

Systemic lupus erythematosus and COVID-19: what we know so far

We read with interest the recent report by Mathian *et al*¹ about 17 patients with systemic lupus erythematosus (SLE) and COVID-19, which has paved the way to a constellation of articles aiming to find clues on potential peculiarities in COVID-19 epidemiology and course among patients with SLE. An ongoing debate has also recently grown on the role of hydroxychloroquine (HCQ), with increasing data disconfirming a protective effect of this drug towards severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in general and specifically also in patients with SLE.^{2,3} We were thus prompted to summarise the evidence published so far on this latter topic to look for recurrent clinical or epidemiological patterns among different studies/cohorts. To this aim, we analysed all studies published in the English literature until June, 30th 2020 and identified 20 articles describing a total of 4059 patients with SLE, 255 of whom with a PCR-confirmed or presumptive (ie, based on symptoms or radiological findings) diagnosis of COVID-19 (table 1).

The occurrence of COVID-19 cases among patients with SLE was investigated within disease-specific²⁻⁷ (n=6) or general rheumatology (n=5)⁸⁻¹² cohorts, total (n=2)^{13,14} or patients with only SLE hospitalised for COVID-19 (n=2),^{1,15} infected patients with rheumatic diseases (n=3),¹⁶⁻¹⁸ multinational registries (n=1)¹⁹ or population statistics (n=1).²⁰ Based on previous estimates about the local prevalence of SLE and on actual data from two studies,^{13,20} we found that only four to six studies^{2,9-11,13,14} included in their analysis at least 5% of the expected SLE population within their region/area. Considering those studies where a cohort denominator was available, 41 (0.9%)/4307 patients with SLE had a PCR-confirmed diagnosis of COVID-19, only slightly exceeding the expected prevalence of COVID-19 in the general population. In addition, 72 (3.7%)/1953 patients had symptoms consistent with COVID-19 without PCR confirmation. Establishing a presumptive diagnosis of COVID-19 in patients with SLE is challenging, since multiple symptoms (such as fever, myalgia or dyspnoea) might be part of the clinical spectrum of SLE. Recently, we and others^{2,3,10} described the prevalence of symptoms potentially related to COVID-19 within a whole lupus cohort. Data from these works suggest that patients with SLE might frequently develop one or more symptoms among rhinorrhoea, myalgia (both 19% frequency), cough (18%), sore throat (17%), fever (11%) and less frequently (but potentially more specifically) diarrhoea (10%), conjunctivitis (9%), dyspnoea (8%), anosmia or ageusia (5%) and chest pain (5%). Association analyses between HCQ use and COVID-19 were available from six studies,^{2,3,5,14,17,19} three of which^{2,3,5} with data from patients with SLE who did not develop COVID-19: 101 (69%)/147 patients with SLE and COVID-19 were taking HCQ, compared with 526 (71%)/736 patients with SLE without COVID-19, suggesting that antimalarials may not per se be sufficient to prevent COVID-19 in patients with SLE. Little is still known about COVID-19 severity in patients with SLE. Cohort-based studies reproducibly show that COVID-19 prevalence in SLE is probably similar to that of the general population, possibly with marked dependence on containment measures such as home confinement.^{2,8} Although these studies are strengthened by the large number of screened patients, they can underrepresent patients with severe COVID-19, who might not be contactable at time of interview. Conversely, case

series of hospitalised or infected patients as well as disease registries might be limited by reporting biases (preferential reporting of severe cases), small sample sizes and absence of appropriate control groups, but still highlight the potential association between comorbid SLE and difficult or even fatal COVID-19 course.^{1,12,19}

Giuseppe A. Ramirez ^{1,2}, Luca Moroni^{1,2}, Emanuel Della-Torre ^{1,2}, Maria Gerosa,^{3,4} Lorenzo Beretta ^{5,6}, Enrica P. Bozzolo,² Lorenzo Dagna ^{1,2}

¹Università Vita Salute San Raffaele, Milano, Italy

²Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milano, Italy

³Unit of Clinical Rheumatology, Azienda Socio Sanitaria Territoriale Gaetano Pini, Milano, Italy

⁴Department of Clinical Science of Community Health and Research Center for Adult and Pediatric Rheumatic Diseases, University of Milan, Milano, Italy

⁵Referral Center for Systemic Autoimmune Diseases, La Fondazione IRCCS Ca' Granda Ospedale Maggiore di Milano Policlinico, Milano, Italy

⁶University of Milan, Milano, Lombardia, Italy

Correspondence to Dr Giuseppe A. Ramirez, Università Vita Salute San Raffaele, 20132 Milano, Italy; ramirez.giuseppe@vhs.it

Acknowledgements We are grateful to the B.I.R.D. Foundation Europe, Costozza di Longare (VI), Italy for its support to the School of Allergy and Immunology of the Università Vita-Salute San Raffaele, Milan, Italy.

