Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Impact of hydroxychloroquine used as DMARD on SARS-CoV-2 tests and infection evolution in a population of 871 patients with inflammatory rheumatic and musculoskeletal diseases

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The *in vitro* efficacy of synthetic antimalarial agents against SARS coronavirus 2 (SARS-CoV-2) has been described [1,2], as well as a potential *in vivo* effect, especially on nasopharyngeal PCR [3]. The effect on SARS-CoV-2 infection of treatment with hydroxychloroquine (HCQ), used as a disease-modifying anti-rheumatic drug (DMARD) with long-term impregnation, is unknown. The objective of this study was to evaluate the impact of HCQ, used as DMARD, on the rate of positivity of the SARS-CoV-2 nasopharyngeal PCR, and on the clinical signs of infection with SARS-CoV-2, its severity and evolution in the French iRMD (inflammatory rheumatic and musculoskeletal diseases) -COVID-19 cohort.

We conducted a multicentre retrospective study between 13 April 2020 and 29 July 2020 based on the French iRMD-COVID-19 cohort [4]. From the cohort, we selected all subjects aged over 18 years and macthed subjects with ongoing HCQ treatment with patients without at the time of infection with SARS-CoV-2. Matching criteria were age (±5 years), gender, comorbidities considered as associated with poor prognosis (at least one vs. none), an immunosuppressive treatment, and use of nasopharyngeal PCR to diagnose COVID-19. (statistical analysis in Online material, supplementary data S1).

We analysed 871 patients and finally matched 71 HCQ-treated patients with 191 controls. (Table 1, Table 2 and Online material, supplementary data S2). The 71 HCQ-treated patients (94% women) had a mean age of 53 ± 16 years. The patients were receiving HCQ for systemic lupus ($n = 42$), Sjögren's syndrome ($n = 6$), other systemic iRMDs ($n = 9$) or for chronic inflammatory rheumatism: rheumatoid arthritis ($n = 11$), other ($n = 3$).

We report a comparative study of COVID-19 patients receiving HCQ for an iRMD versus controls, derived from a population of 871 iRMD COVID-19 patients. We found no difference in terms of either clinical symptoms, severity or proportion of positive nasopharyngal PCR in patients on HCQ compared to matched controls. Matching criteria have been described as risk factors for COVID-19-related death [5]. The present findings are derived from observational retrospective analyses, which are subject to well-known limitations. No information was available on HCQ treatment duration, dose and blood concentration, useful for verifying adherence [6]. It should be noted, however, that HCQ has a long half-life [7] and its concentration would remain within a sufficient range over the course of COVID-19. The frequency of corticosteroids treatment was higher in the HCQ group and its influence is questionable. The percentage of positive nasopharyngeal PCR was not lower in the HCQ group. Our *in vivo* data do not support the described potential *in vitro* effect [1]. Numerous studies have used HCQ to treat or to prevent COVID-19, with no significant effect [8–10]. One could argue that the targeted blood concentration of HCQ would only be reached after several weeks [6], which could have blunted its effects. A strength of our study is that the chronic impregnation of HCQ probably eliminates this putative bias.

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Table 1
Patient characteristics and COVID-19 assessment of HCQ-treated patients and their matched controls.

