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Keywords: Brazil; Coronavirus Disease (COVID)-19; Epidemiology; Inflammation; Pandemic; Public Health.

Article

Epidemiological Profile of Bechcet's Disease in Hospitalized Patients Infected with SARS-CoV-2 in Brazil: A Serial Case Report and a Literature Review

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Abstract: The literature is scarce in the evaluation of Behçet's disease (BD) among individuals during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Then, an epidemiological study was conducted using the data from 46 hospitalized patients with BD and coronavirus disease (COVID)-19 representing a prevalence of 2,11 patients per 100,000 inhabitants. From the study sample, 58.7% (27 patients) were female, and 67.4% (31 patients) were White. The main symptoms were fever (40; 87.0%), cough (38; 82.6%), dyspnea (35; 76.1%), and peripheral saturation below 95% (35%, 76.1%). The need for intensive care unit support occurred for 39.1% (18) patients. Also, 21.7% (10) patients needed invasive ventilatory support and 47.8% (22) needed non-invasive ventilatory support. A total of 73.9% (34) of patients lived, and 26.1% (12) of patients died. Only the presence of respiratory discomfort [37.9% vs. 5.9%] was more common among those who died. Patients with BD were not at an increased risk of worse COVID-19 outcomes in Brazil.

Keywords: Brazil; coronavirus disease (COVID)-19; epidemiology; inflammation; pandemic; public health

1. Introduction

Behçet's disease (BD) is an inflammatory condition that is characterized by oral aphthous ulcers, genital ulcers, uveitis, and skin lesions [1,2]. The disease manifests itself by recurrent attacks of acute inflammation, rather than a continuous chronic inflammatory state [2,3]. The condition is strongly linked with the presence of Human Leukocyte Antigen B51 (HLA-B51) genetic allele along with environmental factors [4]. In Japan, the incidence of the HLA-B51 allele among patients with BD is higher when compared to those without the disease [4]. For example, a study demonstrated that carriers of the HLA-B51 allele have a 6.7 higher chance of having the disease in Japan when compared to noncarriers [2]. Epidemiologically, this condition is rare, ranging from 0.64 per 100,000 inhabitants in the United Kingdom and 0.12-0.33 per 100,00 inhabitants in the United States of America. The onset is typically in middle age, in the third or the fourth decade of life [1,2].

The BD is characterized by vascular injuries, mainly from large vessels affected by the vasculitis of the vasa vasorum, alongside hypercoagulability [1–3]. Aneurysms of large vessels and thromboses of vena cavae may develop. Medium-sized vessels are also involved and may result in thrombophlebitis of the lower extremities or pulmonary arterial aneurysms [5,6]. Venous thrombosis is far more common than arterial lesions. In addition, neutrophils from patients with BD have

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augmented superoxide production, enhanced chemotaxis, and excessive lysosomal enzyme production, leading to tissue injuries [2]. The cytokine production profile of T cells in patients with BD is skewed toward the T-helper 1 (Th1)-type of immune responses, especially during flares of the disease. Although the condition has been considered an aseptic inflammatory disease, bacteria are rarely found in histological examination. Some authors suggest both viral (e.g., herpes virus) and bacterial (e.g., *Streptococcus* spp.) roles in the pathogenesis of the disease [2,3].

The diagnosis of the BD is made by a combination of nonspecific symptoms and laboratory findings [6]. In 1990, diagnostic criteria were proposed by the International Study Group for Behcet's disease to improve diagnostic accuracy [6]. In 2003, the BD research committee in Japan revised the diagnostic criteria. The cardinal symptoms of BD include recurrent aphthous ulcers on the oral mucosa, skin lesions, ocular lesions, and genital ulcerations. Additional symptoms may include arthritis, epididymitis, gastrointestinal, vascular, or central nervous system lesions [7]. Importantly, early diagnosis and therapeutic intervention are essential to optimize outcomes in patients with BD. Treatment may require medical therapy with immunosuppressive or corticosteroid, interventional radiological techniques, or surgical ablation or resection [8].

Since December 2019, a novel viral infection with severe acute respiratory syndrome emerged from the Wuhan Province, in China [9]. Later, it was labeled severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has transformed into a worldwide challenge, resulting in ~700 million cases and ~7 million deaths. The disease, popularly named coronavirus disease (COVID)-19, was officially declared a pandemic by the World Health Organization on 11 March 2020 [9]. There is a current theory that the risk of severe COVID-19 and its associated complications is considered to be increased in patients with preexisting and underlying medical conditions or comorbidities [10]. In this matter, this theory raises the question of whether patients with autoimmune diseases or vasculitis are at increased risk of COVID-19 [11]. Although not proven for COVID-19, in general, rheumatic conditions, immunosuppression, and comorbidities are associated with a higher risk of serious infections due to immunosuppression and the presence of chronic inflammation [12]. In this context, BD is classified as a muti-systemic chronic disease, a variable type of vasculitis that affects vessels of all types [13,14]. Due to a lack of further studies on whether the chronic inflammatory territory impacts the course of COVID-19, there is not much information regarding medical recommendations for these patients mainly among those who required hospitalization with the need for intensive care.

In this context, it was conducted an epidemiological investigation in Brazil using the data from OpenDataSUS (https://opendatasus.saude.gov.br/) to describe the epidemiological profile of BD in hospitalized patients infected with SARS-CoV-2. The data was, then, compared to other published studies regarding the same premise using a literature review.

2. Materials and Methods

2.1. Epidemiological Study

It was conducted an epidemiological investigation in Brazil using the data from OpenDataSUS (https://opendatasus.saude.gov.br/), which is a Brazilian open dataset that encompasses demographic and clinical information of hospitalized patients only.

The study evaluated 3,551,556 patients hospitalized in Brazil with severe acute respiratory syndrome, and data collection covered the period from December 29th, 2019, to April 6th, 2023. From the totality of original data, it was selected only patients with BD (n = 46/2,180,719) among those with COVID-19 (n = 2,180,719/3,551,556; 61.4%) notified in the Data-SUS database. The study enrolled only individuals with a positive and confirmatory laboratory diagnostic test for COVID-19.

The study comprised the following characteristics of these patients: sex (male and female), age (years), race (White, Black, Asian, Indigenous, and *Pardos* – individuals with multiracial background), level of education, place of residence (Urban, peri-urban, and rural), presence or absence of nosocomial infection, clinical signs (e.g., fever, cough, sore throat, dyspnea, respiratory discomfort, oxygen saturation below 95%, diarrhea, vomiting, abdominal pain, fatigue, loss of smell, loss of taste, and other symptoms), comorbidities (e.g., cardiopathy, hematological disease, Down syndrome, liver

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disease, asthma, diabetes mellitus, neurological disease, chronic respiratory disease, immunosuppression, kidney disease, and obesity), vaccination status against Influenza, need for intensive care unit (presence or absence), need for mechanical ventilation support (invasive, non-invasive, and none), discharge criterium (clinical or laboratory criteria), outcome (clinical recovery or death), and vaccination status against COVID-19 (presence or absence).

Before to procedure with the statistical analysis, the missing data imputation was performed using the XLSTAT (2007) Statistical Software for Excel. The multiple imputations were performed using two methods which included Markov Chain Monte Carlo Multiple (MCMC) and Nonlinear Iterative PArtial Least Squares (NIPALS) methods. The statistical analysis was performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Macintosh, Version 28.0). The descriptive analysis is presented using absolute numbers (N) and percentages (%) for categorical data and mean ± standard deviation, and median (95% confidence interval) for numerical data (age). The inferential analysis to identify death predictors was performed using the Fisher Exact test or Chi-square test for categorical data and the Mann-Whitney U test for numerical data. The odds ratio (OR) and its 95% confidence interval (95%CI) were also calculated and presented in the study. An alpha error of 0.05 was applied in the study.

