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Prevalence of SARS-COV-2 infection and outcomes in Greek sarcoidosis patients

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Abstract. *Background and aim:* There is limited data on the prevalence of SARS-COV-2 in sarcoidosis patients and the underlying parameters linked to severity. We aimed to conduct a national multicenter study to explore the prevalence of SARS-COV-2 in sarcoidosis patients and investigate its impact on hospitalization and infection rates, describe the characteristics of the infected population and assess the role of these characteristics in determining the likelihood of infection or hospitalization. *Methods:* We recruited all the adult sarcoidosis patients with who were examined across eight Greek Health Interstitial Lung Disease Referral Centers from the beginning of the pandemic until August 1, 2022. All the data was collected using structured questionnaires. *Results:* 530 sarcoidosis patients with a mean age of 54±12 years, 60% of whom were females, were recruited. 43% of them were under corticosteroid treatment, and 39% were under additional immunosuppression. 18% of Greek sarcoidosis patients were infected by the virus, which is a lower rate than the general population. The infection was mainly mild. Only one-fifth of the infected sarcoidosis patients required hospitalization, and no deaths or ICU admissions were recorded. Vaccination was found to be associated with a reduced likelihood of infection. Younger age, a longer period since diagnosis, abnormal PET-CT findings, and immunosuppression were associated with an increased probability of infection. *Conclusions:* The COVID-19 infection rate among Greek sarcoidosis patients was lower than the general population. Fewer than 20% needed hospitalization. There were no deaths or ICU admissions. Vaccination reduces the likelihood of infection. Younger age, longer diagnosis, abnormal PET-CT findings, and immunosuppression increased the chance of infection.

Key words: hospitalization, sarcoidosis, SARS-COV-2

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Introduction

Since its declaration by the World Health Organization (WHO) on March 11, 2020, the coronavirus disease 2019 (COVID-19) pandemic has become the fifth pandemic to hit the world since the 1918-1920 flu pandemic (1). SARS-CoV-2 can be transmitted easily through direct, indirect, or close contact with infected individuals, as well as through infected secretions like saliva and respiratory secretions (1). The severity of symptoms for those infected with SARS-CoV-2 can vary widely, from no symptoms to severe illness (1). Elderly individuals and those with chronic respiratory diseases are more susceptible to developing severe symptoms (1-3). This pandemic has brought to light the potential risks faced by patients with sarcoidosis. Sarcoidosis can be a debilitating and life-altering disease that affects multiple organs in the body, constituting mainly a lung-dominant condition. The formation of small lumps of cells, called granulomas, can cause damage to vital organs such as the heart and central nervous system (1,4). While the exact cause is still unknown, it is important to recognize the potential severity of this disease. Researchers have found that factors such as race, age, and gender can contribute to its prevalence and incidence rates (5). Arkemat et al. reported higher prevalence and incidence rates in Canada (143/100.00 and 6.8/100.000/year, respectively) and lower in Belgium (2/100.000 and 0.3/100.000/year, respectively) (5). The variation in recorded characteristics across datasets and the different data analysis methods used are the most important causes of its epidemiological variation (5). Recent research has suggested that sarcoidosis may be triggered by infectious pathogens. Mycobacterium spp. and Propionibacterium acnes are the most implicated organisms (6), while viral infections such as those caused by herpes viruses have also been proposed as a possible initiating factor (7). Using metagenomic sequencing, researchers have identified possible infectious causes in half of the ocular and periocular sarcoidosis cases they analyzed (8). However, there are only a few studies that directly demonstrate the effects of these pathogens on the development of granulomas in humans (6,9). The COVID-19 pandemic has raised concerns about its impact on patients with sarcoidosis. Evidence suggests that COVID-19 can lead to a dysregulation of the immune system, potentially generating autoimmune phenomena (10). At the same time, patients with sarcoidosis may be more susceptible to COVID-19 pneumonia due to underlying lung disease and chronic immunosuppressive treatment (11). However, contradictory data exist regarding the rates of infection between the sarcoidosis group and the general population (12). It remains unclear whether certain clinical parameters increase the vulnerability of severe respiratory viral illness and hospitalization (11-15). It has been reported that patients with moderate to severe impaired pulmonary function, pulmonary fibrosis, cardiac involvement, and/or comorbidities, which are more prevalent in the sarcoidosis population, are at an increased risk of adverse outcomes and mortality due to COVID-19 (13-15). Medical treatment with corticosteroids may also delay viral clearance, but additional follow-up of these patients is needed to determine the accurate results (16). Furthermore, there have been reports of SARS-COV-2 being related to the onset or re-exacerbation of sarcoidosis (17,18). Given the potential impact of COVID-19 on sarcoidosis, it is crucial that these individuals take necessary precautions and closely monitor their health during the pandemic. In Greece, sarcoidosis is the most common interstitial lung disease, accounting for 34% of ILD cases, with an annual incidence rate of 1.07 cases per 100,000 (19). However, there is limited data on the prevalence of SARS-COV-2 in sarcoidosis patients globally, as well as on the underlying clinical parameters linked to severity. To address this gap, a study was conducted to investigate the prevalence of COVID-19 infection and outcomes in Greek sarcoidosis patients, describe the characteristics of the infected population, and assess the effects of these characteristics on the likelihood of infection or hospitalization. The findings of this study will help inform strategies to better protect patients with sarcoidosis during the COVID-19 pandemic and improve their clinical outcomes.