	HCQ-treated patients ($n = 71$)	Matched controls[a] ($n = 191$)	ASD (%)
Age (years)			
18–54	41 (57.7)	100 (52.4)	
55–64	12 (16.9)	33 (17.3)	
65–74	10 (14.1)	29 (15.2)	
≥ 75	8 (11.3)	29 (15.2)	
Mean ± SD	53 ± 16	55 ± 16	12.6
Female gender	67 (94.4)	179 (93.7)	2.7
Comorbidities			
Respiratory disease (all)	9 (12.7)	33 (17.3)	12.9
Interstitial lung disease	2 (2.8)	9 (4.7)	10.0
COPD	2 (2.8)	8 (4.2)	7.5
Asthma	5 (7.0)	19 (9.9)	10.4
Cardiac disease (all)	10 (14.1)	21 (11.0)	9.3
Coronary heart diseases	6 (8.5)	19 (9.9)	5.2
Stroke	4 (5.6)	4 (2.1)	18.4
Diabetes	5 (7.0)	19 (9.9)	10.4
Obesity[b]			16.4
< 30	48 (76.2)	112 (69.1)	
30–39.9	13 (20.6)	45 (27.8)	
≥ 40	2 (3.2)	5 (3.1)	
Hypertension	19 (26.8)	56 (29.3)	5.7
Past history of cancer	7 (9.9)	8 (4.2)	22.3
Chronic renal failure	12 (16.9)	7 (3.7)	44.7
No. of patients with at least 1 comorbidity	60 (84.5)	163 (85.3)	2.3
Disease history			138
Systemic auto-immune diseases	55 (77.5)	41 (21.5)	
Chronic inflammatory arthritis	14 (19.7)	117 (61.3)	
Vasculitis	0 (0.0)	23 (12.0)	
Auto-inflammatory diseases	1 (1.4)	2 (1.0)	
Other	1 (1.4)	8 (4.2)	
Rheumatic disease or AI^{2}D treatments			
Corticosteroid	31 (43.7)	61 (31.9)	24.4
Daily prednisone doses ≥ 10 mg or equivalent	10 (32.3)	28 (47.5)	31.4
NSAIDs	5 (7.0)	17 (8.9)	6.9
Colchicine	2 (2.8)	10 (5.2)	12.3
Methotrexate	19 (26.8)	48 (25.1)	3.7
Leflunomide	1 (1.4)	12 (6.3)	25.6
Salazopyrine	2 (2.8)	0 (0.0)	ND
Mycophenolate mofetil/mycophenolic acid	11 (15.5)	4 (2.1)	48.7
Azathioprine	3 (4.2)	1 (0.5)	ND
IVIG	1 (1.4)	3 (1.6)	ND
Biologics			
Anti-TNF	3 (4.2)	46 (24.1)	59.4
Anti-IL6	0 (0.0)	4 (2.1)	ND
Anti-CD20	2 (2.8)	11 (5.8)	14.6
Anti-IL17a	0 (0.0)	4 (2.1)	ND
Anti-IL1	0 (0.0)	1 (0.5)	ND
Abatacept	0 (0.0)	6 (3.1)	25.5
JAK inhibitor	0 (0.0)	3 (1.6)	ND
Belimumab	2 (2.8)	0 (0.0)	ND
Other biologics	3 (4.2)	7 (3.7)	2.9
No. of patients with at least 1 immunosuppressive drug	37 (52.1)	107 (56.0)	7.9
COVID-19 assessment			
PCR test performed	49/71 (69.0)	137/191 (71.7)	6.0
Positive PCR test	41/48 (85.4)	111/137 (81.0)	11.8
CT-scan performed	33/68 (48.5)	75/179 (41.9)	13.4
Positive CT-scan	28/33 (84.8)	60/75 (80.0)	12.8

COPD: chronic obstructive pulmonary disease; AI^{2}D: autoimmune and autoinflammatory diseases; NSAIDs: non-steroidal anti-inflammatory drugs; HCQ: hydroxychloroquine; IVIG: intravenous immunoglobulins; ASD: absolute standardised difference; SD: standard deviation. Values are presented as frequency (percentage) unless otherwise indicated. ND indicates not done for binary variables with frequency < 5 in the matched sample.

[a] Matched on age (±5 yrs), gender, comorbidity (at least one vs. none), use of immunosuppressive drugs (at least one vs. none), and use of PCR test for COVID-19.

[b] 37 missing values ($n = 8$ in HCQ-treated patients).

Table 2
COVID-19 outcome in HCQ-treated patients and their matched controls.

	HCQ-treated patients (n = 71)	Matched controls[a] (n = 191)	OR (95%CI)[b]
Severity of disease outcome			
Ambulatory	39/71 (54.9)	120/191 (62.8)	Reference category
Hospitalisation	24/71 (33.8)	53/191 (27.7)	1.75 (0.86 to 3.56)
Death/intensive care unit	8/71 (11.3)	18/191 (9.4)	1.94 (0.69 to 5.41)
Death	4/68 (5.9)	12/183 (6.6)	1.18 (0.32 to 4.31)

OR: odds ratio; CI: confidence interval; NS: non-significant; Values are presented as no. /No. (%).
[a] Matched on age (±5 yrs), gender, comorbidity (at least one vs. none), use of immunosuppressive drugs (at least one vs. none), and use of PCR test for COVID-19.
[b] Calculated using multinomial or binary logistic regression models adjusted for matching factors.

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Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2021.105226.

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