Contributors GAR designed the study, collected and analysed the data and drafted the manuscript. All authors contributed to the design of the study and to revise it critically for important intellectual content. All authors contributed in revising the manuscript and approved its final version.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

This article is made freely available for use in accordance with BMJ's website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may use, download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

© Author(s) (or their employer(s)) 2020. No commercial re-use. See rights and permissions. Published by BMJ.



To cite Ramirez GA, Moroni L, Della-Torre E, *et al*. *Ann Rheum Dis* Epub ahead of print: [please include Day Month Year]. doi:10.1136/annrheumdis-2020-218601

Received 17 July 2020

Revised 26 July 2020

Accepted 27 July 2020

Ann Rheum Dis 2020;0:1–3. doi:10.1136/annrheumdis-2020-218601

ORCID iDs

Giuseppe A. Ramirez <http://orcid.org/0000-0002-2889-366X>

Emanuel Della-Torre <http://orcid.org/0000-0002-9192-4270>

Lorenzo Beretta <http://orcid.org/0000-0002-6529-6258>

Lorenzo Dagna <http://orcid.org/0000-0002-7428-315X>

REFERENCES

- Mathian A, Mahevas M, Rohmer J, *et al*. Clinical course of coronavirus disease 2019 (COVID-19) in a series of 17 patients with systemic lupus erythematosus under long-term treatment with hydroxychloroquine. *Ann Rheum Dis* 2020;79:837–9.
- Ramirez GA, Gerosa M, Beretta L, *et al*. COVID-19 in systemic lupus erythematosus: data from a survey on 417 patients. *Semin Arthritis Rheum*. In Press 2020.
- Gendebien Z, von Frenckell C, Ribbens C, *et al*. Systematic analysis of COVID-19 infection and symptoms in a systemic lupus erythematosus population: correlation with disease characteristics, hydroxychloroquine use and immunosuppressive treatments. *Ann Rheum Dis* 2020;annrheumdis-2020-218244.

