

Prevalence and clinical features of COVID-19 in a large cohort of 199 patients with sarcoidosis

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Research article

Keywords: sarcoidosis, COVID-19, SARS-CoV-2

Posted Date: July 20th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-41653/v1>

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1 **Prevalence and clinical features of COVID-19 in a large cohort of 199 patients with**
2 **sarcoidosis**

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22 **Conflict of interest:** The authors have declared that no conflict of interest exists.

23

24 **Word Count:** 1496 words, 10 217 characters (including spaces), 2 tables, 20 references.

25 **Declarations**

26

27 Ethics approval and consent to participate:

28 The study was approved by our institutional ethics review board "Ethics committee of
29 research in Sorbonne University". All patients gave informed consent.

30

31 Consent for publication:

32 Not applicable.

33

34 Availability of data and materials:

35 The datasets used and/or analyzed during the current study are available from the
36 corresponding author on reasonable request.

37

38 Competing interests:

39 The authors declare that they have no competing interests.

40

41 Funding:

42 The authors declare that they have no source of funding.

43

44 Authors' contributions:

45 ACD contributed to the conception and design of the work.

46 ACD and CM wrote the manuscript.

47 ACD, CM, LL, SB, CL, ML, GL, CC, CCA, FD, MV and DS collected the data.

48 CM have drafted the work

49 PC supervised the findings of this work.

50 All authors approved the final manuscript.

51

52 Acknowledgements:

53 We thank all patients and all physicians involved in the care of the patients.

54 **Abstract**

55 **Objective:** To investigate the prevalence, clinical features and outcomes of coronavirus
56 disease 2019 (COVID-19) among sarcoidosis patients.

57 **Methods:** We retrospectively collected features of COVID-19 in a cohort of patients with
58 sarcoidosis followed in a single tertiary university hospital.

59 **Results:** Among 199 sarcoidosis patients [mean age 58.8 (\pm 14) years, 86 (43.2%) men], 26
60 (13%) were diagnosed with COVID-19 [definite (n=7), probable (n=12) and possible (n=7)].
61 Twenty-four out of 26 patients (92%) had at least one comorbidity, and 11/26 (42%) had two
62 or more comorbidities. Demographic and clinical features of COVID-19 positive patients
63 were similar to those of COVID-19 negative patients. The administration of
64 hydroxychloroquine or immunosuppressant was not associated with the occurrence or the
65 severity of COVID-19. Four out of 26 (15.4%) COVID-19 positive patients required
66 admission to hospital and two of them died. Hospitalized patients [mean age of 61 (\pm 11.5)
67 years] were receiving higher doses of long term treatment with corticosteroids than non-
68 hospitalized patients; 4/4 had pulmonary and 2/4 cardiac involvement of sarcoidosis, and all
69 one or more comorbidity.

70 **Conclusion:** The prevalence of COVID-19 in sarcoidosis is slightly higher to that of the
71 general population. Almost half of the COVID-19 positive patients have two or more
72 comorbidities and about 15% present a severe course.

73

74 **Word count:** 200 words.

75

76 **Keywords:** sarcoidosis; COVID-19; SARS-CoV-2

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78

79 **List of abbreviations:**

80 ACE: angiotensin-converting enzyme,
81 ARB: angiotensin II receptor blocker,
82 ARDS: severe acute respiratory syndrome,
83 COVID-19: coronavirus disease 2019,
84 ECMO: extracorporeal membrane oxygenation
85 IL6: interleukin 6,
86 NSAID: nonsteroidal anti-inflammatory drug,
87 SARS-CoV-2: severe acute respiratory syndrome coronavirus 2,
88 SD: standard deviation,
89 TNF: tumor necrosis factor.

90

91 **Key messages:**

92 **What is already known about this subject?**

93 Since the outbreak of COVID-19, many data have been published in the general population
94 and in some disease-specific groups, but data are lacking for patients with sarcoidosis.

