



Moderate or Severe Impairment in Pulmonary Function is Associated with Mortality in Sarcoidosis Patients Infected with SARS-CoV-2

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Abstract

Purpose To investigate whether sarcoidosis patients infected with SARS-CoV-2 are at risk for adverse disease outcomes.

Study Design and Methods This retrospective study was conducted in five hospitals within the Mount Sinai Health System during March 1, 2020 to July 29, 2020. All patients diagnosed with COVID-19 were included in the study. We identified sarcoidosis patients who met diagnostic criteria for sarcoidosis according to accepted guidelines. An adverse disease outcome was defined as the presence of intubation and mechanical ventilation or in-hospital mortality. In sarcoidosis patients, we reported (when available) the results of pulmonary function testing measured within 3 years prior to the time of SARS-CoV-2 infection. A multivariable logistic regression model was used to generate an adjusted odds ratio (aOR) to evaluate sarcoidosis as a risk factor for an adverse outcome. The same model was used to analyze sarcoidosis patients with moderate and/or severe impairment in pulmonary function.

Results The study included 7337 patients, 37 of whom (0.5%) had sarcoidosis. The crude rate of developing an adverse outcome was significantly higher in patients with moderately and/or severely impaired pulmonary function (9/14 vs. 3/23, $p = 0.003$). While the diagnosis of sarcoidosis was not independently associated with risk of an adverse event, (aOR 1.8, 95% CI 0.9–3.6), the diagnosis of sarcoidosis in patients with moderately and/or severely impaired pulmonary function was associated with an adverse outcome (aOR 7.8, 95% CI 2.4–25.8).

Conclusion Moderate or severe impairment in pulmonary function is associated with mortality in sarcoidosis patients infected with SARS-CoV-2.

Keywords COVID-19 · Sarcoidosis · Pulmonary sarcoidosis · Pulmonary function tests

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Introduction

Sarcoidosis is a systemic inflammatory disease that can affect any organ within the body. Approximately 90% of sarcoidosis patients exhibit involvement of the lungs and nearly all patients manifest involvement of disease in more than one organ. Approximately one-third of patients suffer from chronic disease. The majority of these patients require treatment with immunosuppressive therapies, such as prednisone. In 2010, the peak age at incidence of sarcoidosis was 50 to 69 years in women and 40 to 59 years in men [1].

The 2019–20 coronavirus pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Published data suggest that a majority of coronavirus disease 2019 (COVID-19) deaths have occurred among adults aged ≥ 60 years and among persons with serious underlying conditions [2–4]. These outcome data prompted us to ask whether sarcoidosis is an underlying condition that

predisposes patients infected with SARS-CoV-2 to adverse disease outcomes.

In this retrospective study, we sought to determine whether (1) the rate of intubation or in-hospital mortality in sarcoidosis patients with COVID-19 is increased compared to those without sarcoidosis and (2) whether various comorbid illnesses and/or clinical factors are associated with higher rates of intubation or in-hospital mortality in sarcoidosis patients with COVID.

Methods

Study Design

The study was approved by the IRB of the Mount Sinai Hospital (Protocol: IRB-20-03537) prior to data collection. Informed consent was waived by the IRB committee.

We conducted a multicenter retrospective study in five hospitals within the Mount Sinai Health System (Mount Sinai Hospital, Mount Sinai Brooklyn, Mount Sinai Queens, Mount Sinai Morningside and Mount Sinai West) during the period of March 1, 2020 to July 29, 2020.

All patients who tested positive for SARS-CoV-2 were included in the study. The diagnosis of COVID-19 was performed using real-time reverse transcription polymerase chain reaction (rRT-PICR) by nasopharyngeal swab. Selected sarcoidosis patients met diagnostic criteria for sarcoidosis according to the guidelines of the American Thoracic Society/European Respiratory Society (ERS)/World Association of Sarcoidosis and Other Granulomatous Diseases [5]. Organ involvement was defined according to the WASOG Sarcoidosis Organ Assessment Tool [5]. Among 37 patients with sarcoidosis, 13 were diagnosed with COVID-19 at Hospitals affiliated with Mount Sinai, other hospitals or an urgent care facility.