Correspondence

Table 1 Pooled data about the occurrence of COVID-19 in patients with SLE

General demographics								
Reference	Setting	Country	Estimated country SLE prevalence (cases/100 000 inhabitants)	Reference region/ area	Population (millions)	Expected SLE cases in region/area (thousands)	Number of patients with SLE described	Estimated coverage of total SLE cases for region/ area (%)
Chen <i>et al</i> ⁴	Cohort	China	40*	Hubei	59	22	101	0.5
Mathian <i>et al</i> ¹	Hospitalised patients	France	50†	Unspecified	NA	NA	17	NA
D'Silva <i>et al</i> ¹⁶	Infected patients	USA	20–150‡	Massachusetts	7	1–10	10	NA
Favalli <i>et al</i> ⁸	Cohort	Italy	50–70§	Lombardy	10	5–7	62	0.9–1.2
Emmi <i>et al</i> ⁹	Cohort	Italy	50–70§	Tuscany	4	2–3	117	4.5–6.3
So <i>et al</i> ²⁰	Population	China (Hong-Kong)	100 ²⁰	Hong Kong	8	8	NA	NA
Bozzalla Cassione <i>et al</i> ⁵	Cohort	Italy	50–70§	Lombardy and Emilia Romagna	15	7–10	165	1.6
Huang <i>et al</i> ¹⁵	Hospitalised patients	China	40 ¹	Hubei	59	22	3	<0.1
Konig <i>et al</i> ¹⁹	Registry	NA	NA	NA	NA	NA	80	NA
Pablos <i>et al</i> ¹³	Cohort/hospitalised patients	Spain	80–210¶	NA	3	2***	2253	100
Wallace B <i>et al</i> ¹⁷	Infected patients	USA	20–150‡	Michigan	10	2–15	5	<0.1–0.3
Holubar <i>et al</i> ⁶	Cohort	France	50†	Occitanie	6	3	120	4.1
Zen <i>et al</i> ¹⁰	Cohort	Italy	50–70§	Veneto	5	2–3	397	11.6–16.2
Quartuccio <i>et al</i> ¹¹	Cohort‡‡	Italy	50–70§	Province of Udine	0.5	0.2–0.3	38	12–16
Gartshteyn <i>et al</i> ¹⁴	Cohort/hospitalised	USA	20–150‡	New York	9	4–29	18 (screened 450)	2.9–21.9
Ramirez <i>et al</i> ²	Cohort	Italy	50–70§	Lombardy	10	5–7	417	5.8–8.1
Fredi <i>et al</i> ¹²	Cohort	Italy	50–70§	Lombardy	10	5–7	12	ND
Nuño <i>et al</i> ¹⁸	Infected patients	Spain	80–210¶	Madrid	7	5–14	13	ND
Vezzoli <i>et al</i> ⁷	Cohort	Italy	50–70§	Lombardy	10	5–7	6	≤0.1
Gendebien <i>et al</i> ³	Cohort	Belgium	Unknown	Unspecified	NA	NA	225	NA
COVID-19 epidemiology								
	End of observation	Prevalence of COVID-19 in region/ area (%)**	Total SLE+COVID-19: N (%)	PCR-confirmed SLE+COVID-19: N (%)	Presumptive SLE+COVID-19: N (%)	Hospitalisations (%)	Use of HCQ in SLE+COVID-19: N (%)	Use of HCQ in SLE without COVID-19 N (%)
Chen <i>et al</i> ⁴	29 February 2020	0.1	2 (2.0)	2 (1.2)	ND	ND	ND	ND
Mathian <i>et al</i> ¹	6 April 2020	NA	17 (NA)	17 (NA)	0 (NA)	NA	17/17 (100)	ND
D'Silva <i>et al</i> ¹⁶	8 April 2020	0.2	10 (NA)	10 (NA)	ND	ND	ND	ND
Favalli <i>et al</i> ⁸	10 April 2020	0.6	8 (12.9)	0 (0)	8 (12.9)	ND	ND	ND
Emmi <i>et al</i> ⁹	14 April 2020	0.2	4 (3.4)	0 (0)	4 (3.4)	0.0	ND	ND
So <i>et al</i> ²⁰	15 April 2020	<0.1	0 (0.0)	0 (0)	0 (0)	0.0	ND	ND
Bozzalla Cassione <i>et al</i> ⁵	16 April 2020	0.6	12 (7.3)	4 (2.4)	8 (4.8)	0.6	10/12 (83)	127/153 (83)
Huang <i>et al</i> ¹⁵	16 April 2020	0.1	3 (NA)	NA	NA	NA	ND	ND
Konig <i>et al</i> ¹⁹	17 April 2020	NA	80 (NA)	NA	NA	NA	51/80 (64)	ND
Pablos <i>et al</i> ¹³	17 April 2020	0.6	14 (NA)	14 (0.6)	ND	NA	ND	ND
Wallace B <i>et al</i> ¹⁷	20 April 2020	0.4	5 (NA)	ND	ND	NA	4/5 (80)	
Holubar J <i>et al</i> ⁶	24 April 2020	0.1	8 (6.7)	0 (0)	8 (6.7)	0.0	ND	ND
Zen <i>et al</i> ¹⁰	25 April 2020	0.4	15 (3.8)	1 (0.3)	14 (3.5)††	0.3	ND	ND
Quartuccio <i>et al</i> ¹¹	25 April 2020	0.2	0 (NA)	0 (NA)	0 (NA)	NA	ND	ND

Continued

Table 1 Continued

COVID-19 epidemiology

	End of observation	Prevalence of COVID-19 in region/ area (%)**	Total SLE+COVID-19: N (%)	PCR-confirmed SLE+COVID-19: N (%)	Presumptive SLE+COVID-19: N (%)	Hospitalisations (%)	Use of HCQ in SLE+COVID-19: N (%)	Use of HCQ in SLE without COVID-19 N (%)
Gartshteyn <i>et al</i> ¹⁴	26 April 2020	1.8	18 (4.0)	10 (2.2)	8 (1.8)	0.8	13/18 (72)	ND
Ramirez <i>et al</i> ²	27 April 2020	0.7	14 (3.4)	5 (1.2)	9 (2.2)	0.2	11/14 (79)	259 (69)
Fredi <i>et al</i> ¹²	1 MAY 2020	0.8	ND	5 (ND)	7 (ND)	ND	ND	ND
Nuño <i>et al</i> ¹⁸	8 June 2020	1.1	13 (NA)	ND	ND	ND	ND	ND
Vezzoli <i>et al</i> ⁷	ND	NA	2 (NA)	ND	2 (NA)	NA	ND	ND
Gendebien <i>et al</i> ³	ND	NA	18 (8.0)	5 (2.0)	13 (5.8)	0.9	12/18 (67)	140 (68)

*According to Xiang *et al. Rheum Int*, 2009.

†According to Arnaud *et al. Autoimmun Rev*, 2014.

‡According to Lawrence *et al. Arthr Rheum*, 1998, Chakravarty *et al. Arthr Rheum*, 2007 and Pons-Estel *et al. Semin Arthr Rheum*, 2010.

§According to Benucci *et al. Med Sci Monit*, 2005 and to the report by the Society-of-Patients with Rheumatic Diseases of the Emilia-Romagna Region (Il Notiziario del Malato Reumatico, 2015; 43).

