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Risk and outcome of COVID-19 infection in sarcoidosis patients: results of a self-reporting questionnaire

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Abstract. *Background:* It has been suggested that sarcoidosis patients, especially those on immunosuppressive medications, are at increased risk for COVID-19 infection and more severe disease. *Methods:* A questionnaire was developed in four languages (English, Dutch, Italian, and Spanish). The questionnaire queried whether patients had been infected with COVID-19 and outcome of the infection. Risk factors for COVID-19 infection were collected. *Results*: A total of 5200 sarcoidosis patients completed the questionnaire with 116 (2.23%) reporting infection and 18 (15.8%) required hospitalization. Increased hazard ratio (HR) for COVID-19 infection were seen for those with a COVID-19 infected roommate (HR=27.44, p<0.0001), health care provider (HR=2.4, p=0.0001), pulmonary sarcoidosis (HR=2.48, p=0.001), neurosarcoidosis (HR=2.02, p<0.01), or rituximab treatment (HR=5.40, p<0.0001). A higher rate of hospitalization was found for those with underlying heart disease (HR=3.19 (1.297-7.855), p<0.02). No other feature including race, other immunosuppressive agent, age, or underlying condition was associated with a significant increased risk for infection or more severe disease. *Conclusion*: The overall rate of COVID-19 was 2.23%, suggesting an increased rate of COVID-19 infection. However, when an analysis of the questionnaires of sarcoidosis and non-sarcoidosis patients was performed in one localized area over this time period, the rate of COVID-19 infection was similar in both groups. Sarcoidosis patients who cohabitated with COVID-19 infected individuals, worked in health care, had pulmonary or neurologic sarcoidosis, or were treated with rituximab had an increased risk for COVID-19 infection. No significant increased risk for hospitalization could be identified based on age, race, gender or any specific immunosuppressive treatment. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (4): e2020009)*

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Introduction

The COVID-19 pandemic has dramatically changed and challenged the practice of medicine. Both sarcoidosis patients and their health care providers are concerned that sarcoidosis may increase the risk of contracting COVID-19 and may be associated with poor outcomes from COVID-19 infection (1). Sarcoidosis patients may have several risk factors associated with an increased rate and a poor outcome from COVID-19 infection including underlying lung disease and the use of glucocorticoids and other immunosuppressive agents (2;3). However, it is not clear that use of immunosuppressive therapy alone is a risk factor for increased rate of COVID-19 infection (4;5). A worse outcome from COVID-19 infection may be result of the common presence of other co-morbidities including heart disease, diabetes, and hypertension (2;6-8). Because of the potential risk of COVID-19 infection in those receiving immunosuppressive medications, sarcoidosis experts have proposed modifying the treatment of sarcoidosis (9). However, these recommendations were based almost exclusively on expert opinion and extrapolation from other medical conditions because of the absence of sarcoidosis-specific outcome data concerning COVID-19 infection.

Because of the lack of specific information concerning risk of acquiring COVID-19 infection and its outcomes in sarcoidosis patients, we initiated an IRB approved questionnaire survey of sarcoidosis patients between April and July 2020 to investigate the prevalence of COVID-19 infection, clinical outcomes and possible risk factors for contracting COVID-19 in several sarcoidosis cohorts across several countries. The questionnaire was distributed through several platforms and was available in four languages: English, Dutch, Italian, and Spanish. Five versions of the questionnaire that were minimally different (vide infra) were distributed to various cohorts. One version of the questionnaire was distributed to sarcoidosis patients who participated in a previously described registry (10). In order to compare these findings with another high-risk group, we also surveyed a cohort of breast cancer patients during this time period. The results of these five questionnaires were pooled and analyzed to provide data concerning the frequency, severity, potential risk factors and outcomes for COVID-19 infection in sarcoidosis patients.