Data were retrieved from the electronic health record (Epic, Epic Systems Corporation, Verona WI). Demographics collected included age, sex and race. The presence of specific comorbid illnesses (Coronary Artery Disease, Congestive Heart Failure, Diabetes Mellitus, Hypertension, Chronic Kidney Disease, Chronic Obstructive Pulmonary Disease, Asthma, Obesity, Cancer and Smoking) was recorded from the medical records. Race was self-reported. Obesity was defined as body mass index (BMI) over 30 kg/m². Smoking history was defined as past or present smoking. Recorded outcome data included the presence of intubation and mechanical ventilation or in-hospital mortality.

The type and dose of systemic anti-inflammatory medication at the time of SARS-CoV-2 infection were recorded. When available, the results of pulmonary function testing measured within 6 months and 3 years from the time of SARS-CoV-2 infection were also extracted for analysis.

Pulmonary function was measured using two different reference standards (National Health and Nutrition Examination Survey III [6] and Global Lung Function Initiative [7]).

Statistical Analysis

Our exposure was sarcoidosis status, and our primary outcome was severe COVID-19 course which was defined as either intubation and mechanical ventilation or in-hospital mortality.

Using univariable analysis, we compared different demographics and comorbidities between sarcoidosis and non-sarcoidosis patients. We used the Mann Whitney U-test and Fisher's exact test to evaluate continuous and categorical variables, respectively.

A multivariable logistic regression model was used to generate an adjusted odds ratio (aOR) to evaluate sarcoidosis as a risk factor for an adverse outcome. The model was also adjusted for risk factors (demographics and comorbidities) known to associate with adverse outcomes related to COVID-19. We used the same model to analyze sarcoidosis patients with moderately and/or severely impaired pulmonary function, but did not use this model to analyze immunosuppressive medications. A correlation matrix was constructed to assess the possible collinearity between covariates in the models. Adjusted odds ratios (aOR) with 95% confidence intervals (CI) are reported. All analyses were performed with Python (Python software foundation, version 3.6.5). A two-sided *p* value < 0.05 was considered statistically significant.

Results

We identified 7337 patients who met inclusion criteria, 37 of whom (0.5%) had known sarcoidosis. The characteristics of the entire study cohort (*N* = 7337) are presented in Table 1.

The rate of admission was not significantly different between sarcoidosis and non-sarcoidosis patients (59.5% vs. 68.5%, *p* = 0.286). The crude mortality rate was lower in sarcoidosis patients, compared to control subjects but the finding was not statistically significant (16.2% vs. 20.6%, *p* = 0.683). The rates of intubation and mechanical ventilation were higher in sarcoidosis patients, though not significantly (24.3% vs. 15.8%, *p* = 0.172).

With respect to COVID-19 patients without sarcoidosis, COVID-19 patients with sarcoidosis were significantly more likely to be of African American race, past or present smokers and obese. Sarcoidosis patients were also more likely to have COPD.

The clinical characteristics of the sarcoidosis patients and their systemic anti-inflammatory medications at the time of SARS-CoV-2 infection, are listed in Supplementary

Table 1 Characteristics of the entire study cohort ($N=7337$)

	Sarcoidosis patients ($n=37$, 0.5%)	Non-sarcoidosis patients ($n=7300$, 99.5%)	<i>p</i> value
Demographics			
Age, median (IQR), year	55.0 (50.0–65.0)	62.0 (48.0–74.0)	0.038
Male, <i>N</i> (%)	16 (43.2)	4054 (55.5)	0.139
African American, <i>N</i> (%)	24 (64.9)	1891 (25.9)	<0.001
Caucassians, <i>N</i> (%)	4 (10.8)	1720 (23.6)	0.367
Comorbidities			
CAD, <i>N</i> (%)	4 (10.8)	1205 (16.5)	0.504
CHF, <i>N</i> (%)	7 (18.9)	778 (10.7)	0.109
DM, <i>N</i> (%)	14 (37.8)	2739 (37.5)	1.000
HTN, <i>N</i> (%)	20 (54.1)	4080 (55.9)	0.869
CKD, <i>N</i> (%)	5 (13.5)	1073 (14.7)	1.000
COPD, <i>N</i> (%)	8 (21.6)	518 (7.1)	0.004
Asthma, <i>N</i> (%)	7 (18.9)	934 (12.8)	0.318
Obesity, <i>N</i> (%)	20 (54.1)	1973 (27.0)	<0.001
BMI, median (IQR)	30.6 (25.4–35.6)	27.4 (23.8–32.3)	0.017
Cancer, <i>N</i> (%)	5 (13.5)	895 (12.3)	0.800
Smoking, <i>N</i> (%)	16 (43.2)	1485 (20.3)	0.002
Outcomes			
Admitted, <i>N</i> (%)	22 (59.5)	5002 (68.5)	0.286
Mortality, <i>N</i> (%)	6 (16.2)	1502 (20.6)	0.683
Intubation and MV, <i>N</i> (%)	9 (24.3)	1150 (15.8)	0.172
Mortality/intubation and MV, <i>N</i> (%)	12 (32.4)	1816 (24.9)	0.339

