly cyclophosphamide and mycophenolate. Similar results were described regarding all rheumatological diseases.<sup>24 39 40</sup> The impact of immunosuppressive treatment could explain our results and the difference between COVID-19 outcomes in SLE and RA compared with SPA, considering the larger use of GCs in the first two groups and the possible need to choose

more significant immunosuppressive therapies in such patients.

On the contrary, the role of HCQ was widely discussed since it was considered to be protective in the first phases of the pandemic, but subsequent studies have definitely proved that its use is not linked to COVID-19 prognosis.<sup>21 22 31 39–42</sup>

These pieces of evidence are consistent with our results and could confirm that patients with AIIRD should not discontinue ongoing antirheumatic treatments during the COVID-19 pandemic; therapeutic changes in occurrence of COVID-19 infection should be discussed case by case as stated in European Alliance of Associations for Rheumatology recommendations.<sup>43</sup> The Italian CONTROL-19 registry was based on SIR's national network of rheumatologists, who guaranteed a nationwide coverage; obtained results reflect temporal and geographical distribution of the Italian population reported by official sources and this supports the validity of this initiative.

Our study has some limitations. Interpreting our results, it has to be considered that only patients with a molecular diagnosis of SARS-CoV-2 infection were included in the study; this made the register comparable with the official data, but asymptomatic and mild forms of the disease could have not been analysed and this could have enriched our cohort with the most severe cases.

PCR positivity was registered according to patients' reports in milder or asymptomatic cases, so we have to consider that it could be a non-quantifiable amount of missing data.

Moreover, the number of patients affected by SLE is low and smaller compared with those with RA and SPA, resulting in a lack of statistical power, particularly when adjusting for confounding factors.

Finally, it is important to underline that this study reflects COVID-19 outcomes in patients with SLE, before vaccination, in the first phase of the pandemic. Nowadays, COVID-19 epidemiology and severity have probably changed as reported from recent real-life data. Interestingly, a recent paper published by Jiang *et al* described data comparing the risk of SARS-CoV-2 infection and its related severe sequelae between patients with SLE and the general population, according to COVID-19 vaccination status. While unvaccinated patients with SLE were at higher risk of SARS-CoV-2 infection and its severe sequelae than the general population, no such difference was observed among vaccinated populations, confirming the importance of vaccination in this cohort of patients.<sup>44</sup>

This suggests that it is of paramount importance to continue to collect information on the outcome of COVID-19 in patients affected by SLE and, generally, by all AIIRDS, to improve our knowledge of the history of such infection in these patients.

## CONCLUSIONS

Our data suggest that COVID-19 prognosis in patients with SLE is not different from RA, while patients with SPA

had a more favourable outcome, independently from the presence of possible confounders such as age, sex, disease activity and pulmonary disease.

In addition, some demographic or clinical characteristics such as age, hypertension and PDN use seem to carry a higher risk of a severe form of the infectious disease in patients with lupus. Finally, COVID-19 outcomes in AIIRDs resulted to be influenced by age, sex, comorbidities such as pulmonary disease, active disease and GC therapy.

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