Methods

A questionnaire regarding COVID-19 infection was developed by three of the authors (RPB, EEL, and MAJ). The questionnaire was approved by the University of Cincinnati Institutional Review Board and is shown in Supplement S-1. IRB approval for the FSR questionnaire was obtained from Advarra (Columbus, MD), where the registry number for the FSR Registry is Pro00008556 and modification number for this sub-study is: MOD00087736.

The questionnaire queried whether patients had been infected with COVID-19. If infected, they were asked to provide details regarding level of care (treated at home, hospital, or intensive care unit). They were also queried concerning risk factors for COVID-19 infection including household contacts and whether they were health care providers. The patients were asked if they had underlying medical conditions associated with increased risk for COVID-19 infection. They were also asked to provide information regarding their age, sex, and self-declared race. They provided their current residence, including their state for those living in the United States. Patients with sarcoidosis were queried about the duration of disease, specific organ involvement, and current and past immunosuppressive therapy. The questionnaire responses were collected in an anonymous manner with no patient identifiers captured. At time of completing the questionnaire, patients were asked to provide consent for use of their questionnaire responses. The distribution was meant to reach as wide an audience as possible. Patients were enrolled without incentives, since the survey was anonymous. Respondents were asked to complete the questionnaire even if they did not have any symptoms related to COVID-19 infection. There was no restriction for patients to complete more than one questionnaire.

A total of five questionnaires were distributed (Supplement S-1 to S-4). Table 1 summarizes the features of the five questionnaires. All were based on the University of Cincinnati/Albany Medical Center (UC/AMC) questionnaire. The same questionnaire was distributed to those patients who were Foundation for Sarcoidosis Research (FSR) registry. The questionnaire was translated into Dutch and distributes by the Dutch Sarcoidosis Society (Sarcoidose.nl) and the ild care foundation. The Italian Asso-

Table 1. Summary of Questionnaires used in Study

Title of questionnaire	Questionnaire version	Invitation distribution	Sarcoidosis patient group	Control group	Dates of Survey	Method of capture	Comments
UC/AMC	UC/AMC English	Posted on FSR website and all patients see at Cincinnati clinic	World wide including Cincinnati OH USA	Cincinnati OH USA	4/1/2020 to 7/1/2020	REDCap	For those in USA, state also indicated
FSR	UC/AMC English	Invitation to those in FSR registry	World wide	N/A	4/6/2020 to 7/1/2020	SurveyMonkey	
Dutch	Dutch version UC/AMC	Members of Sarcoidose.nl, and advertisement at the ILD Center of Excellence, Nieuwegein, the Netherlands	Netherlands	N/A	6/29/2020 to 7/29/2020	SurveyMonkey	Collected also if on no medication for sarcoidosis and patient's BMI
Italian	Italian version of UC/AMC	e-mail contacts of the Italian Association for Sarcoidosis patients (ACSI)	Italy	N/A	4/1/2020 to 7/1/2020	Google Forms	
Spanish	Spanish version of UC/AMC	recruited through membership of the Spanish association of patients with sarcoidosis (ANES-Asociación Española de) using e-mail contact	Spain	N/A	May 2020	Google Forms	

UC/AMC: University of Cincinnati/Albany Medical Center; FSR: Foundation for Sarcoidosis Research; N/A: not available; ild care: interstial lung disease care; BMI: body mass index
REDcap: Research electronic data capture https://redcap.research.cchmc.org/
SurveyMonkey: www.surveymonkey.com
Google Forms: https://www.google.com/intl/en-US/forms/about/

ciation for Sarcoidosis patients (ACSI) prepared the Italian version of the COVID-19 questionnaire. The Spanish association of patients with sarcoidosis (ANES-Asociación Española de) prepared a Spanish version of the COVID-19 questionnaire.

Statistics

The hazard ratio (HR) with 95% confidence interval (CI) was calculated for various factors for each questionnaire using a statistical software package (MedCalc Software limited, Ostend, Belgium). For those questions which were identical (except for language), the results were summed. HR were calculated for the individual questionnaires and for summary data when available. A p value of less than 0.05 was considered significant.