HTN hypertension, CAD coronary artery disease, DM diabetes mellitus, CHF congestive heart failure, CKD chronic kidney disease, COPD chronic obstructive pulmonary disease, BMI body mass index

Table S1. With respect to organ involvement, 35/37 (95.0%) of patients exhibited involvement of the lungs and 13/37 (35.1%) manifested cutaneous sarcoidosis (excluding Erythema Nodosum).

Slightly more than one half (51.4%) of the sarcoidosis patients were taking one or more systemic anti-inflammatory medications at the time of their infection. Indeed, 11/37 (29.7%) patients were taking prednisone. Treatment was indicated for active pulmonary sarcoidosis in 8 patients (21.6%) and active cutaneous sarcoidosis in 6 patients (16.2%).

There were 24 patients (64.9%) who underwent pulmonary function testing within 6 months of infection. In addition, 31 (83.9%) patients underwent spirometry and 29 (78.4%) patients underwent diffusing capacity within 3 years of infection.

The crude rate of developing an adverse outcome (mortality and the need for mechanical ventilation) from SARS-CoV-2 infection was significantly higher in patients with moderate and/or severe impairment in pulmonary function (Supplementary Table S2). Whereas 9/14 (64.3%) patients with moderately and/or severely reduced spirometry or diffusing capacity developed an adverse outcome, only 3/23 (13.0%) without these physiologic deficits developed an adverse outcome ($p=0.003$).

Multivariable analysis (Table 2), of SARS-CoV-2-infected patients with and without sarcoidosis, revealed age, male sex, cardiovascular disease, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease and obesity to be risk factors for intubation and mechanical ventilation or in-hospital mortality. The diagnosis of sarcoidosis was not associated with intubation and mechanical ventilation or in-hospital mortality (aOR 1.8, 95% CI 0.9–3.8), but the diagnosis of sarcoidosis in patients with moderately and/or severely impaired pulmonary function was associated with this adverse outcome (aOR 7.8, 95% CI 2.4–25.8).

Discussion

This retrospective study is the first to evaluate sarcoidosis patients infected with SARS-CoV-2. Our results did not show a significant association between sarcoidosis and mortality. Yet, the risk of intubation and mechanical ventilation or in-hospital mortality was highest in patients with moderately and/or severely impaired pulmonary function (aOR 7.8). Interestingly, we were unable to identify in any other COVID-19 studies, data that correlate severity in pulmonary function with adverse COVID-19 outcomes.

Table 2 Multivariable analysis for mortality related to COVID-19 infection

Feature	aOR	95% CI	p value
(a)			
Age decile	1.6	1.5–1.7	<0.001
Male sex	1.4	1.2–1.6	<0.001
CVD	1.3	1.1–1.5	<0.001
DM	1.5	1.3–1.7	<0.001
CKD	1.9	1.6–2.2	<0.001
COPD	1.6	1.3–2.0	<0.001
Cancer	1.1	1.0–1.3	0.116
Obesity	1.5	1.3–1.7	<0.001
Smoking	0.8	0.7–0.9	0.004
Sarcoidosis	1.8	0.9–3.8	0.107
(b)			
Age decile	1.6	1.5–1.7	<0.001
Male sex	1.4	1.2–1.6	<0.001
CVD	1.3	1.1–1.5	<0.001
DM	1.5	1.3–1.7	<0.001
CKD	1.9	1.6–2.2	<0.001
COPD	1.6	1.3–1.9	<0.001
Cancer	1.1	1.0–1.3	0.104
Obesity	1.5	1.4–1.8	<0.001
Smoking	0.8	0.7–0.9	0.003
Sarcoidosis with moderate or severe abnormalities in pulmonary function	7.8	2.4–25.8	0.001

The model was adjusted for risk factors known to associate with adverse outcomes related to COVID-19 infection and for sarcoidosis (a) or sarcoidosis accompanied by moderate or severe abnormalities in pulmonary function (b). The dependent variable for an adverse outcome is death or intubation and mechanical ventilation.

aOR adjusted odds ratio, CI confidence interval, CVD cardiovascular disease, DM diabetes mellitus, CKD chronic kidney disease, COPD chronic obstructive pulmonary disease

In keeping with previous studies, [2–4] age, male sex, cardiovascular disease, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease and obesity were risk factors for intubation and mechanical ventilation or in-hospital mortality.