2.2. Literature Review

A literature review was conducted to elucidate the impact of COVID-19 among patients with BD. The following descriptors were used "(Behçet's disease OR Behçet disease) and (COVID-19 OR Coronavirus Disease OR SARS-CoV-2)". In the review, the following markers were collected: title of the manuscript, year of publication, first author name, journal where the study was published, impact factor of the journal, objective(s), method(s), result(s), and conclusion(s). The search for the literature review was done on 02 October 2023.

The complete search list can be read as follows:

(Behçet's disease OR Behçet disease) and (COVID-19 OR Coronavirus Disease OR SARS-CoV-2)

("behcet syndrome"[MeSH Terms] OR ("behcet"[All Fields] AND "syndrome"[All Fields]) OR "behcet syndrome"[All Fields] OR ("behcet s"[All Fields] AND "disease"[All Fields]) OR "behcet s disease"[All Fields] OR ("behcet syndrome"[MeSH Terms] OR ("behcet"[All Fields] AND "syndrome"[All Fields]) OR "behcet syndrome"[All Fields] OR ("behcet"[All Fields] AND "disease"[All Fields]) OR "behcet disease"[All Fields])) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication]) OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields]) AND ("disease"[MeSH Terms] OR "disease"[All Fields] OR "diseases"[All Fields] OR "disease s"[All Fields] OR "diseased"[All Fields])) OR ("sars cov 2"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[All Fields]))

Translations

Behcet's disease: "behcet syndrome"[MeSH Terms] OR ("behcet"[All Fields] AND "syndrome"[All Fields]) OR "behcet syndrome"[All Fields] OR ("behcet's"[All Fields] AND "disease"[All Fields]) OR "behcet's disease"[All Fields]

Behcet disease: "behcet syndrome"[MeSH Terms] OR ("behcet"[All Fields] AND "syndrome"[All Fields]) OR "behcet syndrome"[All Fields] OR ("behcet"[All Fields] AND "disease"[All Fields]) OR "behcet disease"[All Fields]

COVID-19: ("COVID-19" OR "COVID-19"[MeSH Terms] OR "COVID-19 Vaccines" OR "COVID-19 Vaccines"[MeSH Terms] OR "COVID-19 serotherapy" OR "COVID-19 serotherapy"[Supplementary Concept] OR "COVID-19 Nucleic Acid Testing" OR "covid-19 nucleic

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acid testing" [MeSH Terms] OR "COVID-19 Serological Testing" OR "covid-19 serological testing"[MeSH Terms] OR "COVID-19 Testing" OR "covid-19 testing"[MeSH Terms] OR "SARS-CoV-2" OR "sars-cov-2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "NCOV" OR "2019 NCOV" OR (("coronavirus"[MeSH Terms] OR "coronavirus" OR "COV") AND 2019/11/01[PDAT] : 3000/12/31[PDAT]))

Coronavirus: "coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields]

Disease: "disease"[MeSH Terms] OR "disease"[All Fields] OR "diseases"[All Fields] OR "disease's"[All Fields] OR "diseased"[All Fields]

SARS-CoV-2: "sars-cov-2"[MeSH Terms] OR "sars-cov-2"[All Fields] OR "sars cov 2"[All Fields].

3. Results

3.1. Patient's Characteristics

The study analyzed data from 46 patients with BD and COVID-19 from the Data-SUS database in Brazil representing a prevalence of 2,11 patients per 100,000 hospitalized individuals due to COVID-19. Of the 46 patients, 39.1% (18 patients) were, mainly, from the state of São Paulo, 15.2% (7 patients) were from Minas Gerais and 8.7% (4) were from the Federal district (Table 1). From the study sample, 58.7% (27 patients) were female. Regarding race, 67.4% (31 patients) were White and 32.6% (15 patients) were *Pardos* (Multiracial background). All patients lived in urban areas. Regarding the presence of nosocomial infections, only 2 (6.3%) patients presented a positive result (Table 2). The mean age was 45.31 ± 2.04 years [median of 44 (95%CI = 36-54.50) years]. It was not possible to evaluate the level of education due to the high number of missing data (>40%) which unfeasible multiple imputations.

Table 1. Distribution of the hospitalized patients with Behçet's disease during the infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Brazil.

State and Federal District	N (%)
Bahia	2 (4.3%)
Ceará	3 (6.5%)
Federal District	4 (8.7%)
Goiás	1 (2.2%)
Minas Gerais	7 (15.2%)
Pernambuco	2 (4.3%)
Paraná	3 (6.5%)
Rio de Janeiro	3 (6.5%)
Rio Grande do Sul	2 (4.3%)
São Paulo	18 (39.1%)

%, percentages; N, number of individuals. It was presented only the data from states that presented at least one individual with Behçet's disease and coronavirus disease (COVID-19) in Brazil.

Table 2. Epidemiological profile of the hospitalized patients with Behçet's disease during the infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [coronavirus disease (COVID)-19] in Brazil.

Marker	Group	N (%)
Sex	Female	27 (58.7%)
	Male	19 (41.3%)
Race	White people	31 (67.4%)
	Pardos (Multiracial background)	15 (32.9%)
Place of residence	Urban	46 (100.0%)

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Presence of nosocomial infection	Yes	2 (4.3%)
	No	44 (95.7%)
Fever	Yes	40 (87.0%)
	No	6 (13.0%)
Cough	Yes	39 (84.8%)
	No	7 (15.2%)
Sore throat	Yes	7 (15.2%)
	No	39 (84.8%)
Dyspnea	Yes	35 (76.1%)
	No	11 (23.9%)
Respiratory discomfort	Yes	29 (63.0%)
	No	17 (37.0%)
Oxygen saturation below 95%	Yes	35 (76.1%)
	No	11 (23.9%)
Diarrhea	Yes	7 (15.2%)
	No	39 (84.8%)
Vomiting	Yes	5 (10.9%)
	No	41 (89.1%)
Other symptoms	Yes	34 (73.9%)
	No	12 (26.1%)
Cardiopathy	Yes	19 (41.3%)
	No	27 (58.7%)
Diabetes mellitus	Yes	4 (8.7%)
	No	42 (91.3%)
Antiviral	Yes	4 (8.7%)
	No	42 (91.3%)
Need of intensive care unit	Yes	18 (39.1%)
	No	28 (60.9%)
Ventilatory support	Invasive	10 (21.7%)
	No-invasive	22 (47.8%)
	None	14 (30.4%)
Discharge criterium	Laboratorial criterium	40 (87.0%)
	Clinical criterium	6 (13.0%)
Outcomes	Cured	34 (73.9%)
	Death	12 (26.1%)
Vaccine against COVID-19	Yes	9 (19.6%)
	No	37 (80.4%)

%, percentages; N, number of individuals.

3.2. Clinical Symptoms and Comorbidities

Regarding the presence of symptoms, the main symptoms were fever (40; 87.0%), cough (38; 82.6%), dyspnea (35; 76.1%), peripheral saturation below 95% (35%, 76.1%), and other symptoms (34; 73.9%). Regarding the presence of comorbidities, 41.3% (19 patients) presented cardiopathy and 8.7% (4) presented diabetes mellitus. It was not possible to evaluate the following markers due to the high number of missing data (>40%): abdominal pain, fatigue, loss of smell, loss of taste, hematological disease, Down syndrome, liver disease, asthma, neurological disease, chronic respiratory disease, immunosuppression, kidney disease, and obesity.

3.3. Treatment and Outcome

A total of 8.7% (4) patients had taken antiviral medicine. Regarding the need for intensive care, 39.1% (18 patients) needed intensive care unit support; in addition, 21.7% (10) patients needed

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invasive ventilatory support, 47.8% (22) patients needed non-invasive ventilatory support and 30.4% (14 patients) did not receive ventilatory support. For discharge criteria, 87.0% (40) patients were discharged under laboratory criteria, while 13.0% (6) patients were discharged under clinical criteria. Regarding the outcome, 73.9% (34) of patients lived, and 26.1% (12) of patients died. Regarding the vaccination against COVID-19, only 19.6% (9 patients) had taken vaccines. It was not possible to evaluate the vaccination status against Influenza due to the high number of missing data (>40%) which unfeasible multiple imputations.