Results

Supplement Figures S1-S5 show the numbers of patients who completed the questionnaire for each site, including those who did not give consent for final analysis or were excluded for other reasons. Table 2 summarizes the values for 5200 sarcoidosis patients who were analyzed. A total of 116 (2.23%) reported COVID-19 infection. The overall rate of COVID-19 infection is shown for each site and ranged from 0.8 to 4.76%. As shown in the table, there was no significant difference in the rate of infection based on sex, race, or age. In the Dutch questionnaire an additional question revealed that 96 out of 973 COVID-19 negative patients (10%) reported COVID-19 symptoms but were not tested.

The results of the individual questionnaires are provided in Supplement S5-S9. Table 3 summarizes

Table 2. Rate of COVID-19 infection for five questionnaires and total

	UC/AMC	FSR	Dutch	Italy	Spain	Total
Total number Sarcoidosis patients	1972	1616	996	511	105	5200
Number COVID positive	66	13	23	9	5	116
Rate of COVID	3.35%	0.80%	2.31%	1.76%	4.76%	2.23%
Percent COVID-19 based on gender						
Male	3.70%	0.72%	1.42%	1.44%	3.57%	2.18%
Female	3.24%	1.59%	2.98%	1.68%	5.19%	2.81%
Percent COVID-19 based on race						
Black	2.88%	3.23%	NA	NA	NA	2.95%
White	3.62%	1.15%	2.31%	1.83%	4.90%	2.66%
Mean age of patients with or without COVID-19 infection						
Age COVID-19 positive, years	54.5 ± 11.39*	54.4 ± 11.29	55.3 ± 6.0	55.8± 8.63	49.80 ± 9.20	53.5 + 9.47
Age, COVID-19 Negative, years	53.0 ± 9.60	56.6 ± 10.39	55.0±10.8	51.8 ± 9.74	44.88 ± 8.82	52.4 + 9.90
Percent COVID-19 infected versus current prednisone therapy						
Yes	3.08%	1.55%	2.02%	0.38%	4.76%	2.68%
No	3.52%	0.62%	2.38%	3.00%	4.76%	2.08%
Percent COVID-19 based on living with COVID-19 infected roommate						
Roommate COVID positive	55.3%	40.0%	26.8%	62.5%	0.0%	52.7%
No roommate with COVID	2.33%	0.68%	1.26%	0.80%	4.95%	1.53%
Percent COVID-19 based on occupation as health care provider						
Health care provider	5.74%	1.20%	3.88%	4.26%	18.75%	5.46%
Not health care provider	3.09%	0.78%	2.13%	1.52%	2.33%	2.82%

NA: not analyzed because less than 10 patients who were this race

*Mean ± standard deviation

Table 3. Hazard ratio for developing COVID-19 infection: Summary of all five questionnaires