95

96 **What does this study add?**

97 We reported the prevalence, clinical features and outcomes of COVID-19 in a cohort of 199
98 patients with sarcoidosis followed in a single French tertiary university hospital. The rate of
99 COVID-19 infections among patients with sarcoidosis appears to be very slightly higher to
100 that of the general population. The rates of hospitalization and mortality appeared to be higher
101 than in the general population.

102

103 **How might this impact on clinical practice or future developments?**

104 Cardiovascular comorbidities that are highly found in sarcoidosis patients probably make
105 them more vulnerable to severe COVID-19. These findings should lead to be cautious for
106 management of sarcoidosis patients during the pandemic.

107 **Introduction**

108 Coronavirus disease 2019 (COVID-19), mediated by SARS-CoV-2 (severe acute respiratory
109 syndrome coronavirus 2) is responsible for a major health crisis worldwide. COVID-19 can
110 be complicated with a severe acute respiratory syndrome (ARDS) and multi-organ failure.
111 Sarcoidosis is a granulomatous disease of unknown origin affecting the lungs, the lymphatic
112 nodes but also the nervous system, the eyes and the heart. The reported incidence among
113 African and Americans in the United States is 35.5/100,000 compared with 10.9/100,000 in
114 Caucasian patients (1). The incidence and the severity of COVID-19 in patients with
115 sarcoidosis remains an unsolved issue. Sarcoidosis can be complicated by interstitial
116 pneumonia leading to severe pulmonary illness. Immunosuppressive drugs are often used
117 making sarcoidosis patients more vulnerable to infections. COVID-19 can be responsible for a
118 cytokine storm syndrome for which immunosuppressive strategy could be beneficial (2, 3).
119 To date, there is no data on clinical features of COVID-19 in sarcoidosis patients. A recent
120 comparative cohort study showed that patients with rheumatic disease and COVID-19
121 infection were more likely to require mechanical ventilation but had similar mortality and
122 hospitalization rates compared to patients without rheumatic disease (4).

123

124 **Methods**

125 This study was performed at the Department of Internal Medicine and Clinical Immunology
126 in the tertiary university hospital Pitié-Salpêtrière (Paris, France). This study was approved by
127 the local Ethic Committee. All patients with sarcoidosis, followed at the department were
128 included. From May, 1st 2020 to 27th May, six weeks after the pandemic peak in France, we
129 systematically contacted by telephone patients followed in our center for sarcoidosis. We
130 investigated their demographic characteristics, disease manifestations of sarcoidosis, the
131 presence of symptoms suggesting SARS-CoV-2 infection, the results of nasopharyngeal PCR
132 if available and their treatments. A definite COVID-19 was defined by the presence of
133 symptoms suggesting SARS-CoV-2 infection with positive nasopharyngeal PCR or serology.
134 A probable COVID-19 was defined by the presence of fever and/or three or more symptoms
135 suggesting SARS-CoV-2 infection associated with a contact with a person infected by SARS-
136 CoV-2 without available nasopharyngeal PCR. A possible COVID-19 was defined by the
137 presence of three symptoms or more suggesting SARS-CoV-2 infection without available
138 nasopharyngeal PCR and without history of contact with infected people.
139 Continuous variables are presented as mean (\pm SD) and categorical variables as number (%).
140 Statistical comparisons were performed by using the Mann-Whitney test for quantitative

141 unpaired data, and the Chi-Square test for categorical variables. All statistical tests were two-
142 tailed with a significance level of 0.05. Statistical significance was evaluated using GraphPad
143 Prism version 5.00 for Windows (GraphPad Software, San Diego, CA, USA).

144

145 **Results**

146 One hundred and ninety-nine patients diagnosed with sarcoidosis according to the criteria of
147 the latest American Thoracic Society/European Respiratory Society/World Association of
148 Sarcoidosis and Other Granulomatous Disorders statement on sarcoidosis (5) were included.
149 The mean age of patients was 58.8 (\pm 14) years and 86 (43.2%) were male. Among the cohort,
150 26 (13%) patients were diagnosed with COVID-19 [definite (n=7), probable (n=12) and
151 possible (n=7)].