Methods

Study population

This was a national multicenter retrospective study conducted on adult patients (18 years of age or older) who had a pre-existing diagnosis of sarcoidosis. The study was conducted across eight Greek Health Interstitial Lung Disease Referral Centers, which included the Department of Respiratory Medicine at the University of Thessaly, the Department of

Internal and Respiratory Medicine at the University Hospital of Patras, the 7th Academic Department of Respiratory Medicine "SOTIRIA" General Hospital, the 2nd Academic Department of Respiratory Medicine "ATTIKON" General Hospital at the National and Kapodistrian University of Athens, the Department of Respiratory Medicine of the "G. PAPANIKOLAOU" General Hospital at the Aristotle University of Thessaloniki, the Department of Respiratory Medicine at the University of Crete, the Department of Respiratory Medicine of the General Hospital of Corfu, and the Department of Respiratory Medicine of the University General Hospital of Alexandroupolis. The specialists collected all epidemiological data retrospectively from March 2020, coinciding with the declaration of the COVID-19 pandemic by the World Health Organization, and continued until August 1, 2022. The data collected using structured questionnaires included demographics, time from first diagnosis of sarcoidosis, imaging, lung function tests, the treatment received for sarcoidosis, oral corticosteroid dosages, previous vaccination against SARS-COV-2 and vaccine dosages, as well as COVID-19 infection history, hospitalization history, and outcomes. Informed consent was obtained from all study participants, according to the Helsinki Declaration. The protocol was approved by the Larissa University Hospital Ethics Committee (approval number: 48841/25/10/2019).

Statistical analysis

To analyze the data, the Kolmogorov-Smirnov test was used to determine whether a continuous variable was normally or non-normally distributed. Normally distributed continuous indices were compared with Student's t-test or one-way ANOVA. Non-normally distributed variables were compared using the Mann-Whitney-U and Wilcoxon or Kruskal-Wallis tests. The Pearson's chi-squared test was used to identify whether there was a statistically significant difference between frequencies. Additionally, a binary logistic regression was used to ascertain the effects of age, gender, current smoking, OCS treatment, immunosuppression treatment, imaging, previous vaccination, and number of dosages on the likelihood that participants getting infected with SARS-COV-2 or being hospitalized due to COVID-19. Moreover, to account for the variation in COVID-19 treatment strategies over time, the period of infection for each patient was recorded and included as a covariate in the outcome analysis model. This allowed us to assess the impact of changes in treatment practices, such as the use of high-dose steroid therapy and non-invasive ventilation, on patient outcomes. The data were analyzed using SPSS (IBM SPSS statistics version 25).