	Percent with feature	Total pos	Total neg	Total number	Percent Pos	Hazards Ratio	95% CI	P value
Social factors								
Roommate COVID positive	**1.81%**	**39**	**55**	**94**	**41.49%**	**27.44**	**19.798-38.048**	**<0.0001**
No roommate with COVID		**77**	**5016**	**5093**	**1.51%**			
Health care provider	**8.85%**	**22**	**436**	**458**	**4.80%**	**2.41**	**1.532-3.799**	**0.0001**
Not health care provider		**94**	**4626**	**4720**	**1.99%**			
Current treatment for sarcoidosis								
Current Prednisone								
Yes	**30.93%**	**36**	**1567**	**1603**	**2.25%**	**1.02**	**0.689-1.503**	**>0.10**
No		**79**	**3501**	**3580**	**2.21%**			
If taking prednisone:								
Prednisone >10 mg or more	**22.29%**	**16**	**520**	**536**	**2.99%**	**0.98**	**0.567-1.690**	**>0.10**
Prednisone < 10 mg		**57**	**1812**	**1869**	**3.05%**			
Hydroxychloroquine								
Yes	**9.20%**	**8**	**417**	**425**	**1.88%**	**0.80**	**0.391-1.628**	**>0.10**
No		**99**	**4095**	**4184**	**2.36%**			
anti-TNF monoclonal antibodies (infliximab, adalmumab)								
Yes	**7.89%**	**8**	**389**	**397**	**2.02%**	**0.89**	**0.437-1.812**	**>0.10**
No		**105**	**4531**	**4636**	**2.26%**			
Cytotoxic (methotrexate, azathioprine, mycophenolate, leflunomide)								
Yes	**22.54%**	**27**	**1141**	**1168**	**2.31%**	**1.05**	**0.688-1.615**	**>0.10**
No		**88**	**3926**	**4014**	**2.19%**			
Rituximab								
Yes	**1.28%**	**7**	**53**	**60**	**11.67%**	**5.3993**	**2.621-11.123**	**<0.0001**
No		**100**	**4528**	**4628**	**2.16%**			
Comorbidities								
COPD								
Yes	**11.43%**	**16**	**578**	**594**	**2.69%**	**1.25**	**0.744-2.108**	**>0.10**
No		**99**	**4503**	**4602**	**2.15%**			

(continued)

Table 3 ***(continued).*** Hazard ratio for developing COVID-19 infection: Summary of all five questionnaires

	Percent with feature	Total pos	Total neg	Total number	Percent Pos	Hazards Ratio	95% CI	P value
Diabetes mellitus								
Yes	**10.25%**	**9**	**524**	**533**	**1.69%**	**0.74**	**0.375-1.445**	**>0.10**
No		**107**	**4558**	**4665**	**2.29%**			
Heart disease								
Yes	**10.40%**	**9**	**375**	**384**	**2.34%**	**1.034**	**0.522-2.048**	**>0.10**
No		**75**	**3234**	**3309**	**2.27%**			
Hypertension								
Yes	**19.62%**	**24**	**1003**	**1027**	**2.34%**	**1.07**	**0.686-1.666**	**>0.10**
No		**92**	**4115**	**4207**	**2.19%**			
Organ involvement from sarcoidosis								
Lung								
Yes	**73.09%**	**101**	**3696**	**3797**	**2.66%**	**2.48**	**1.446-4.249**	**0.001**
No		**15**	**1383**	**1398**	**1.07%**			
Cardiac								
Yes	**9.02%**	**15**	**442**	**457**	**3.28%**	**1.5**	**0.878-2.555**	**>0.10**
No		**101**	**4509**	**4610**	**2.19%**			
Neurologic								
Yes	**8.33%**	**18**	**415**	**433**	**4.16%**	**2.02**	**1.234-3.307**	**0.0052**
No		**98**	**4664**	**4762**	**2.06%**			
Demographic features								
Sex								
Male	**32.42%**	**31**	**1420**	**1451**	**2.14%**	**0.7784**	**0.518-1.117**	**>0.10**
Female		**83**	**2941**	**3024**	**2.74%**			
Race								
Black	**32.78%**	**36**	**1399**	**1435**	**2.51%**	**0.9346**	**0.633-1.379**	**>0.10**
White		**79**	**2864**	**2943**	**2.68%**			
Duration of disease								
Sarcoidosis > 5 years	**71.61%**	**75**	**2735**	**2810**	**2.67%**	**1.1012**	**0.713-1.700**	**>0.10**
Sarcoidosis < 5 years		**27**	**1087**	**1114**	**2.42%**			

†Data not available from Dutch registry
CI: confidence interval; anti-TNF: anti-tumor necrosis factor antibody; COPD: chronic obstructive pulmonary disease

the hazard ratio (HR) for developing COVID-19 for all five sites. Forty-one percent of those with a COVID-19 infected roommate had COVID-19 infection (HR=27.44 (19.798-38.048, 95% confidence intervals, p<0.0001)). We did not collect information about which person was diagnosed first with COVID-19. All but the Spanish questionnaire identified a significant increased risk for COVID-19 for those with a roommate with COVID-19. In the Spanish questionnaire, only two patients reported a COVID-19 infected roommate. Neither of these sarcoidosis patients had COVID-19 infection at the time of completing the survey.