3.4. Predictors for Death

Among the epidemiological data analyzed in the study, only one marker was associated with an increased chance of death among hospitalized individuals. In brief, the presence of respiratory discomfort [37.9% vs. 5.9%] was more common among those who died. Also, the age presented a similar distribution between both groups – (patients cured) the mean age was 45.21 ± 2.31 years [median of 44.00 (95%CI = 36.00-54.00) years] and (patients who died) the mean age was 46.00 ± 4.46 years [median of 45.50 (95%CI = 35.25-45.50) years] (*P*-value = 0.861) (Table 3).

3.5. Literature Review

The literature provides conflicting results regarding the outcome of studies already published for patients with BD and COVID-19. In addition, we evaluated 26 published papers from the PubMed databank and compared their results with ours (Tables 4 and 5).

Chang and collaborators (2023) published a retrospective cohort study to evaluate the risk of autoimmune diseases in patients with COVID-19. Their primary endpoint was the incidence of newly recorded autoimmune diseases [15]. The study comprised the information of 3,814,479 participants classified as cases (N = 888,463) and controls (N = 2,926,016) [15]. The study concluded that COVID-19 is associated with a different degree of risk for various autoimmune diseases, including BD [15]. Also, Moreno-Torres and collaborators (2022) described the clinical outcome of systemic autoimmune disease patients hospitalized with COVID-19 in Spain [16]. The study included 117,694 patients and identified a higher mortality rate in systemic autoimmune disease patients that was related to the higher burden of comorbidities, secondary to direct organ damage and sequelae of their condition [16]. In the same way, Al-Adhoubi and collaborators (2022) evaluated the mortality due to COVID-19 among 113 patients with rheumatic disease and concluded that COVID-19 in patients with rheumatic disease have an increased mortality rate in comparison to the general population, with diabetes mellitus, morbid obesity, chronic kidney diseases, interstitial lung disease, cardiovascular disease, obstructive lung disease, and liver diseases as comorbidities being the most severe risk factors associated with death [17].

Fanlo and collaborators (2021) obtained data from 2,789 responders about the presence of uveitis associated with an autoimmune disease to evaluate the impact of COVID-19 [18]. From this cohort, only 28 (12 with BD) individuals presented uveitis and, among them, 14 (6 with BD) had clinical symptoms compatible with COVID-19 [18]. The study demonstrated that patients with uveitis associated with an autoimmune disease, both asymptomatic and symptomatic patients with COVID-19, had similarly received immunosuppressive treatment. In addition, it is important to optimize the COVID-19 diagnosis among this study population [18]. Using a similar approach, Sattui and collaborators (2021) evaluated the outcomes of COVID-19 in patients with primary systemic vasculitis or polymyalgia rheumatica (N = 1,202); and, in this population, severe outcomes were associated with unmodifiable risk factors, such as age, sex, and number of comorbidities, as well as treatments, including high-dose glucocorticoids [19].

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Table 3. Association between the chance of death and the epidemiological profile of the hospitalized patients with Behçet's disease during the infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [coronavirus disease (COVID)-19] in Brazil.

Marker	Group	Death [N (%)]	Cured [N (%)]	*P*-value	OR (95%CI)[c]
Sex	Female	7 (25.9%)	20 (74.1%)	1.000[a]	0.98 (0.26-3.73)
	Male	5 (26.3%)	14 (73.7%)	1	Reference
Race	White people	11 (35.5%)	20 (64.5%)	0.070[b]	7.43 (1.08-178.30)
	Pardos (Multiracial background)	1 (6.7%)	14 (93.3%)	1	Reference
Place of residence	Urban	12 (26.1%)	34 (73.9%)	-	NA
Presence of nosocomial infection	Yes	0 (0.0%)	2 (100.0%)	1.000[b]	NA
	No	12 (27.3%)	32 (72.7%)	1	Reference
Fever	Yes	9 (22.5%)	31 (77.5%)	0.173[b]	0.30 (0.04-2.63)
	No	3 (50.0%)	3 (50.0%)	1	Reference
Cough	Yes	10 (34.5%)	29 (74.4%)	0.865[b]	0.14 (0.12-10.44)
	No	2 (28.6%)	5 (71.4%)	1	Reference
Sore throat	Yes	2 (28.6%)	5 (71.4%)	1.000[b]	1.16 (0.10-8.58)
	No	10 (25.6%)	29 (74.4%)	1	Reference
Dyspnea	Yes	10 (28.6%)	25 (71.4%)	0.701[b]	1.78 (0.29-19.79)
	No	2 (18.2%)	9 (81.8%)	1	Reference
Respiratory discomfort	Yes	11 (37.9%)	18 (62.1%)	**0.034[b]**	**9.38 (1.13-446.6)**
	No	1 (5.9%)	16 (94.1%)	1	Reference
Oxygen saturation below 95%	Yes	9 (25.7%)	26 (74.3%)	1.000[b]	0.92 (0.17-6.58)
	No	3 (27.3%)	8 (72.7%)	1	Reference
Diarrhea	Yes	4 (57.1%)	3 (42.9%)	0.064[b]	4.94 (0.69-41.01)
	No	8 (20.5%)	31 (79.5%)	1	Reference
Vomiting	Yes	3 (60.0%)	2 (40.0%)	0.103[b]	5.09 (0.50-69.84)
	No	9 (22.0%)	32 (78.0%)	1	Reference
Other symptoms	Yes	9 (26.5%)	25 (73.5%)	1.000[b]	1.08 (0.20-7.57)
	No	3 (25.0%)	9 (75.0%)	1	Reference
Cardiopathy	Yes	6 (31.6%)	13 (68.4%)	0.513[a]	1.60 (0.35-7.47)
	No	6 (22.2%)	21 (77.8%)	1	Reference
Diabetes mellitus	Yes	1 (25.0%)	3 (75.0%)	1.000[b]	0.94 (0.02-13.21)
	No	11 (26.2%)	31 (73.8%)	1	Reference
Antiviral	Yes	0 (0.0%)	4 (100.0%)	0.560[b]	NA
	No	12 (28.6%)	30 (71.4%)	1	Reference
Need of intensive care unit	Yes	6 (33.3%)	12 (66.7%)	0.495[a]	1.81 (0.39-8.52)
	No	6 (21.4%)	22 (78.6%)	1	Reference
Ventilatory support	Invasive	4 (40.0%)	6 (60.0%)	0.152[b]	3.76 (0.40-53.04)
	No-invasive	6 (27.3%)	16 (72.7%)	0.361[b]	2.25 (0.38-13.16)
	None	2 (14.3%)	12 (85.7%)	1	Reference

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Discharge criterium	Laboratorial criterium	8 (20.0%)	32 (80.0%)	1	Reference
	Clinical criterium	4 (66.7%)	2 (33.3%)	0.065[b]	7.533 (0.902-97.31)
Vaccine against COVID-19	Yes	1 (11.1%)	8 (88.9%)	0.409[b]	0.30 (0.01-2.75)
	No	11 (29.7%)	26 (70.3%)	1	Reference

%, percentages; 95%CI, 95% confidence interval; N, number of individuals; NA, not applicable; OR, odds ratio. [a], the statistical analysis was performed using the Chi-square test; [b], the statistical analysis was performed using the Fisher Exact test; [c], the conclusions based on statistical analysis must be cautious since the ORs values and its 95%CI may have been influenced by the low number of patients in some groups analyzed. The associations with a significant *P*-value are presented using bold type. An alpha error of 0.05 was adopted in the study.