Results

The study population consisted of 530 patients with sarcoidosis who were examined in the eight Greek Health Interstitial Lung Disease Referral Centers from the beginning of the pandemic until August 1, 2022. Of these patients, 18% (95/530) were infected with SARS-COV-2. All the infected patients were fully recorded. Unfortunately, only 87 non-infected sarcoidosis patients were included in the study, had fully documented, and used as controls. Table 1 presents the main characteristics of sarcoidosis patients and comparisons between genders. The mean age of the study population was 54.2±12.1 years, and 60% of the participants were females. Males were significantly younger than females, with a mean age of 51.7±11.7 years compared to 55.8±12.1 years for females (p=0.026). Among the participants, 54.4% had never smoked, while 12.1% were current smokers. Males were more likely than females to be ever smokers (Table 1). Additionally, males had significantly less FVC% than females (Table 1). Furthermore, 91% of the study population had abnormal chest computed tomography scan findings, and 45% had positive extrathoracic sites of active sarcoidosis on PET-CT. Of the whole participants, 43% (78/182) received corticosteroids as symptom-driven treatment for sarcoidosis of whom 60% (47/78) received prednisolone above 5 mg/day. 39% of the total population (70/182) received additional immunosuppression for the same reason. Moreover, 82% of the (149/182) patients had been previously vaccinated with at least one dosage of a COVID-19 vaccine, with 89% (133/149) receiving the Pfizer vaccine. 73% of the population were vaccinated with more than two dosages.

Table 2 shows a comparison between Sarcoidosis patients who were infected and those who were not. Infected patients had a significantly longer time since their first diagnosis, more frequent abnormal chest scan findings, and positive extrathoracic PET-CT findings, received more frequently

Table 1. The main characteristics of the sarcoidosis patients and comparisons by genders (N=182).

Parameters	Study population (N=182)	Females (n=109)	Males (n=73)	p-value
Age (years)	54.2±12.1	55.8±12.1	51.7±11.7	0.026
Current smokers, n (%)	22 (12)	13 (11)	9 (12)	0.555
Ever-smokers, n (%)	64 (35)	29 (27)	35 (48)	0.003
Nonsmokers, n (%)	99 (54)	70 (64)	29 (40)	0.001
FVC% of predicted	97±19	101±18	90±19	<0.001
DLCO% of predicted	72±30	79±17	80±22	0.813
Time from first diagnosis (years)	6±4	6±4	7±6	0.124
Abnormal findings in chest CT, n (%)	166 (91)	99 (91)	67 (92)	0.523
Abnormal extrathoracic PET-CT, n (%)	82 (45)	51 (47)	31 (42)	0.337
Under any treatment, n (%)	100 (55)	62 (57)	38 (52)	0.386
Under oral corticosteroid treatment, n (%)	78 (43)	47 (43)	31 (43)	0.532
Mean dosage of prednisolone (mg)	10±5	10±6	10±7	0.888
Mean dosage of prednisolone (mg) <5mg	31 (17)	19 (17)	12 (16)	0.393
Mean dosage of prednisolone (mg) >5mg	47 (26)	27 (25)	20 (27)	0.393
Immunosuppression, n (%)	70 (39)	44 (40)	26 (36)	0.374
Vaccination against SARS-COV-2, n (%)	149 (82)	86 (79)	63 (86)	0.285
Pfizer, n (%)	133 (73)	73 (67)	60 (82)	0.397
AstraZeneca, n (%)	18 (10)	11 (10)	7 (10)	0.428
Moderna/Johnson, n (%)	14 (8)	6 (6)	8 (11)	0.473
More than 2 dosages, n (%)	133 (73)	76 (70)	57 (78)	0.047
More than 2 vaccines, n (%)	16 (9)	4 (4)	12 (16)	0.060

Note: Data are expressed as mean ± SD or as frequencies (percentages).
Abbreviations: CT, Computed Tomography; DLCO, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; PET-CT, Positron Emission Tomography and Computed Tomography; SARS-COV-2, severe acute respiratory syndrome Coronavirus 2

immunosuppression treatment than non-infected patients. They were also less frequently vaccinated in comparison to non-infected patients.

Table 3 provides information on the outcomes of infected Sarcoidosis patients. Among those infected, 76 patients, which account for 80% of the total, received treatment at home, without any significant difference between genders. 19 patients, which account for 20% of the total, were hospitalized in a COVID-19 clinic, again without any significant difference between genders. None of the patients required hospitalization in the intensive care unit (ICU), and there were no recorded deaths. Out of the total 95 infected Sarcoidosis patients, 72% fully recovered without experiencing any Sarcoidosis relapse, 10% reported feeling better during the post-hospitalization period, and 9% of the patients continued to experience symptoms for a long time after their recovery.