The overall risk for health care workers to have COVID-19 infection was 2.41 (1.532-3.799, p=0.0001), with nearly five percent of heath care workers who had sarcoidosis reporting COVID-19 infection. For the Spanish questionnaire, 18.8% of heath care workers reported COVID-19 infection, while less than six percent for all other questionnaires. The HR was only significant for the UC/AMC and Spanish questionnaires.

For sarcoidosis immunosuppressive therapy, rituximab treatment was associated with an increased risk of COVID-19 infection (HR=5.40 (2.621-11.123), p<0.0001). Only the UC/AMC and FSR included more than one patient treated with rituximab. However, both of these identified an increased risk with rituximab use. There was no significant increase in risk for COVID-19 infection for those on any other immunosuppressive therapy. For those receiving prednisone, there was no increased risk for patients prescribed 10 mg or more a day versus a lower dose. A total of 425 patients were prescribed hydroxychloroquine. There was no difference in the risk for COVID-19 among the other questionnaires or for the summary data of all sarcoidosis patients compared to all others. In the Dutch questionnaire, patients who reported to receive any medication for sarcoidosis had a decreased COVID-19 risk (HR=0.40, 0.165 to 0.958, P<0.05). There was no significant difference for the larger UC/AMC questionnaire (HR=1.49, 0.916 to 2.437, p>0.10) or for the combined data.

There was no increased risk with any of the associated with age, race, sex, duration of disease, or the comorbidities investigated. In the Dutch questionnaire, there was no difference in HR for those with a BMI above 25.

There was an increased risk for sarcoidosis patients with lung involvement (HR=2.48 (1.446-4.249), p=0.001). However, the FSR was the only individual questionnaire which identified this as a significant risk. The summary identified neurosarcoidosis as an increased risk factor for COVID-19 infection (HR=2.02 (1.234-3.307), p<0.01). For neurosarcoidosis, there was a significant HR seen for the Spanish and FSR questionnaire and borderline for UC/AMC (p=0.0619).

Most patients responding to the UC/AMC questionnaire provided their country of residence or state of residence if they lived in the United States, and the percentage of patients with COVID-19 infection by residence is shown in Table S-10. There was no significant difference in rates of infections between the United States and non-United States residents. For the United States, there was a wide range but not a significantly different rate of infection between states.

For the UC/AMC questionnaire, we analyzed the risk of COVID-19 infection for two groups of patients seen by either EEL or RPB at the University of Cincinnati from April1 to June 30, 2020. During that time, 547 cancer patients were seen at University of Cincinnati (UC cancer). Two (0.37%) reported COVID-19 infection. Only 3 of 541 (0.55%) sarcoidosis patients seen at the UC sarcoidosis clinic during this time reported COVID-19 infection. The hazard ratio for COVID-19 infection in sarcoidosis patients at the University of Cincinnati was not significantly higher than those with cancer (HR=1.52, 0.254 to 9.041, P>0.10).

Outcome of COVID-19 infection

Table 4 shows the reported rate of hospitalization for those with COVID-19 infection for each questionnaire and for the total group. A mean of 15.8% (range 13 to 27%) of COVID-19 infected patients were hospitalized with about one-third cared for in the intensive care unit at some time during hospitalization.