Oztas and collaborators (2022) investigated whether patients (N = 635) regularly using colchicine or hydroxychloroquine have an advantage of protection from COVID-19 or developing less severe disease; and the authors concluded that being on the treatment of regular doses of both drugs was ineffective in preventing COVID-19 and ameliorating its manifestations, despite these medications not causing worse outcomes during the COVID-19 [20]. In addition, Bourguiba and collaborators (2022) identified 117 patients with systemic autoinflammatory diseases and compared them with 1,545 patients with non-autoinflammatory immune-mediated inflammatory disorders demonstrating that the first ones on corticosteroids and with multiple comorbidities were prone to develop more severe COVID-19 phenotypes [21]. On the same theme, Ozcifci and collaborators (2022) performed a cohort study of 1,047 patients with BD to investigate the incidence, clinical characteristics, and outcome of COVID-19. The study demonstrated that the incidence and severity of COVID-19 were not linked with the use of colchicine. However, the cumulative incidence of COVID-19 in patients with BD was greater than in the general population living in Istanbul and Turkey. Besides that, the clinical outcome was not severe, and no deaths were described [22]. In addition, AlBloushi and collaborators (2022) investigated the incidence, severity, and outcomes of COVID-19 in patients (N = 59) with uveitis treated with biological agents [23]. The authors concluded that BD was the most common diagnosis (64.4%) and that uveitis patients under biologic therapy can be silent carriers for COVID-19 [23].

Table 4. Studies that evaluated patients with Behçet's disease infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing the coronavirus disease (COVID)-19.

Title	First author	Journal	Impact factor
Risk of autoimmune diseases in patients with COVID-19: A retrospective cohort study	Chang et al. (2023) [15]	eClinicalMedicine	15.100
Ocular Behçet disease and COVID-19	Accorinti et al. (2022) [24]	European Journal of Ophthalmology	1.922
COVID-19 in patients with Behçet's disease: Outcomes and rate of Behçet's exacerbations in a retrospective cohort	Polat et al. (2022) [25]	Modern Rheumatology	2.862
Adamantiades-Behçet's disease (Behçet's disease) and COVID-19	Zouboulis et al. (2021) [26]	Journal of the European Academy of Dermatology and Venereology	9.228
Clinical course of COVID-19 in a cohort of patients with Behçet disease	Correa-Rodríguez et al. (2021) [10]	Medicina Clinica	3.200
The course of COVID-19 in patients with Behçet's disease	Enginar and Gundogdu (2021) [27]	Reumatologia	1.700

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Clinical course of COVID-19 infections in patients with Behçet's disease in The Netherlands	den Otter et al. (2022) [28]	Clinical and Experimental Rheumatology	4.862
Coronavirus disease 2019 in patients with Behcet's disease: a report of 59 cases in Iran	Shahram et al. (2022) [14]	Clinical Rheumatology	3.650
COVID-19 among patients with Behçet syndrome in the United States	Pakhchanian et al. (2022) [11]	Clinical Rheumatology	3.650
Characteristics and outcomes of Behçet's syndrome patients with Coronavirus Disease 2019: a case series of 10 patients	Yurttaş et al. (2020) [29]	Internal And Emergency Medicine	5.472
Coronavirus disease 2019 (COVID-19) in patients with systemic autoimmune diseases or vasculitis: radiologic presentation	Eslambolchi et al. (2021) [30]	Journal of Thrombosis and Thrombolysis	5.221
Prevalence and clinical course of SARS-CoV-2 infection in patients with Behçet's syndrome	Mattioli et al. (2021) [31]	Clinical and Experimental Rheumatology	4.862
COVID-19 and Behçet's disease: clinical case series	Espinosa et al. (2021) [13]	Annals of the Rheumatic Diseases	27.400
Undiagnosed Behçet's disease complicated by multiple pseudoaneurysms and COVID-19 infection	Mehta et al. (2023) [32]	International Journal of Angiology	0.320
The clinical outcomes of COVID-19 in patients with Behçet's disease: A series of 7 cases and brief review of the literature	Nas et al. (2022) [33]	Eurasian Journal of Medicine	0.302
COVID-19 infection among patients with autoinflammatory diseases: a study on 117 French patients compared with 1545 from the French RMD COVID-19 cohort: COVIMAI - the French cohort study of SARS-CoV-2 infection in patient with systemic autoinflammatory diseases	Bourguiba et al. (2022) [21]	RMD Open	5.806
Frequency and severity of COVID-19 in patients with various rheumatic diseases treated regularly with colchicine or hydroxychloroquine	Oztas et al. (2022) [20]	Journal of Medical Virology	12.700
The incidence, clinical characteristics, and outcome of COVID-19 in a prospectively followed cohort of patients with Behçet's syndrome	Ozcifci et al. (2022) [34]	Rheumatology International	3.580
Implications of COVID-19 infection on patients with uveitis under biologic treatment	AlBloushi et al. (2022) [23]	British Journal of Ophthalmology	3.806
Erythema nodosum in Behçet's disease in remission: Think COVID-19?	El Hasbani et al. (2023) [35]	SAGE Open Medical Case Reports	0.149
Interplay between Adamantiades-Behçet's disease and COVID-19 – a case series from the German registry of Adamantiades-Behçet's disease	Lim et al. (2023) [36]	Journal of the European Academy of Dermatology and Venereology	9.228
COVID-19 mortality in patients with rheumatic diseases: A real concern	Al-Adhoubi et al. (2022) [17]	Current Rheumatology Reviews	1.500
Impact of novel coronavirus infection in patients with uveitis associated with an autoimmune disease: Result of the COVID-19-GEAS patient survey	Fanlo et al. (2021) [18]	Archivos de la Sociedad Española de Oftalmología	0.209

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Profound weakness and blurry vision in a pandemic: A case report	O'Keefe et al. (2021) [37]	Clinical Practice and Cases in Emergency Medicine	0.270
Outcomes of COVID-19 in patients with primary systemic vasculitis or polymyalgia rheumatica from the COVID-19 Global Rheumatology Alliance physician registry: a retrospective cohort study	Sattui et al. (2021) [19]	The Lancet Rheumatology	25.400
Systemic autoimmune diseases in patients hospitalized with COVID-19 in Spain: A nation-wide registry study	Moreno-Torres et al. (2022) [16]	Viruses	5.818

Pakhchanian and collaborators (2022) performed a cohort study consisting of 141 patients with BD and COVID-19 and 864,533 patients with COVID-19 without BD [11]. They found that patients with BD were not at an increased risk of worse COVID-19 outcomes when compared to the general population in the United States of America [11]. Also, Polat and collaborators (2022) published a retrospective cohort study to evaluate the COVID-19 outcomes in patients with BD [25]. Out of a total of 648 patients, 59 presented a positive SARS-CoV-2 test; three of them were hospitalized, and none were admitted to the intensive care unit or died [25]. Despite no deaths, the study showed that 32.2% of the patients suffered from exacerbation of at least one symptom related to the disease [25]. In the same way, Enginar and Gundogdu (2022) evaluated the frequency and clinical course of COVID-19 in patients with BD among 203 patients with the disease and a control group of 200 individuals [27]. The study did not identify any difference between both groups for the frequency of SARS-CoV-2 infection, length of hospital stays, lung involvement, intensive care unit admission, and mortality [27].

Table 5. Description of the previous published studies that evaluated patients with Behçet's disease (BD) who were infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing the coronavirus disease (COVID)-19 – literature review.

First author	Objective(s)	Method(s)	Result(s)	Conclusion(s)
Chang et al. (2023) [15]	To verify the association between COVID-19 and autoimmune diseases and to reveal discrepancies across the sex, age, and race of participants.	This retrospective cohort study based on the TriNetX U.S. Collaborative Network provides a closer insight into the association between COVID-19 and autoimmune diseases and reveals discrepancies across age, sex, race, adverse socioeconomic status, lifestyle-related variables, and comorbidities of participants. Between January 2020, and December 2021, 3,814,479 participants were included (888,463	After matching, the COVID-19 cohort exhibited higher risks of rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, dermatopolymyositis, systemic sclerosis, Sjögren's syndrome, mixed connective tissue disease, BD, polymyalgia rheumatica, vasculitis, psoriasis, inflammatory bowel disease, celiac disease, type 1 diabetes mellitus, and mortality.	COVID-19 is associated with a different degree of risk for various autoimmune diseases.