To determine the effects of various factors on the likelihood of participants being infected with SARS-COV-2, a backward stepwise binary logistic regression was conducted. Initially, all available predictors, which included age, gender, ever smoking, FVC% and DLCO/VA values, years from first diagnosis, imaging staging, OSC treatment, OCS dosages, immunosuppression treatment, previous vaccination, and number of received vaccine dosages, were included in the model. Some predictors were removed due to lack of statistical significance. These included gender, smoking status, lung function parameters, chest CT, OSC treatment and dosage, and number of vaccination dosages. None of these variables showed a significant association with a higher or lower likelihood of exhibiting SARS-COV-2 infection. The model was able to explain 50% (Nagelkerke R2) of the variance in SARS-COV-2 infection and accurately classified 72% of cases (Table 4). It found that

Table 2. Comparisons between infected and non-infected Sarcoidosis patients (N=182).

Parameters	Infected (n=95)	Non-infected (n=87)	p-value
Females, n (%)	58 (61)	51 (59)	0.488
Age (years)	53±10	55±12	0.199
Current smokers, n (%)	7 (7)	15 (17)	0.098
Ever-smokers, n (%)	32 (34)	32 (37)	0.267
Nonsmokers, n (%)	52 (55)	47 (54)	0.407
FVC% of predicted	99±17	94±21	0.077
DLCO% of predicted	80±19	80±20	0.911
Time from first diagnosis (years)	7±6	5±3	0.027
Abnormal imaging findings in chest scan, n (%)	94 (99)	72 (83)	0.014
Abnormal extrathoracic PET-CT, n (%)	63 (66)	19 (22)	<0.001
Under any treatment, n (%)	53 (56)	47 (54)	0.532
Under oral corticosteroid treatment, n (%)	40 (42)	38 (44)	0.373
Mean dosage of prednisolone (mg) >5mg	25 (26)	22 (25)	0.430
Immunosuppression, n (%)	47 (49)	23 (26)	0.008
Vaccination against SARS-COV-2, n (%)	72 (76)	77 (86)	<0.001
Pfizer, n (%)	61 (64)	72 (83)	0.048
AstraZeneca, n (%)	6 (6)	13 (15)	0.039
Moderna/Johnson, n (%)	10 (11)	4 (5)	0.209
More than 2 dosages, n (%)	67 (71)	66 (76)	0.514

Note: Data are expressed as mean ± SD or as frequencies (percentages).
Abbreviations: DLCO, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; PET-CT, Positron Emission Tomography and Computed Tomography; SARS-COV-2, severe acute respiratory syndrome Coronavirus 2

Table 3. Records regarding the SARS-COV-2 infection in sarcoidosis patients, (n=95).

Parameters	Study population (n=95)	Females (n=55)	Males (n=40)	p-value
Hospitalization among infected, n (%)	19 (20)	10 (25)	9 (16.5)	0.395
Treatment at home, n (%)	76 (80)	45 (81.8)	31 (77.5)	0.395
Full recovery, n (%)	76 (80)	43 (78.2)	33 (82.5)	0.413
Improvement, n (%)	10 (10.5)	5 (9)	5 (22.5)	0.182
Remaining symptoms for a long time, n (%)	9 (9.5)	7 (12.7)	2 (5)	0.417

Note: Data are expressed as frequencies (percentages).

individuals who were younger, had been diagnosed with sarcoidosis for a longer period, had positive extrathoracic PET-CT, received immunosuppression, and were not vaccinated were more likely to exhibit SARS-COV-2 infection.

Moreover, a backward stepwise binary logistic regression was performed to ascertain the effects of age, gender, ever smoking, respiratory function, years from first diagnosis, OCS treatment, mean OCS dosage, immunosuppression treatment, previous vaccination, number of received vaccine dosages on the likelihood that participants have been hospitalized due to SARS-COV-2. No parameter was linked to the likelihood of hospitalization.

Discussion

As with other immune-mediated diseases, sarcoidosis patients have been considered at-risk during the COVID-19 pandemic. SARS-COV-2 infection

Table 4. Backward stepwise binary logistic regression to ascertain the effects of several variables on the likelihood that participants have been infected with SARS-COV-2.