For 105 of the COVID-19 infected patients we had information regarding current immunosuppressive therapy. Nineteen (18.1%) of these were hospitalized. Table 5 summarizes these outcomes and calculates the HR for hospitalization for various immunosuppressive therapies. There were no

Table 4. Outcome of COVID-19 infected patients

	UC/AMC	FSR	Dutch	Italy	Spain	Total
Home	57	8	20	7	4	96
Hospitalized (%)	9 (17.6%)	3 (27.3%)	3 (13.0%)	2 (22.2%)	1 (20%)	18 (15.8%)
Unknown		2				

Table 5. Outcome of sarcoidosis patients infected with COVID-19 versus immunosuppressive therapy*

DRUG	Home	Hospital	Percent in hospital	HR	95% CI	p
All patients	86	19	18.1%			
Prednisone						
Yes	29	5	14.7%	0.75	0.293-1.901	>0.10
No	57	14	19.7%			
If prednisone						
Prednisone ≥ 10 mg	13	2	13.3%	0.76	0.186-3.106	>0.10
Prednisone < 10mg	47	10	17.5%			
anti-TNF monoclonal antibodies (infliximab, adalmumab)						
Yes	5	2	28.6%	1.65	0.473-5.740	>0.10
No	81	17	17.3%			
Hydroxychloroquine						
Yes	7	1	12.5%	0.67	0.103-4.416	>0.10
No	79	18	18.6%			
Cytotoxic (methotrexate, azathioprine, mycophenolate, leflunomide)						
Yes	17	7	29.2%	1.97	0.873-4.440	>0.10
No	69	12	14.8%			
Rituximab						
Yes	6	1	14.3%	0.78	0.121-5.006	>0.10
No	80	18	18.4%			

*Data not available on all patients.
HR: hazard ratio; anti-TNF: anti-tumor necrosis factor antibody;

Table 6. Outcome of COVID-19 infection versus underlying comorbidities*

	Home	Hospital	Number pos	Rate	HR	95% CI	P
Total							
DM	9	2	11	11.46%	1.19	0.308-4.585	>0.10
no DM	72	13	85				
HTN	14	5	19	19.79%	2.03	0.784-5.234	>0.10
no HTN	67	10	77				
COPD	12	3	15	15.63%	1.35	0.432-4.217	>0.10
no COPD	69	12	81				
Heart disease	8	5	13	13.54%	3.19	1.297-7.855	0.0115
no heart disease	73	10	83				
Any feature	**35**	**7**	**42**	**43.75%**	**1.12**	**0.444-2.854**	**>0.10**
No feature	**46**	**8**	**54**				

DM: diabetes mellitus; HTN: hypertension; COPD: chronic obstructive pulmonary disease; HR hazard ratio.
*Summary data from UC/AMC, FSR, and Dutch

significant HR with any specific therapy. For the 96 COVID-19 infected patients from three questionnaires (UC/AMC, FSR, and Dutch), we were able to analyze the clinical outcome versus presence of diabetes, hypertension, COPD, and heart disease. Table 6 shows the results of this analysis. Only those with underlying heart disease had an increased rate of hospitalization (HR=3.19, 1.297-7.855, p<0.02).

Discussion

In this analysis of five surveys of sarcoidosis patients from the USA and Europe concerning COVID-19 infection, we found evidence that the rate of COVID-19 infection in sarcoidosis patients was higher than in the general population. We found that sarcoidosis patients who were healthcare workers or were living with a person infected with COVID were at higher risk of COVID infection; these data have been reported in the general population (12;13) and support the well-established fact that COVID-19 is highly infectious and is easily transmitted to individuals who are in close proximity to an actively infected person (14). In regard to immunosuppressive therapy, only rituximab was associated with increased risk for COVID-19 infection in sarcoidosis patients. The lack of association of prednisone use with the development of COVID-19 infection held even when comparing ≥ 10 versus < 10 mg/day. In sarcoidosis patients with diabetes, hypertension, heart disease, and co-existing chronic obstructive pulmonary disease no increased risk of acquiring COVID-19 infection was identified, even though these comorbidities have also been identified as risk factors for COVID-19 infection (6;8;15).