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		cases and 2,926,016 controls).		
Accorinti et al. (2022) [24]	To determine in patients with BD and ocular involvement the presence of SARS-CoV-2 infection and its influence on the course of ocular disease.	The study investigated 65 patients with Ocular BD living in Lazio, Italy, and attending the Uveitis Center of the Sapienza University of Rome. Of these patients, 8 patients resulted positive for a polymerase chain reaction (PCR) nasopharyngeal swab.	SARS-CoV-2 infection was found in 12.3% of 65 patients with ocular involvement and 3.84% of Lazio inhabitants, and it was unrelated to the use of immunosuppressive drugs. COVID-19 symptoms in patients with ocular involvement were mild, with one patient requiring hospitalization for interstitial pneumonia. None of the SARS-CoV-2 infected patients presented any uveitis relapses during the infection and in a subsequent median follow-up of 6 months.	Ocular involvement seems to be a risk factor for developing SARS-CoV-2 infection. Usually, this infection has a mild course and does not impact the course of uveitis.
Polat et al. (2022) [25]	To investigate the outcomes of COVID-19 in a cohort of patients with BD and to reveal the rate of BD exacerbations due to COVID-19.	Patients who have been followed with a diagnosis of BD were retrospectively investigated for a positive COVID-19 test. Data regarding demographics, clinical features, and COVID-19 outcomes were collected from medical records for patients with a positive diagnosis. Patients with COVID-19 were reached via phone numbers, and BD Current Activity Form scores for pre- and post-COVID-19 BD symptoms were calculated.	Out of a total of 648 patients with BD, 59 were detected to have a positive COVID-19 diagnosis. Three of the 59 patients (5.0%) were found to be hospitalized, none of them was admitted to the intensive care unit (ICU) or died. An increasing trend in the frequency of comorbid diseases and older age was observed in hospitalized patients. 32.2% of patients with BD suffered from exacerbation of at least one symptom related to BD.	The study observed no ICU admission or mortality with COVID-19 in the patients with BD. However, a substantial number of patients suffered from exacerbation of BD symptoms.
Zouboulis et al. (2021) [26]	To evaluate and create a list of measurements to be taken from	The researchers analyzed the available data of patients and the	In a survey of 2,789 Spanish patients, 28 had uveitis due to systemic autoimmune disease.	The prevalence of COVID-19 in patients with ABD is lower

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	patients with Adamantiades-BD (ABD) and their physicians during the COVID-19 pandemic.	existing literature based on the current evidence. Data from a telematic survey with 2,789 patients from Spain.	Among them, 12 were patients with ABD; with 6 reporting clinical manifestations compatible with COVID-19. Moreover, among 2,135 consecutive patients with COVID-19 presented to Hospital Clínic in Barcelona, Spain, 4 (0.19%) were co-diagnosed with ABD, and 3 were hospitalized. In all 4 patients, ABD activity during the first COVID-19 symptoms was low. No patient required ICU treatment or mechanical ventilation. Further, 51 of 54 ambulatory patients with ABD in Konya, Turkey continued their immunological treatment during the pandemic period; none of them developed COVID-19. Lastly, among 10 patients with ABD in Istanbul, Turkey with COVID-19, 8 were hospitalized. Two patients were admitted to the ICU and 1 patient, not been on treatment for ABD before getting COVID-19, died. COVID-19 symptoms were mild in the 9 patients who survived, and 3 patients reported exacerbations of their ABD-associated oral ulcers or arthralgia.	than that in the general population. This may be due to patients with ABD having been especially careful with social shielding. ABD appears not to be associated with a more severe COVID-19 course.
Correa-Rodríguez et al. (2021) [10]	To assess the prevalence of COVID-19 in a cohort of patients with BD and investigate	A retrospective study was conducted among 244 patients with BD. Each participant completed an online	The prevalence of COVID-19 was 14.75%. Regarding the dose of colchicine, the presence of ageusia was lower in patients taking 0.5	The prevalence of COVID-19 among patients with BD seems to be higher than that

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	whether those patients with long-term treatment have reduced or increased prevalence of COVID-19-related clinical outcomes.	questionnaire regarding demographics, medical conditions, dispensed colchicine, tumor necrosis factor inhibitors (TNFi) or oral glucocorticoids, COVID-19 diagnosis, clinical symptoms, and recovery.	mg/day of colchicine when compared to those taking 1.5 mg/day. The prevalence of dyspnea was higher in patients taking TNFi when compared with those without therapy. About oral glucocorticoids, no significant differences were found.	among the general population in Spain. Continuous TNFi therapy might increase the prevalence of worse clinical outcomes such as dyspnea; oral glucocorticoids and colchicine apparently did not protect the COVID-19-related clinical outcomes of patients with BD.
Enginar and Gundogdu et al. (2021) [27]	To evaluate the frequency and clinical course of COVID-19 in patients with BD.	The study included patients diagnosed with BD who were being followed up in the Dermatology and Rheumatology clinics. Patients who applied to the clinics and were not diagnosed with any rheumatological disease were taken as the control group. The medical records were examined retrospectively. A record was made of age, gender, additional systemic disease, for SARS-CoV-2, colchicine treatment dose, whether or not a PCR test was performed, disease course in patients diagnosed with COVID-19, length of stay in hospital, and the need or not for ICU admission.	Evaluation was made of 203 patients with BD and a control group of 200 individuals. No difference was determined between the groups in respect of age and gender. A PCR test for the SARS-CoV-2 was applied to 56 patients in the BD group, and 18 were reported positive, and to 80 subjects in the control group, of which 32 were determined positive. No difference was determined between the groups in terms of PCR test positivity. No difference was determined between the groups in length of stay in hospital, lung involvement, ICU admissions, and mortality rates. In the patients with BD group, in all the parameters there was no significant difference between	The results of this study showed no increased risk for patients with BD when compared to the normal population concerning the frequency of SARS-CoV-2 infection, length of hospital stay, lung involvement, ICU admission, and mortality.

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			those who were positive or negative for COVID-19.	
den Otter et al. (2022) [28]	To investigate the cumulative incidence and the severity of COVID-19 in patients with BD.	A retrospective cohort study of patients with BD was conducted. The researchers obtained the data from electronic patient files and through telephone interviews between February 2020 and May 2021. The main outcomes were COVID-19 diagnosis, disease duration, hospitalization, ICU admission, and mortality. The secondary outcome was adherence to quarantine measures as recommended by the government.	A total of 185 patients with BD were included; 58% of the patients were receiving colchicine, 30% anti-tumor necrosis factor-alpha (TNF-α), 16% azathioprine, and 8% systemic steroids. A total of 30 patients (16.2%) were positive for COVID-19. Within the cohort, the cumulative incidence of COVID-19 was therefore 16.2%, which is increased when compared to the general Dutch population. Four out of 30 (13%) patients were admitted to the hospital. There was no COVID-19-related mortality observed.	Patients with BD have a higher risk for COVID-19, without an increase of virus-related mortality. The course of COVID-19 disease in this cohort is relatively mild, with a lower admission rate than expected of patients using immunosuppressive medication.
Shahram et al. (2022) [14]	To present the clinical characteristics, disease course, management, and outcomes of COVID-19 in patients with BD.	In this retrospective cohort study, the authors retrieved patients with BD and with COVID-19. Demographic data, comorbidities, features related both to BD and COVID-19, treatments, and outcomes were collected. Comparisons between patients with or without hospitalization were performed.	The study described 61 episodes of COVID-19 in 59 patients with BD. The prevalence was 0.69%. The median disease duration was 162 months. BD features were similar except for a higher rate of arterial involvement and positive pathergy test in infected patients. Thirty-five episodes (62.5%) happened in non-active patients; 39% had a comorbid disease. COVID-19 manifestations were the same as the general population. Flu-like symptoms were the most common (85%), followed by fever (66%), ageusia/anosmia (56%), headache (51%),	The incidence of COVID-19 in patients with BD was not higher than the general population in Iran. They showed milder forms of disease with lower morbidity and mortality rates. Most were on immunosuppressive drugs or had a comorbidity apart from BD. No significant effect on the BD course was shown.