						95% C.I. for EXP(B)	
	B	S.E.	Wald	Sig.	Exp(B)	Lower	Upper
Age	-0.066	0.030	4.691	0.030	0.936	0.882	0.994
Years from first diagnosis	0.259	0.106	5.975	0.015	1.296	1.053	1.596
PET-CT	2.015	0.689	8.549	0.003	7.498	1.943	28.940
Immunosuppression	1.462	0.673	4.717	0.030	4.316	1.153	16.153
Vaccination	-2.389	1.208	3.907	0.048	0.092	0.009	0.980
Constant	2.320	1.808	1.645	0.200	10.172		

Abbreviations: PET-CT, Positron Emission Tomography-Computed Tomography
Notes: Variables excluded: Ever smoking, OCS treatment, previous vaccination, vaccination dosages

was found to be prevalent among Greek sarcoidosis patients with 18% of them being infected, of whom one-fifth were hospitalized. However, the prevalence of COVID-19 among the general Greek population was higher compared to the prevalence found in sarcoidosis patients. As of August 1st, 2022, the prevalence of COVID-19 in Greeks was 44.2%, with 4.71 million people infected out of a total population of 10.64 million (20).

There is relatively little research available on the prevalence of SARS-COV-2 infection among sarcoidosis patients worldwide. One study conducted by Baughman et al. used a self-reported questionnaire to estimate a prevalence rate of 2.23% among 5200 patients with sarcoidosis (73% with pulmonary sarcoidosis, 9% with cardiac sarcoidosis and 8% with neurosarcoidosis), with no difference between genders. Out of those who were infected, 15.8% required hospitalization, according to the same study (12). The mean age of those infected sarcoidosis patients was similar to that of the infected Greek patients in our study. Interestingly, the authors found no significant difference in the infection rates between the sarcoidosis group and the general population (12). Those with pulmonary sarcoidosis (HR=2.48, p=0.001), neurosarcoidosis (HR=2.02, p<0.01), or undergoing rituximab treatment (HR=5.40, p<0.0001) showed an increased hazard ratio for COVID-19 infection (12). Another study conducted in France found that out of 199 sarcoidosis patients, 4% were diagnosed with COVID-19 with no difference between genders, which is higher than the rate observed in the general population in France (21). The mean age of the infected patients was 50.6±8.3 years, 72% had pulmonary involvement, 17% cardiac and 36% neurological involvement (21). In the same study by Desbois et al., the rate of hospitalization and death reached 37.5% and 12.5%, respectively, higher than the rate of death due to SARS-COV-2 infection in the general population (21). In our study, no ICU entrance and deaths were recorded although 66% of the infected patients had an extended disease with positive PET-CT for extrathoracic sarcoidosis, 42% received prednisolone (and 26% received a prednisolone dosage above 5mg) and 46% received immunosuppression. Hadi et al. noted a COVID-19 mortality rate of 4.3 % among 954 patients carried a diagnosis of pulmonary sarcoidosis (15). Morgenthau et al., in a cohort of 37 patients with sarcoidosis, reported a mortality rate of 16.2 % (11). The markedly higher mortality rates reported in earlier studies were likely secondary to the inclusion of only hospitalized patients, who are expected to carry higher disease-related morbidity. Moreover, the high vaccination rates observed in our study were another factor significantly associated with better outcomes, including a reduced likelihood of SARS-CoV-2 infection and the need for hospitalization. Patients with sarcoidosis may be more susceptible to infections due to lymphopenia and suppression of the immune response (22). High doses of OCS, which are commonly used as a first-line treatment for sarcoidosis, may also increase the risk of infectious diseases. However, it is not yet clear whether this also applies to COVID-19. In addition to glucocorticoids, other medications such as methotrexate, which is commonly used as a steroid-sparing alternative, and biologic medications like TNF-alpha inhibitors and B-cell depleting therapy may also be necessary for refractory disease (22). The use of OCS or immunosuppressive drugs during