The current data surveyed sarcoidosis patients mostly in United States and Europe from April through July 2020. This time frame co-indices with the onset of the pandemic in these two parts of the world. In our analysis of a questionnaire administered to 5200 sarcoidosis patients, 2.23% or 22,308 cases per million had become infected with COVID-19 during this time. During the time period in which this questionnaire was administered, the number of confirmed cases of COVID-19 in the United States was estimated as 1,060 per million (https://en.wikipedia.org/wiki/Template:COVID-19_pandemic_data/United_States_medical_cases). The same site reported that the cumulative rate of COVID-19 infection in Spain was 5197 per 1 million, Italy 3853 per 1 million, and Netherlands 3141 per 1 million. How-

ever, the rate of infection for COVID-19 infection in the general population may be higher. For example, a recent survey using serologic testing found that 2.5% of the Italian population had acquired COVID-19 infection by July 15, 2020 (http://www.salute.gov.it/imgs/C_17_notizie_4998_0_file.pdf). While there was some variation in the rates of COVID-19 infection from the various questionnaires, overall there was no significant difference in the rate of COVID-19 infection. This was also true when examining the UC/AMC questionnaire, which included 1601 (3.1% infected) responders from US versus 361 (4.2% infected) from outside the United States.

These data suggest that the rate of COVID infection is higher in sarcoidosis patients than the general population. However, the rate of COVID-19 infection varies by the time period as well as from country to country and even within the United States. It is therefore possible, that the rate of COVID-19 in sarcoidosis patients was no different from the general population. A significant number of the sarcoidosis patients completing the UC/AMC questionnaire were seen at the University of Cincinnati Sarcoidosis Clinic, which is in southwestern Ohio. As of July 1, 2020, the reported cumulative rate of COVID-19 infection for this area was 5103 per 1 million (https://coronavirus.ohio.gov/wps/portal/gov/covid-19/dashboards/overview). This is similar to the rate of 5545 per 1 million for our sarcoidosis patients and 3656 per 1 million for the cancer patients. The lower rate of COVID-19 infections for sarcoidosis patient at University of Cincinnati clinic versus other patients completing the questionnaires may be due to lower overall rate of COVID-19 infection in the area and/or the more rigorous criteria for diagnosis, since at our clinic we required verification by culture. This criterion may underestimate the number of cases of COVID-19 infection (16). The hospitalization rates for COVID-19 may be more accurate, since such cases are usually confirmed by cultures.

For sarcoidosis patients, we identified five features associated with increased for COVID-19 infection. Sarcoidosis patients with a COVID-19 infected roommate had a greater than 20-fold increased risk for COVID-19 infection. In one meta-analysis, the risk of in home transmission of disease has been estimated as ten-fold (17). There was also a nearly two-fold increased risk for sarcoidosis patients who were health care workers. This increased risk has been noted for some time (12). The higher risk in Spain may be a reflection that some areas were hit sooner than other parts of the world. The widespread use of N-95 and other respiratory policies later in the pandemic and in other parts of the world may have blunted this risk factor (13;18). Comorbidities in sarcoidosis include diabetes, hypertension, heart disease, and co-existing chronic obstructive pulmonary disease (10;19). These have also been identified as risk factors for COVID-19 infection and more severe disease (2;6;8;15). However, in the current study, none of these was associated with an increased risk for infection.

In regards to immunosuppression therapy, only rituximab was associated with increased risk for COVID-19 infection for sarcoidosis patients. This is not surprising, since rituximab has been noted to have increased the risk for acquiring viral infections (20). In addition, viral infections are more severe when patients are receiving rituximab. We studied only seven patients with COVID-19 infection treated with rituximab.