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			and pulmonary involvement (48%). There was no change in BD symptoms in 74%. Fifteen patients (25.4%) were hospitalized, and one patient (1.7%) died. Receiving glucocorticoids and cytotoxic drugs was associated with an increased rate of hospitalization.	
Pakhchanian et al. (2022) [11]	To evaluate the hospitalization, ICU admission, and case fatality rate of patients with BD and COVID-19.	In this retrospective comparative cohort study, the authors used the TriNetX database. The authors included all adults with a pre-existing diagnosis of BD who were diagnosed with COVID-19 between January 20, 2020, and June 18, 2021. The comparative cohort included adult patients with COVID-19 and without BD. The primary outcomes were hospitalization and severe COVID-19, which was defined as a composite outcome of mortality, ICU admission, mechanical ventilation, acute kidney injury, acute respiratory distress syndrome, ischemic stroke, venous thromboembolism, and/or sepsis, within 45 days of COVID-19 diagnosis.	The cohort consisted of 141 patients with BD and COVID-19 and 864,533 patients with COVID-19 and without BD. Patients with BD were of a similar age and more likely to be female. Most patients with BD (58%) were prescribed glucocorticoids, with 18% colchicine, and 12% azathioprine in the preceding year of COVID-19 diagnosis. The hospitalization rate was 18% in the BD cohort. The risk of hospitalization and severe COVID-19 did not differ between BD with COVID-19 and the comparative cohort both in unadjusted and propensity score matching analyses.	Patients with BD were not at an increased risk of worse COVID-19 outcomes when compared to the general population.
Yurttaş et al. (2020) [29]	To present a case series of BD with COVID-19 and	The authors enrolled 10 patients with BD (5 male) diagnosed	In total, 6 of 10 patients were diagnosed with pneumonia of which 3	The authors concluded that none of the

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	describe their presentation, disease course, management, and outcomes.	with COVID-19, between April and May 2020. Five patients were retrieved from the Cerrahpasa Medical Faculty COVID-19 inpatient database (N = 767). The remaining contacted the authors to ask whether they should continue their medication after having been diagnosed elsewhere. Data regarding initial signs and symptoms, laboratory analyses, and detailed medical treatment related to COVID-19 were retrieved via the "Ministry of Health Public Health Data Management System" database. Additionally, the authors assessed whether patients had any exacerbation of BD lesions during infection.	were PCR positive. The remaining 4 had tested positive with mild-to-moderate symptoms. Three patients reported exacerbations of oral ulcers or arthralgia. Additionally, 8 patients were hospitalized of whom 2 were admitted to the ICU. All patients received first-line treatment for COVID-19. One patient died from severe respiratory failure. One patient developed deep vein thrombosis.	drugs seemed to prevent COVID-19 since 9 of 10 patients were using either an immunosuppressive drug or colchicine. Nonetheless, the authors note that their sample was small and calls for further investigation for better correlation since the high frequency of pneumonia and occurrence of thrombosis in patients with auto-immune chronic conditions was described.
Eslambolchi et al. (2021) [30]	To evaluate the risk of COVID-19 and complications in patients with preexisting medical conditions such as rheumatic autoimmune disease or vasculitis.	Computed tomography (CT) has been employed as a diagnostic tool in the evaluation of patients with clinical suspicion of SARS-Cov-2 infection. The authors discussed chest CT features in patients with COVID-19 and underlying rheumatic diseases or vasculitis.	The chest CT images of a known case of BD with clinical findings in favor of COVID-19 and laboratory-confirmed COVID-19 pneumonia. A patch of ground-glass opacification/opacity was noted in the left upper lobe, consistent with COVID-19 pneumonia. There is a nodular density in the central lingula, which can be suggestive of nodular involvement of	The risk of COVID-19 and its associated complications is increased in patients with preexisting medical conditions. Patients with rheumatologic diseases and vasculitis can be at an increased risk of infection, due to

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			pulmonary parenchyma in BD. Nodular opacity can be a sign of vasculitis and parenchymal involvement in BD.	underlying impairment of immunity and adverse effects of corticosteroids or other immunosuppressive therapies on the immune system.
Mattioli et al. (2021) [31]	To assess the prevalence of SARS-CoV-2 infection among patients with BD, evaluating the possible association between demographic and clinical features and the risk of infection. Moreover, to evaluate the association between BD activity and treatment, and the risk of SARS-CoV-2 infection.	A survey was conducted on patients with BD followed at the Behçet's Centre of the Careggi University Hospital, Florence, Italy. Confirmed cases of SARS-CoV-2 infection were defined by nasopharyngeal swab positivity. The authors also evaluated the possible association between BD disease activity and treatment, and the risk of SARS-CoV-2 infection by collecting demographic and clinical parameters for disease activity using the BD Current Activity Form.	Out of 335 patients with BD contacted, 14 cases of SARS-CoV-2 were identified between April 2020 and February 2021, suggesting a prevalence of COVID-19 among patients with BD of 4.2%, in line with the data of the general population in Italy (4.4%). When comparing clinical features between SARS-CoV-2 cases and matched SARS-CoV-2 negative patients with BD, it was found that the presence of different disease manifestations did not differ between the two groups. SARS-CoV-2 cases and controls were also comparable in terms of immunosuppressive therapy, with the only exception of corticosteroids (71.4% vs. 35.7%), whose daily dose was higher in cases than controls, suggesting that the right timing of usage and the more appropriate dosage of corticosteroid are a key question for the better management of these patients.	Patients with BD do not seem to be at a greater risk of SARS-CoV-2 infection or severe complications when compared with the general population.

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Espinosa et al. (2021) [13]	To describe the characteristics of 4 patients with BD and COVID-19.	The authors describe the first single-center experience of COVID-19 in patients who fulfilled the international criteria for BD, including clinical characteristics, antiviral and immunomodulatory treatment, and outcomes. The researchers used nasopharyngeal swab samples for all PCR.	The patients with BD had a COVID-19 clinical picture resembling the general population, and the severity of COVID-19 was mild in all cases. Two of the patients were receiving immunosuppressive agents at COVID-19 diagnosis.	The potential protective role of disease-modifying antirheumatic drugs and immunomodulatory agents in COVID-19 is unknown.
Mehta et al. (2023) [32]	To evaluate the describe a case of a 54-year-old patient with multiple pseudoaneurysms in the course of COVID-19 in the presence of immunosuppression.	The authors report the case of a 54-year-old man who presented with a 2-week history of symptoms attributable to infrarenal aortic and left tibioperoneal trunk pseudoaneurysms, defined by CT angiography which also revealed right lower lobe pulmonary artery and right anterior tibial arterial aneurysms. A prior history of recurrent oral ulceration, periodic fever, cerebral venous sinus thrombosis, and aseptic endocarditis with pulmonary emboli invoked a diagnosis of BD. Immunosuppression was commenced, following synchronous endovascular and	The experience with the study's patient presenting with life- and limb-threatening aneurysmal pathology, not all of which were amenable to endovascular intervention, supports the use of open surgery while ensuring that the patient obtains intensive immunosuppressive therapy to prevent postprocedural inflammatory changes, leading to adverse events such as anastomotic pseudoaneurysm. Careful consideration should be given to the use of immunosuppressive therapy in conditions such as BD when there is a risk of COVID-19.	Definitive guidelines are needed for the safe and effective treatment of patients with BD without altering their prognosis.