152 COVID-19 positive sarcoidosis patients

153 Patients with COVID-19 consisted of 13 (50%) men with a mean age of 50.3 (\pm 13.6) years.
154 Main features of sarcoidosis included involvement of lungs (73%), lymph nodes (50%), heart
155 (15.4%), central nervous system (23.1%) and eyes (46.2%). Twenty-four (92%) patients had
156 at least one comorbidity [hypertension (26.9%), diabetes (23.1%), heart failure (7.7%),
157 coronary artery disease (7.7%), chronic obstructive lung disease/asthma (19%), overweight
158 (65.4%) or malignant tumors (3.8%)]. Eleven (42.3%) patients had two or more
159 comorbidities. Six of them were ex-smokers and three were active smokers. Demographic and
160 clinical features of patients COVID-19 positive were similar to those of sarcoidosis patients
161 COVID-19 negative (**Table 1**). The administration of hydroxychloroquine was not associated
162 with a decreased occurrence of symptomatic COVID-19 (given in 13.9% of patients COVID-
163 19 negative vs 11.5% of infected patients, $p=1$). The use of immunosuppressant was not
164 significantly associated with a higher risk of symptomatic COVID-19 (39.3% in patients
165 COVID-19 negative vs 38.4% in COVID-19 positive patients, $p=0.96$).

166 At the onset of COVID-19, patients infected were receiving ARBs/ACE inhibitors (23.1%),
167 HMGCoa reductase inhibitors (15.4%), corticosteroids [84.6%, mean dose of 8.6(6) mg/day],
168 hydroxychloroquine (11.5%), immunosuppressant (38.4%), IL-6 inhibitors (7.7%), and TNF
169 inhibitors (3.8%). Main symptoms of COVID-19 in this cohort of sarcoidosis patients are
170 listed in **Table 2**. Specific treatments for COVID-19 consisted in lopinavir/ritonavir and
171 pristinamycin (n=1), hydroxychloroquine (n=2), azithromycin (n=1) and withdrawal of
172 immunosuppressant (n=2).

173 COVID-19 positive sarcoidosis patients requiring hospitalization

174 Among the 26 patients with COVID-19, four (15.4%) required admission to hospital
175 [medicine ward (n=2) and intensive care unit (n=2)], one required mechanical ventilation, one
176 high flow nasal cannula and two died. One woman (73 years) with sarcoidosis associated with
177 Takayasu arteritis died at the emergency room because of acute respiratory insufficiency. One
178 man (49 years) with stage 4 pulmonary sarcoidosis, diabetes and history of pulmonary
179 embolism, was admitted to hospital 10 days after COVID-19 onset. He did not receive
180 specific treatments for COVID-19. He required mechanical ventilation and died 20 days after
181 hospital admission.

182 All patients requiring admission to hospital [50% of male gender, mean age of 61(11.5) years]
183 presented pulmonary sarcoidosis (stage II/III for two and stage IV for one), two of them had
184 cardiac sarcoidosis and none had neurological sarcoidosis. All of them had at least one
185 comorbidity [hypertension (n=1), diabetes (n=2), coronary artery disease (n=1), Takayasu
186 (n=1), heart failure (n=1), and overweight (n=4)]. Three (75%) of them had two or more
187 comorbidities. None of them was an active smoker. At the onset of COVID-19, three patients
188 were receiving corticosteroids [mean dose of 12.3 (7-20) mg/day], one mycophenolate mofetil
189 and one leflunomide. None was receiving hydroxychloroquine.

190

191 **Discussion**

192 To our knowledge, this study is the first report on the prevalence, clinical presentation and
193 outcome of COVID-19 in patients with sarcoidosis. The prevalence of infected patients (13%)
194 in our cohort of sarcoidosis patients does seem significantly different to that estimated
195 COVID-19 prevalence in Ile de France (9.9%) and Grand-Est (9.3%), both regions being the
196 most affected by the pandemic in France (6). Our results are consistent with previous data on
197 cohort of patients with other inflammatory and autoimmune disorders (4).