Sarcoidosis is a multi-organ disease and the effect of sarcoidosis on different organs may affect the patient's ability to avoid COVID-19 infection. In this study, we found that patients with lung or neurologic involvement were at increased risk for COVID-19 infection. Chronic lung disease has been identified as a risk factor for infection and more severe disease (21).

In terms of the outcomes of COVID-19 infected sarcoidosis patients, we found that less than twenty percent required hospitalization. In a recent, retrospective study of 37 sarcoidosis patients with COVID-19 infection, the rate of hospitalization for infection was 60% and no different from the non-sarcoidosis patients seen at that center (3). However, the rate of adverse outcome as defined by requiring intubation and/or mortality was significantly higher than the non-sarcoidosis patients (3). The current study would have missed the very severe cases, at least the ones who died, as it was a study analyzing a self-reported questionnaire. In our study, the use of immunosuppressive therapy was not associated with a significant increased risk for hospitalization. The overall outcome of these patients appears more favorable than that reported in rheumatoid arthritis patients treated with immunosuppression (22-24). In one study (23), the use of $\geq$ 10 mg per day

of prednisone or its equivalent was associated with increased risk. That study analyzed 600 COVID-19 infected patients and our study may have been underpowered to detect that difference. Interestingly, that study found that anti-TNF therapy was associated with a significantly lower risk for COVID-19 infection (23).

Hydroxychloroquine has been proposed as a potential therapy for patients with COVID-19 infection and ongoing studies are evaluating this drug (25). Over 400 of our sarcoidosis patients were receiving hydroxychloroquine at time of survey. There was no change in the rate of infection or rate of hospitalization for the seven patients who developed COVID-19 infection while on hydroxychloroquine. This has also been noted in a study of patients treated with hydroxychloroquine for various rheumatologic conditions (23).

Several comorbidities have been associated with a worse clinical outcome from COVID-19 infection (7;8;21;23). We were able to analyze the outcome of 96 sarcoidosis patients with COVID-19 infection and reported comorbidities. Underlying heart disease was associated with an increased risk for hospitalization. Other comorbidities examined included diabetes, COPD, and hypertension were not felt to be significant risk factors.

There are several limitations to our study. The questionnaire did not try to quantitate severity of disease, especially significant pulmonary fibrosis. Therefore, we could not comment on impact of severe lung disease on risk or outcome of COVID-19 infection. Because of the low number of incident cases, we may have been underpowered to detect smaller, but significant risk factors including comorbidities and the impact of immunosuppression therapy. The questionnaires were completed by the patients, usually on-line. With the exception of those seen at the University of Cincinnati, there was no attempt to verify COVID-19 infection. Patients who had severe disease or even died would be unlikely to be able to complete the questionnaire, so this group was underrepresented. Also, the rate of COVID-19 infection in sarcoidosis patients varies based on local conditions and time into the pandemic. The rate of COVID-19 infection in the general population during the study period may be better understood over time, especially as serologic testing becomes more widely used. However, the rate of infection for COVID-19 infection in the general population may be higher. We compared our results to a standard reporting site which provided cumulative rates for various parts of the world. In the sub-study at University of Cincinnati, the rate of infection was not significantly different from cancer patients seen at the same time period. Future reports may provide a better understanding of the rate of COVID-19 infection in the community studied. Future rates may be affected as vaccines become available. Vaccines for other conditions have proved to be effective in preventing infections in sarcoidosis patients (26).

In summary, our data suggests an increased rate of COVID-19 infection in sarcoidosis patients. However, when compared to non-sarcoidosis patients in the same area and time of the study, the rate of COVID-19 infection was not significantly different. The most obvious risk factor for COVID-19 infection was having a roommate with COVID-19. This means that hygiene measures and distancing are extremely important at home as well as in public. To facilitate research on prevalence and risk factors of COVID-19 infection in chronic diseases, sarcoidosis specifically, it would be helpful to report in population registries not only numbers of patients with COVID-19, but also their characteristics, such as comorbidities and medication use.

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