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		open arterial intervention, except for the pulmonary artery aneurysm.		
Nas et al. (2022) [33]	Seven patients with BD and COVID-2019 were presented, and the drugs used, prognosis, accompanying diseases, hospitalization, and complications were discussed.	Pre- and post-clinical data, radiological and laboratory findings and treatment prognosis of 7 patients who contracted COVID-19 were presented.	The study enrolled 7 patients with COVID-19 and BD. Three of the patients had comorbidities. The patient with total vision loss caused by BD had the longest hospital stay. In the case series, one hospitalized patient who was not on colchicine experienced an increased frequency of oral aphthous ulcers. The patient was clinically stable and received follow-up care; however, she was re-prescribed colchicine upon worsening of her oral ulcer complaints after COVID-19.	Patients with BD are no more susceptible to COVID-19 than the normal population, but 2 patients required support in the hospital setting (antibiotics and steroids) because of their comorbidities.
Bourguiba et al. (2022) [21]	To describe the epidemiological features associated with severe disease form and death.	A national multicentric prospective cohort study was conducted from the French Rheumatic and Musculoskeletal Diseases COVID-19 cohort. Patients with systemic autoinflammatory diseases were matched with patients with non-systemic autoinflammatory diseases on age ± 7 years, gender, and number of comorbidities to consider important confounding factors. The impact of systemic autoinflammatory diseases on the	The study identified 117 patients with systemic autoinflammatory diseases and compared them with 1,545 patients with non-autoinflammatory immune-mediated inflammatory disorders. A total of 67 patients had a monogenic systemic autoinflammatory disease (64 with familial Mediterranean fever). Other systemic autoinflammatory diseases were BD (N = 21), undifferentiated systemic autoinflammatory diseases (N = 16), adult-onset Still disease (N = 9), and systemic-onset juvenile idiopathic arthritis (N = 5). Ten	As identified in the whole French Rheumatic and Musculoskeletal Diseases COVID-19 cohort, patients with systemic autoinflammatory diseases on corticosteroids and with multiple comorbidities are prone to develop more severe COVID-19 forms.

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		severity of COVID-19 was analyzed using multinomial logistic regression for severity in 3 classes (mild, moderate, and severe with mild status as a reference). Fine-Gray regression model for length of hospital stay and a binomial logistic regression model for risk of death at 30 days were applied.	adults developed severe form (8.6%). Six patients died. All children had a benign disease. After matching on age ± 7 years, sex, and number of comorbidities, no significant difference between the two groups in length of stay and the severity of infection was noted. Thus, the weight of comorbidities appeared more important than the underlying disease; indeed 41/117 (35%) patients with COVID-19 and systemic autoinflammatory disease displayed one or more comorbidities	
Oztas et al. (2022) [20]	To investigate whether users of regular doses of colchicine or hydroxychloroquine had an additional advantage in terms of prevention of COVID-19 or its severity.	The study was conducted between June and September 2020, in patients with familial Mediterranean fever and BD who had been taking colchicine and in patients with systemic lupus erythematosus, rheumatoid arthritis, and Sjogren's syndrome who had been taking hydroxychloroquine for at least 3 months. The electronic records of the patients who had visited in rheumatology outpatient clinics of Istanbul University-Cerrahpasa and Istanbul University for the last 2 years were reviewed.	A total of 635 colchicine users (373 familial Mediterranean fever and 262 BD) and their 643 contacts as well as 317 hydroxychloroquine users (197 systemic lupus erythematosus, 79 rheumatoid arthritis, and 41 Sjogren's syndrome) and 333 contacts were included. Anti-SARS-CoV-2 nucleocapsid IgG was positive in 43 (6.8%) colchicine users and 35 (5.4%) contacts. COVID-19-related symptoms were described by 29 (67.4%) of 43 patients and 17 (48.6%) of 35 contacts, and hospital admission was observed in 5 (11.6%) and 1 (2.9%) of these subjects, respectively. It was observed higher rates of symptomatic	Being on the treatment of regular doses of colchicine or hydroxychloroquine was not effective in the prevention of COVID-19 and ameliorating its manifestations. Nevertheless, these medications did not cause worse outcomes during the COVID-19 either.

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		Patients treated with any biologic or anti-cytokine treatments were not included. Patients and their household contacts who were not taking colchicine or hydroxychloroquine were invited to participate by phone calls. Demographic features of the participants were recorded, and all of them were questioned for COVID-19 diagnosis or its known symptoms (fever, cough, myalgia, headache, dyspnea, sore throat, diarrhea, loss of smell, and taste) before study entry. COVID-19-associated hospitalizations including ICU were checked from the electronic health records. Patients and controls who were diagnosed with COVID-19 with a positive PCR test before antibody assessment were also included.	COVID-19 and more hospitalization among colchicine users, when compared with household contacts despite similar seropositivity for SARS-CoV-2, however, these findings were not significant. Likewise, daily use of hydroxychloroquine at standard doses did not show any additional benefit for symptoms and hospitalizations due to COVID-19.	
Ozcifci et al. (2022) [57]	To describe the incidence, clinical characteristics, disease course, management, and outcome in a cohort of patients with BD and COVID-19.	The authors defined a cohort of 1,047 patients with BD who were aged between 16 and 60 years and seen routinely before the pandemic at the multidisciplinary outpatient clinic. The researchers followed prospectively this cohort from the	Of the 1,047 (599 male) patients, 592 (344 males) (56.5%) were tested for COVID-19 at least once. Of these 592, 215 (127 male) were tested positive. The median number of PCR tests was higher among those who were tested positive when compared to those who were tested negative. Of	Patients with BD have an increased risk of testing positive for SARS-CoV-2 suggesting caution during the follow-up of these patients. Despite increased incidence, the

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		beginning of April 2020 until the end of April 2021. During 13 months of follow-up of the 1,047 (599 males) patients, 592 (56.5%) were tested for SARS-CoV-2 PCR at least once and 215 (20.5%) were tested positive.	the 377 (218 male) patients who tested negative, 10 had pneumonia specific to COVID-19 and 5 were hospitalized. There were 92 patients (8.8%) who were living outside of Istanbul in the cohort and of these, 35 (38.0%) tested positive. The most common symptoms on follow-up were dyspnea/chest pain, neuropsychiatric complaints, blood pressure dysregulations, arrhythmia, and cough. Further investigation revealed none of the patients suffered myocardial infarction, stroke, or cerebrovascular event. Despite increased incidence, the clinical outcome of COVID-19 was not severe and there was no mortality.	clinical outcome of COVID-19 was not severe and there was no mortality.
AlBloushi et al. (2022) [23]	To investigate the incidence, severity, and outcomes of COVID-19 in patients with uveitis treated with biologic agents during the COVID-19 pandemic.	In this prospective study, it was included all patients with uveitis treated with biological agents and tested for COVID-19 between May and October 2020.	A total of 59 patients were identified. BD was the most common diagnosis (64.4%). Infliximab was the most frequent biologic agent used (61%). Nine (15.3%) patients were tested positive for COVID-19. None of the patients with positive COVID-19 tests developed any COVID-19-related symptoms during follow-up. Of the 9 patients with positive COVID-19 tests, only 2 patients had uveitis flare-ups after the biological suspension.	Uveitis patients under biologic therapy can be silent carriers for COVID-19.