While it is not surprising that 95% of the sarcoidosis patients exhibited lung involvement, [8] it is intriguing that 35.1% of these patients manifested skin disease (excluding Erythema Nodosum). The scientific rationale for this finding is unclear. The finding may reflect that the Mount Sinai Health System is a tertiary referral center for sarcoidosis patients, most of whom suffer from chronic manifestations of disease, such as those in the skin.

Interestingly, nearly one half (48.6%) of the sarcoidosis patients were not taking systemic anti-inflammatory therapy at the time of their infection. Of the 19 patients who were receiving these medications, 29.7% were taking a daily dose

of prednisone of ≤ 15 mg and 5 were taking a weekly dose of methotrexate (≤ 15 mg). Among the remaining 3 patients, one was taking Mycophenolate, Azathioprine and Infliximab (5 mg/kg every 6 weeks), respectively.

Unfortunately, our study was underpowered to determine whether the use of systemic anti-inflammatory therapies, which were received at the time of infection, was associated with an adverse outcome. It is remarkable to note, however, that the sarcoidosis cohort consisted of patients who were not our most clinically complex/severe or chronically ill patients. Only 9 patients were being treated for active pulmonary sarcoidosis and 14/37 (37.8%) demonstrated impaired pulmonary function. Similarly, only 4 patients exhibited cardiac involvement. Typically, cardiac sarcoidosis is treated with moderate or high doses of systemic anti-inflammatory therapy [9–12]. It is reasonable to hypothesize that treatment with higher doses of these therapies may predispose patients to infection with SARS-CoV-2.

There are several limitations to our study. First, it is a retrospective study and, therefore, subject to selection bias. The number of patients with sarcoidosis was small. As a result, it is debatable whether our conclusions may be generalizable to all sarcoidosis patients. While sarcoidosis is a rare disease, we expected that our cohort would be larger [13]. The small size of our cohort could be attributed to several factors. It is conceivable that sarcoidosis, which is characterized by a hyperimmune, highly polarized Th1 response, may protect against the development of COVID-19. Alternatively, sarcoidosis patients, many of whom are medically underserved, did not have adequate access to COVID testing [14]. Additional studies are needed to explore these hypotheses.

Our study is also hindered by missing pulmonary function data. Most of the sarcoidosis patients received their diagnosis more than 10 years prior to the diagnosis of COVID and, therefore, did not regularly undergo pulmonary function testing before the SARS-CoV-2 infection. Finally, the absence of pulmonary function data diminished the statistical power needed to precisely determine whether an adverse outcome was associated with moderate or severe deficits in obstruction, restriction and/or gas exchange.

These limitations notwithstanding, our study is the first to evaluate sarcoidosis patients infected with SARS-CoV-2. It confirms that sarcoidosis patients with COVID-19 are more likely to require mechanical ventilation and die if they have pre-existing moderate and/or severe impairment in pulmonary function. The results of our study may provide a foundation for future prospective studies, which further examine outcomes in sarcoidosis patients infected with SARS-CoV-2.

Author Contributions AM and EK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. AM, ML, RF, DR, EK—Concept and

design. All authors—Acquisition, analysis, or interpretation of data. AM, EK—Drafting of the manuscript. All authors—Critical revision of the manuscript for important intellectual content. EK—Statistical analysis. All authors—Administrative, technical, or material support. All authors—Approval of final draft.

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Compliance with Ethical Standards

Conflict of interest Adam S. Morgenthau, Matthew A Levin, Robert Freeman, David L. Reich, and Eyal Klang have no relevant conflict of interest.

Ethical Approval The study was approved by the IRB of the Mount Sinai Hospital (Protocol: IRB-20-03537) prior to data collection. Informed consent was waived by the IRB committee.

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