198 The rate of infected patients with severe symptoms requiring hospitalization reached 15%,
199 which is about four times higher than the rate of hospitalizations in the general population in
200 France, estimated at respectively 3.6% and 3.5% (2.1 - 5.4) for all the French population and
201 patients aged 50 to 59 years-old, the age group corresponding to the median age of sarcoidosis
202 patients in our cohort (6). In the same line, the rate of death is 7.7% in our cohort. However,
203 this should be considered with caution given the small number of patients concerned although
204 this mortality rate seems to be higher than that estimated in the population aged from 50 to 59
205 years old in France (than 1%) (6). This mortality rate may be explained by the high
206 prevalence of comorbidities in sarcoidosis patients, as 92% COVID-19 positive sarcoidosis
207 patients in our cohort had one or more comorbidities. The rate of diabetes in our cohort is two

208 to three times higher than that of the general population (<10% before 60 years in France) (8).
209 The prevalence of diabetic patients in our sarcoidosis cohort reached 23% for patients with
210 COVID-19 and 50% for hospitalized patients, compared to 6% and 14% respectively in a
211 New York series reporting patients with an immune-mediated inflammatory disease COVID-
212 19 positive (9). The body mass index of sarcoidosis patients is also particularly high (10).
213 Indeed, diabetes, hypertension and obesity are risk factors known to be associated with poor
214 prognosis in COVID-19 positive patients, increasing the rate of hospitalizations and mortality
215 (11 – 15). The mortality rate in diabetic COVID-19 positive patients was reported to reach
216 7.8% (16) and 30% in hospitalized patients, which is quite similar to the mortality rate found
217 in our cohort. Consistently, all hospitalized patients in the present study have at least one
218 comorbidity. It should be noted that one of the two dead patients had severe cardiovascular
219 comorbidities, and that the second had stage four sarcoidosis pulmonary involvement (17).
220 In our cohort, the high rate of patients with metabolic syndrome can partly be explained by a
221 high rate of systemic corticosteroid therapy, i.e. 85% of COVID-19 patients and 75% of
222 hospitalized patients compared to 9% and 29% respectively in the study by Haberman et al
223 (18). Our results are consistent with those of previous studies showing that the use of systemic
224 corticosteroids is a risk factor for a severe course of COVID-19, particularly in inflammatory
225 bowel diseases (19). None of the hospitalized patients was a daily smoker or ex-smoker,
226 which is consistent with several studies finding a low proportion of smokers among patients
227 with a moderate to severe outcome. However, the relationship between smoking and COVID-
228 19 outcome is controversial, with multiple conflicting reports in the current literature (15, 20).

229

230 **Conclusion**

231 In conclusion, the rate of COVID-19 infections among patients with sarcoidosis appears to be
232 very slightly higher to that of the general population. The rates of hospitalization and
233 mortality appeared to be higher than in the general population.

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Table 1: Clinical characteristics of sarcoidosis patients without and with COVID-19