COVID-19 for patients with sarcoidosis is a controversial topic. These drugs are generally considered to increase the risk of severe infection, while interrupting them could lead to a relapse of sarcoidosis. The American College of Rheumatology has recommended that corticosteroids should not be abruptly stopped regardless of infection status. However, there are also reports encouraging medication adjustment during COVID-19 (23). On the other hand, immunosuppressants should be stopped or withheld regardless of COVID-19 severity (23). In this study, we found that individuals who were infected with SARS-COV-2 were more likely to have received immunosuppression treatment compared to those who were not infected. Furthermore, the likelihood of contracting the virus increased 4.3 times for those who had received immunosuppression treatment. Only one study by Baughman et al. found that rituximab was associated with an increased risk of contracting COVID-19, while other immunosuppressive therapies were not (13). According to our study, almost half (42.8%) of the Greek sarcoidosis population received OCS, with a mean dosage of prednisolone of 10±5 mg. However, interestingly, we did not find any association between higher OCS dosages and a higher likelihood of SARS-COV-2 infection. When assessing the risk for severe COVID-19 in patients with chronic respiratory diseases such as sarcoidosis, it is important to consider risk factors beyond treatments with immunosuppressants. Other factors such as higher age, comorbidities, and male gender can also increase the risk for severe COVID-19 (24-28). Therefore, a comprehensive assessment of risk factors is necessary to determine the appropriate management and care for these patients (24-28). According to our study, gender and smoking status did not significantly affect the susceptibility to infection or worse outcomes in sarcoidosis patients. However, we did find that younger age was associated with an increased risk of infection in patients with sarcoidosis. Although there are conflicting reports, some studies have found no significant increased risk for hospitalization based on age, race, gender, or any specific immunosuppressive treatment (12). In our study, we did not find any significant links between the aforementioned parameters and the likelihood of hospitalization. However, it's important to note that the small number of infected patients in our study limits the statistical power for detecting significant predicting factors. Further research is needed to better understand the factors that increase the likelihood of hospitalization in sarcoidosis patients with COVID-19. Our study revealed that the longer period of suffering from sarcoidosis and the presence of abnormal PET-CT results were linked to a higher probability of SARS-COV-2 infection. This finding is likely since more advanced sarcoidosis is associated with a higher vulnerability to infection. It is generally accepted that patients with refractory sarcoidosis, like those with other immune-mediated diseases, may be at a higher risk of infections and poor outcomes from respiratory infections. However, it is not yet clear whether this also applies to COVID-19. Furthermore, according to published data, other factors that increase the risk of COVID-19 include lung attack and multisystemic disease, including neurosarcoidosis (24-28). PET-CT imaging has shown promising results in assessing disease activity, multisystemic involvement, and guiding immunosuppression in sarcoidosis patients (29,30). However, there are no published data regarding the role of PET-CT as a marker for COVID-19 susceptibility. Our study provides evidence that patients with abnormal PET-CT findings were 7.4 times more likely to exhibit SARS-COV-2 infection than patients who had a negative PET-CT. This finding suggests that PET-CT may be a useful tool for predicting COVID-19 susceptibility in sarcoidosis patients and warrants further investigation (29,30). In addition to the risk factors previously mentioned, moderate to severely decreased lung function and the presence of comorbidities traditionally associated with glucocorticoid use have been identified in the literature as independent risk factors for worse COVID-19 outcomes in sarcoidosis patients (26-28). These factors have been associated with greater rates of intubation and in-hospital mortality compared to the general population (25-27). Therefore, it is important to consider these risk factors when assessing the management and care of sarcoidosis patients with COVID-19. In Greece, the COVID-19 vaccination program started in late December 2020. While there are a few case reports supporting the onset of sarcoidosis after COVID-19 vaccination (31-35), most of the available literature suggests that vaccines are safe and effective in patients with autoimmune disorders and those taking immunosuppressive medications. However, there is limited and conflicting data on the efficacy of vaccination in sarcoidosis patients (31-35).

In our study, the great majority of patients (83.7%) were vaccinated for SARS-COV-2. We found that vaccination was associated with a significantly reduced likelihood of exhibiting SARS-COV-2 infection or hospitalization. Furthermore, in our study, we recognized that COVID-19 treatment strategies had changed significantly over time, so we included the period of infection as a factor in our analysis. This was important because treatments like high-dose steroids and non-invasive ventilation were not used consistently throughout the pandemic. By considering when each patient was infected, we were able to better assess how different factors, such as vaccination status and disease severity, truly affected outcomes. This approach helped us ensure that our results were accurate and not influenced by changes in treatment practices over time. As a result, our findings provided a clearer understanding of what had really impacted the health of sarcoidosis patients during the pandemic.Interestingly, we found that 72% fully recovered without experiencing any sarcoidosis relapse, 10% had an improvement but without full recovery, and 9% of the patients continued to experience symptoms for a long time after their recovery. To our knowledge, no previous studies have investigated the post-discharge symptoms among previously hospitalized due to COVID-19 sarcoidosis patients. A significant limitation of the study was that the comorbidities, post-discharge COVID-19-related symptoms and vaccination timepoints were not recorded in this cohort. To facilitate research on the outcomes of COVID-19 infection in sarcoidosis, it would be helpful to report the aforementioned patients' characteristics in population registries. However, this is the first study in Greece that followed retrospectively the prevalence of sarcoidosis and disease's outcomes from the pandemic's beginning until August 1, 2022, assessing the impact of several parameters on the likelihood that sarcoidosis participants have been infected with SARS-COV-2 or hospitalized.