¶According to Cortes Verdu *et al. Rheumatology*, 2020 and Pablos *et al Ann Rheum Dis*, 2020.

At the end of observation for each study. *Rounded actual figure (2.253) rather than estimate is reported. ††Considering patients with 'fever plus cough plus one more symptom'.¹⁰ ‡‡Only patients on biologic disease-modifying antirheumatic drugs or small-molecule disease-modifying antirheumatic drugs were considered.

HCQ, hydroxychloroquine; NA, not applicable; ND, no data; SLE, systemic lupus erythematosus.

- Chen C, Yao B, Yan M, *et al*. The plight of patients with lupus nephritis during the outbreak of COVID-19 in Wuhan, China. *J Rheumatol* 2020;jrheum.200452.
- Bozzalla Cassione E, Zanframundo G, Biglia A, *et al*. COVID-19 infection in a northern-Italian cohort of systemic lupus erythematosus assessed by telemedicine. *Ann Rheum Dis* 2020.
- Holubar J, Le Quintrec M, Letaief H, *et al*. Monitoring of patients with systemic lupus erythematosus during the COVID-19 outbreak. *Ann Rheum Dis* 2020;annrheumdis-2020-217919.
- Vezzoli P, Di Mercurio M, Carugno A, *et al*. Cutaneous lupus erythematosus patients in a high-epidemic COVID-19 area, Bergamo, Italy. *Dermatol Ther* 2020;79.
- Favalli EG, Gerosa M, Murgio A, *et al*. Are patients with systemic lupus erythematosus at increased risk for COVID-19? *Ann Rheum Dis* 2020.
- Emmi G, Bettiol A, Mattioli I, *et al*. SARS-CoV-2 infection among patients with systemic autoimmune diseases. *Autoimmun Rev* 2020;19:102575.
- Zen M, Fuzzi E, Astorri D, *et al*. SARS-CoV-2 infection in patients with autoimmune rheumatic diseases in northeast Italy: a cross-sectional study on 916 patients. *J Autoimmun* 2020;112:102502.
- Quartuccio L, Valent F, Pasut E, *et al*. Prevalence of COVID-19 among patients with chronic inflammatory rheumatic diseases treated with biologic agents or small molecules: a population-based study in the first two months of COVID-19 outbreak in Italy. *Joint Bone Spine* 2020. doi:10.1016/j.jbspin.2020.05.003. [Epub ahead of print: 20 May 2020].
- Fredi M, Cavazzana I, Moschetti L, *et al*. COVID-19 in patients with rheumatic diseases in northern Italy: a single-centre observational and case-control study. *Lancet Rheumatol* 2020.
- Pablos JL, Abasolo L, Alvaro-Gracia JM, *et al*. Prevalence of hospital PCR-confirmed COVID-19 cases in patients with chronic inflammatory and autoimmune rheumatic diseases. *Ann Rheum Dis* 2020. doi:10.1136/annrheumdis-2020-217763. [Epub ahead of print: 12 Jun 2020].
- Gartshteyn Y, Askanase AD, Schmidt NM, *et al*. COVID-19 and systemic lupus erythematosus: a case series. *Lancet Rheumatol* 2020.
- Huang Y, Chen Z, Wang Y, *et al*. Clinical characteristics of 17 patients with COVID-19 and systemic autoimmune diseases: a retrospective study. *Ann Rheum Dis* 2020. doi:10.1136/annrheumdis-2020-217425. [Epub ahead of print: 16 Jun 2020].
- D'Silva KM, Serling-Boyd N, Wallwork R, *et al*. Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: a comparative cohort study from a US 'hot spot'. *Ann Rheum Dis* 2020. doi:10.1136/annrheumdis-2020-217888. [Epub ahead of print: 26 May 2020].
- Wallace B, Washer L, Marder W, *et al*. Patients with lupus with COVID-19: University of Michigan experience. *Ann Rheum Dis* 2020;annrheumdis-2020-217794.
- Nuño L, Novella Navarro M, Bonilla G, *et al*. Clinical course, severity and mortality in a cohort of patients with COVID-19 with rheumatic diseases. *Ann Rheum Dis* 2020. doi:10.1136/annrheumdis-2020-218054. [Epub ahead of print: 30 Jun 2020].
- Konig MF, Kim AH, Scheetz MH, *et al*. Baseline use of hydroxychloroquine in systemic lupus erythematosus does not preclude SARS-CoV-2 infection and severe COVID-19. *Ann Rheum Dis* 2020;annrheumdis-2020-217690.
- So H, Mak JWY, Tam L-S. No systemic lupus erythematosus with COVID-19 in Hong Kong: the effect of masking? *J Rheumatol* 2020;jrheum.200605.