	Patients without COVID-19 (n=173)	Patients with COVID-19 (n=26)	<i>p</i>
Clinical features			
Age (mean, SD)	53.2(14.1)	50.3(13.6)	0.32
Male gender, n(%)	73(42.2)	13(50)	0.64
Involvements of sarcoidosis			
Lung involvement, n(%)	124(71.7)	19(73)	0.95
Stage of pulmonary involvement II/III, n(%)	73(42.2)	14(60.8)	0.5
Stage of pulmonary involvement IV, n(%)	5(2.9)	1(3.8)	0.58
Vital capacity (%), mean (SD)	79.2(38)	80.9(37)	
Total lung capacity (%), mean (SD)	77.3(33.4)	76.8(33.2)	
Diffusing capacity for carbon monoxide (%), mean (SD)	64.5(31.2)	69.3(29.3)	
Lymph nodes, n(%)	80(46.2)	13(50)	0.83
Cardiac, n(%)	30(17.3)	4(15.4)	1
Neurological, n(%)	63(36.4)	6(23.1)	0.39
Ophthalmological, n(%)	67(38.7)	12(46.2)	0.61
Other comorbidities			
One or more other comorbidity, n(%)	136(78.6)	24(92)	0.6
Hypertension, n(%)	53(30.6)	7(26.9)	0.8
Diabetes, n(%)	36(20.8)	6(23.1)	0.83
Cardiac failure, n(%)	8(4.6)	2(7.7)	0.63
Chronic respiratory disease (chronic obstructive lung disease or asthma) , n(%)	22(12.7)	5(19)	0.39
Malignant tumor, n(%)	27(15.6)	1(3.8)	0.21
Body Mass Index (mean, SD), n(%)	27.6(7)	27.1(4.8)	0.85
Smoking habits			
Ex-Smoker, n(%)	40(23.1)	6(23.1)	0.99
Daily smoker, n(%)	19(11)	3(11.5)	1
Treatments			
NSAID, n(%)	10(5.8)	2(7.7)	0.66
ACE inhibitors or ARBs, n(%)	39(22.5)	6(23.1)	0.96
HMGCoa reductase inhibitors, n(%)	29(16.8)	4(15.4)	1
Hydroxychloroquine, n(%)	24(13.9)	3(11.5)	1
Corticosteroids, n(%)	117(67.6)	22(84.6)	0.47
Corticosteroids dosage, mg/day mean(SD)	6.7(3.4)	8.6(6)	0.29
Immunosuppressants, n(%)	68(39.3)	10(38.4)	0.96
Methotrexate, n(%)	38(22)	4(15.4)	0.62
Mycophenolate mofetil, n(%)	23(13.3)	3(11.5)	1
Azathioprin, n(%)	2(1.2)	1(3.8)	0.35
TNF inhibitors, n(%)	11(6.4)	1(3.8)	1
IL-6 inhibitors, n(%)	2(1.2)	2(7.7)	0.09

320 ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blocker, COVID-19:
321 Coronavirus disease 2019, IL6: interleukin 6, NSAID: nonsteroidal anti-inflammatory drug,
322 SD: standard deviation, TNF: tumor necrosis factor
323

324 **Table 2:** Clinical characteristics and outcome of COVID-19 in sarcoidosis patients

	Patients with COVID-19 (n=27)
Symptoms of COVID-19	
Asthenia, n(%)	16(61.6)
Fever, n(%)	18(69.3)
Cough, n(%)	19(73.1)
Rhinorrhea, n(%)	10(38.5)
Anosmia, n(%)	5(19.2)
Dysgeusia, n(%)	7(26.9)
Headaches, n(%)	17(65.4)
Myalgia, n(%)	14(53.8)
Shortness of breath, n(%)	12(46.2)
Chest pain, n(%)	8(30.8)
Diarrhea, n(%)	6(23.1)
Cutaneous lesions, n(%)	4(15.4)
Duration of symptoms, mean (SD) days	16.6(13.8)
Chest findings: extension of ground-glass opacities and/or consolidation	
<10%	1(25%)
10-25%	1(25%)
25-50%	2(50%)
Treatments	
Hydroxychloroquine, n(%)	2(7.7)
Antibiotic therapy, n(%)	2(7.7)
Antiviral therapy, n(%)	1(3.8)
Tocilizumab, n(%)	0(0)
Increase or initiation of corticosteroids, n(%)	0(0)
Withdrawal or decrease of immunosuppressants, n(%)	2(7.7)
Outcomes	
Admission to hospital, n(%)	4(15.4)
Admission to Intensive care, n(%)	2(7.7)
Invasive ventilation, n(%)	1(3.8)
Oxygen therapy, n(%)	2(7.7)
High flow nasal cannula, n(%)	1(3.8)
ECMO, n(%)	0(0)
Death, n(%)	2(7.7)
Discharged, n(%)	2(7.7)

325 COVID-19: Coronavirus disease 2019, ECMO: extracorporeal membrane oxygenation, SD:
 326 standard deviation.