Conclusions

According to this two-year follow-up study since the beginning of the SARS-COV-2 pandemic, 18% of Greek sarcoidosis patients were infected by the virus, which is a lower rate than the general population. The infection was mainly mild, and patients were medicated at home. Only one-fifth of infected sarcoidosis patients required hospitalization due to the infection, and no deaths or ICU admissions were recorded. After hospitalization, 9.4% of patients experienced residual symptoms. Most of the sarcoidosis patients were vaccinated for SARS-COV-2, which was found to be associated with a reduced likelihood of infection. 43% of sarcoidosis patients were under corticosteroid treatment, and 39% were under additional immunosuppression. Younger age, a longer period since diagnosis, abnormal PET-CT findings, and immunosuppression were associated with an increased probability of infection. However, no parameter was linked to a greater likelihood of hospitalization.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Ethics Approval: Informed consent was obtained from all study participants, according to the Helsinki Declaration. The protocol was approved by the Larissa University Hospital Ethics Committee (approval number: 48841/25/10/2019).

References

1. Crouser ED, Maier LA, Wilson KC, et al. Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2020;201(8):e26-e51.
2. Papiris SA, Campo I, Mariani F, et al. COVID-19 in patients with pulmonary alveolar proteinosis: a European multicentre study. ERJ Open Res. 2023;9(1):00199-2022.
3. Papiris SA, Bouros D, Markopoulou K, et al. Early COVID-19 lockdown in Greece and idiopathic pulmonary fibrosis: a beneficial "impact" beyond any expectation. Eur Respir J. 2021;57(3):2003111.
4. El Jammal T, Jamilloux Y, Gerfaud-Valentin M, Valeyre D, Sève P. Refractory Sarcoidosis: A Review. Ther Clin Risk Manag. 2020;16: 323-345.
5. Arkema EV, Cozier YC. Sarcoidosis epidemiology: recent estimates of incidence, prevalence and risk factors. Curr Opin Pulm Med. 2020;26 (5):527-534.
6. Saidha S, Sotirchos ES, Eckstein C. Etiology of sarcoidosis: does infection play a role? Yale J Biol Med. 2012;85(1):133-141.
7. Nikoskelainen J, Hänninen P. Antibody response to Epstein-Barr virus in infectious mononucleosis. Infect Immun. 1975;11(1):42-51.
8. Shifera AS, Pockrandt C, Rincon N, et al. Identification of microbial agents in tissue specimens of ocular and periocular sarcoidosis using a metagenomics approach. F1000Res. 2021;10:820.

9. Chen ES, Moller DR. Etiology of sarcoidosis. Clin Chest Med. 2008; 29(3):365-377.
10. Gracia-Ramos AE, Martin-Nares E, Hernández-Molina G. New Onset of Autoimmune Diseases Following COVID-19 Diagnosis. Cells. 2021;10(12):3592.
11. Morgenthau AS, Levin MA, Freeman R, Reich DL, Klang E. Moderate or Severe Impairment in Pulmonary Function is Associated with Mortality in Sarcoidosis Patients Infected with SARS-CoV-2. Lung. 2020;198(5):771-775.
12. Baughman RP, Lower EE, Buchanan M, et al. Risk and outcome of COVID-19 infection in sarcoidosis patients: results of a self-reporting questionnaire. Sarcoidosis Vasc Diffuse Lung Dis. 2020;37(4): e2020009.
13. Kahlmann V, Manansala M, Moor CC, Shahrara S, Wijsenbeek MS, Sweiss NJ. COVID-19 infection in patients with sarcoidosis: susceptibility and clinical outcomes. Curr Opin Pulm Med. 2021; 27(5):463-471.
14. Strykowski R, Patel DC, Neto MR, et al. Rationale and design of the SARCoidosis Outcomes in all respiratory Viral Infectious Diseases (SARCOVID) Study. BMJ Open Respir Res. 2022;9(1):e001254.
15. Hadi YB, Sohail AH, Lakhani DA, Naqvi SF, Kupec JT, Pervez A. Outcomes of SARS-CoV-2 infection in patients with celiac disease: a multicenter research network study. Ann Gastroenterol. 2022; 35(2):164-168.
16. Liu W, Liu Y, Xu Z, et al. Clinical characteristics and predictors of the duration of SARS-CoV-2 viral shedding in 140 healthcare workers. J Intern Med. 2020;288(6):725-736.
17. Capaccione KM, McGroder C, Garcia CK, Fedyna S, Saqi A, Salvatore MM. COVID-19-induced pulmonary sarcoid: A case report and review of the literature. Clin Imaging. 2022;83: 152-158.
18. Behbahani S, Baltz JO, Droms R, et al. Sarcoid-like reaction in a patient recovering from coronavirus disease 19 pneumonia. JAAD Case Rep. 2020;6(9):915-917.
19. Karakatsani A, Papakosta D, Rapti A, et al; Hellenic Interstitial Lung Diseases Group. Epidemiology of interstitial lung diseases in Greece. Respir Med 2009; 103(8):1122-1129.
20. Mathieu E, Ritchie H, Rodés-Guirao L, et al. Greece: Coronavirus pandemic country profile [Internet]. Our World in Data. Available from: https://ourworldindata.org/coronavirus/country/greece.
21. Desbois AC, Marques C, Lefèvre L, et al. Prevalence and clinical features of COVID-19 in a large cohort of 199 patients with sarcoidosis. Clin Exp Rheumatol. 2022;40(1):195-196.
22. Sweiss NJ, Salloum R, Gandhi S, et al. Significant CD4, CD8, and CD19 lymphopenia in peripheral blood of sarcoidosis patients correlates with severe disease manifestations. PLoS One. 2010;5(2): e9088.
23. Kondle S, Hou T, Manansala M, Ascoli C, Novak RM, Sweiss N. Treatment of COVID-19 in Patients With Sarcoidosis. Front Med (Lausanne). 2021;8:689539.
24. Lommatzsch M, Rabe KF, Taube C, et al. Risikoabschätzung bei Patienten mit chronischen Atemwegs- und Lungenerkrankungen im Rahmen der SARS-CoV-2-Pandemie (Risk Assessment for Patients with Chronic Respiratory and Pulmonary Conditions in the Context of the SARS-CoV-2 Pandemic - Statement of the German Respiratory Society (DGP) with the Support of the German Association of Respiratory Physicians (BdP)). Pneumologie. 2021;75(1):19-30.
25. Ungprasert P, Crowson CS, Matteson EL. Sarcoidosis Increases Risk of Hospitalized Infection. A Population-based Study, 1976-2013. Ann Am Thorac Soc. 2017;14(5):676-681.
26. Jain V, Yuan JM. Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis. Int J Public Health. 2020;65(5):533-46.
27. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020;94:91-95.
28. Li J, Huang DQ, Zou B, et al Epidemiology of COVID-19: A systematic review and meta-analysis of clinical characteristics, risk factors, and outcomes. J Med Virol. 2021;93(3):1449-1458.
29. Papiris SA, Georgakopoulos A, Papaioannou AI, et al. Emerging phenotypes of sarcoidosis based on 18F-FDG PET/CT: a hierarchical cluster analysis. Expert Rev Respir Med. 2020;14(2):229-238.
30. Song X, Shao F, Lan X. The Onset of Sarcoidosis After COVID-19 Vaccination Revealed by the 18 F-FDG PET. Clin Nucl Med. 2022;47(10):869-781.
31. Albers CC, Metze D, Steinbrink K, Böhm M. Systemic Sarcoidosis with Cutaneous Tattoo Involvement Following COVID-19 Vaccination. Acta Derm Venereol. 2023;103:adv6244.
32. Shukla AK, Peter A, Bhargava JK, et al. Sarcoidosis presenting as bilateral optic neuritis after ChAdOx1 nCoV-19 vaccination. Monaldi Arch Chest Dis. 2022;93(1).
33. Cazzato G, Ambrogio F, Foti C, et al. Cutaneous Sarcoidosis-like Eruption Following Second Dose of Moderna mRNA-1273 Vaccine: Case or Relationship? Diagnostics (Basel). 2023;13(7):1286.
34. Mohaghegh F, Hatami P, Refaghat A, et al. Unmasking sarcoidosis following SARS-CoV-2 vaccination: A case report. Clin Case Rep. 2022;10(12):e6660.
35. Numakura T, Murakami K, Tamada T, et al. A Novel Development of Sarcoidosis Following COVID-19 Vaccination and a Literature Review. Intern Med. 2022;61(20):3101-3106.