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El Hasbani et al. (2023) [35]	To describe the case of a 35-year-old woman with BD who was in remission while on colchicine for 2 years, until erythema nodosum lesions appeared on her right shin, testing positive for SARS-CoV-2 a few days later.	The authors highlight the case of a 35-year-old woman with pre-existing BD in remission on colchicine presenting with new onset erythema nodosum-like lesions on her right shin being diagnosed with COVID-19 a few days after.	Despite treatment with systemic corticosteroid, the lesions did not resolve, necessitating the initiation of anti-interleukin-6 therapy.	BD flare can occur secondary to COVID-19. While most flare signs resolve with the continuation of the remission treatments, some flares need aggressive treatment such as systemic corticosteroids.
Lim et al. (2023) [30]	To describe the main characteristics of the disease coincidence for BD and COVID-19 and to highlight possible management implications.	A prospective study that assessed patients in the German Registry of ABD who were reported infected with SARS-CoV-2 from March 2020 to October 2022.	The study analyzed 14 patients with COVID-19. In 13 patients, symptoms ranged from asymptomatic to moderate fatigue and transient myalgia. Two patients reported a loss of taste. The study reported no hospitalization and no changes to BD medication in 13 patients. All patients recovered completely, but 2 had long-term sequelae.	The study suggests that systemic ABD is not necessarily with severe COVID-19 course and the ABD treatment does not predispose to SARS-CoV-2 infection.
Al-Adhoubi et al. (2022) [17]	To investigate the outcomes of patients with rheumatic diseases infected with COVID-19 in Oman.	A multi-center retrospective cohort study included patients with underlying rheumatological conditions and COVID-19. Data were collected through the electronic record system and by interviewing the patients through a standard questionnaire.	A total of 113 patients with different rheumatic diseases were included with the following rheumatological diagnoses: rheumatoid arthritis (40.7%), systemic lupus erythematosus (23.1%), psoriatic arthritis (8.0%), BD (7.0%), ankylosing spondylitis (6.2%), other vasculitis, including Kawasaki disease (4.4%), and other diagnoses (10.6%). The mean (SD) age of patients was 43 (14) years, and 82.3% were	COVID-19 in patients with rheumatic diseases have an increased mortality rate in comparison to the general population, with diabetes mellitus, morbid obesity, chronic kidney diseases, interstitial lung disease, cardiovascular disease, obstructive lung disease,

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			female. The diagnosis of COVID-19 was confirmed by PCR test in 84.1% of the patients. The most common symptoms at the time of presentation were fever (86%), cough (81%), headache (65%), and myalgia (60%). Hospitalization due to COVID-19 was reported in 24.1% of the patients, and 52.2% of these patients had received some form of treatment. The intake of immunosuppressive and immunomodulating medications was reported in 91.1% of the patients. During the COVID-19, 68% of the patients continued taking their medications. Comorbidities were present in 39.8% of the patients. Pregnancy was reported in 2% of the patients. The 30-day mortality rate was found to be 3.5%. Diabetes mellitus, obesity, and interstitial lung diseases were the strongest risk factors for mortality. Rituximab was given in 3.8% of the patients, and it was associated with increased mortality among the patients.	and liver diseases as comorbidities being the most severe risk factors associated with death.
Fanlo et al. (2021) [18]	To describe the characteristics of COVID-19 in patients with uveitis associated with systemic autoimmune	Internal Medicine Society and Group of Systemic Autoimmune Disease conducted a telematic survey of patients with systemic	A total of 2,789 patients answered the survey, of which 28 had a diagnosis of uveitis associated with systemic autoimmune disease. The majority (82%) were female and	Both asymptomatic and symptomatic COVID-19 patients with systemic autoimmune

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	disease through telematic survey.	autoimmune disease to learn about the characteristics of COVID-19 in this population.	Caucasian (82%), with a mean age of 48 years. The most frequent systemic autoimmune diseases were BD followed by Sarcoidosis and systemic lupus erythematosus. A total of 46% of the patients were receiving corticosteroid treatment at a mean prednisone dose of 11 mg/day. Regarding infection, 14 (50%) patients reported symptoms compatible with COVID-19, mainly, cough, diarrhea, and dysgeusia. PCR was performed on the nasopharyngeal smear in two patients and one of them (4%) was positive – the patient had a diagnosis of Sarcoidosis.	disease-associated uveitis had received similar immunosuppressive treatment.
O'Keefe et al. (2021) [36]	To describe a clinical case report of COVID-19 in a patient with BD who presented profound weakness and blurry vision.	It was discussed the case of a 22-year-old male with COVID-19 who presented to the emergency department with weakness and vision changes. Brain imaging showed enhancing lesions. History revealed possible autoimmune disease. A diagnosis of BD exacerbated by SARS-CoV-2 infection was made.	During the admission of the patient, he continued to be weak and developed aphasia, right hemiparesis with spasticity, uncontrollable laughter, and urinary incontinence. Initially, steroids were avoided due to COVID-19, but with worsening neurologic symptoms, it was decided that the benefits outweighed the risks, and he was started on one gram IV methylprednisolone daily for 5 days. He was also started on anticoagulation therapy due to both BD and SARS-CoV-2 infection being associated with hypercoagulable states.	More research is needed to understand the relationship between SARS-CoV-2 and the effect it has on autoimmune diseases, such as BD. It must also be noted that during the COVID-19 pandemic patients were initially avoiding seeking medical care, resulting in critical presentations requiring emergent intervention.

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			Prior to discharge after a 16-day admission, he had improvement in his neurologic symptoms, and repeat magnetic resonance imaging demonstrated improvement with near resolution of brain lesions. He was discharged on 40 mg subcutaneous adalimumab every 2 weeks and 60 mg oral prednisone daily with close rheumatology follow-up. Although the patient never developed typical symptoms of SARS-CoV-2, he did have a severe exacerbation of BD, which may have been in part due to this underlying viral illness and his delay in seeking medical attention due to the pandemic.	
Sattui et al. (2021) [19]	To investigate the factors associated with COVID-19 outcomes in patients with primary systemic vasculitis or polymyalgia rheumatica.	In this retrospective cohort study, adult patients (aged ≥18 years) diagnosed with COVID-19 between March 2020, and April 2021, who had a history of primary systemic vasculitis (antineutrophil cytoplasmic antibody-associated vasculitis, giant cell arteritis, BD, or other vasculitis) or polymyalgia rheumatica, and were reported to the COVID-19 Global Rheumatology Alliance registry were included. To assess COVID-19	Of 1,202 eligible patients identified, 733 (61.0%) were women 469 (39.0%) were men, and their mean age was 63.8 years. A total of 374 (31.1%) patients had polymyalgia rheumatica, 353 (29.4%) had antineutrophil cytoplasmic antibody-associated vasculitis, 183 (15.2%) had giant cell arteritis, 112 (9.3%) had BD, and 180 (15.0%) had other vasculitis. Of 1,020 (84.9%) patients with outcome data, 512 (50.2%) were not hospitalized, 114 (11.2%) were hospitalized and did not receive	Among patients with primary systemic vasculitis and polymyalgia rheumatica, severe COVID-19 outcomes were associated with variable and largely unmodifiable risk factors, such as age, sex, and number of comorbidities, as well as treatments, including high-dose glucocorticoids.

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		outcomes in patients, it was used an ordinal COVID-19 severity scale, defined as no hospitalization; hospitalization without supplemental oxygen; hospitalization with any supplemental oxygen or ventilation; or death. Multivariable ordinal logistic regression analyses were used to estimate odds ratio (OR)s, adjusting for age, sex, time period, number of comorbidities, smoking status, obesity, glucocorticoid use, disease activity, region, and medication category. Analyses were also stratified by type of rheumatic disease.	supplemental oxygen, 239 (23.4%) were hospitalized and received ventilation or supplemental oxygen, and 155 (15.2%) died. Higher odds of poor COVID-19 outcomes were observed in patients who were older, were male compared with female, had more comorbidities, were taking 10 mg/day or more of prednisolone compared with none, or had moderate, or high or severe disease activity when compared with those who had disease remission or low disease activity. Risk factors varied among different disease subtypes.	
Moreno-Torres et al. (2022) [16]	To evaluate the clinical outcome of systemic autoimmune disease patients hospitalized with COVID-19 in Spain before the introduction of SARS-CoV-2 vaccines.	A retrospective study with data from population-based hospital discharge diagnoses at the Minimum Basic Data Set of the Spanish National Registry of Hospital Discharges was performed. It records information from all patients discharged at hospitals/clinics across the country since the nineties. Prior studies have been performed using this registry	Among 117,694 patients, only 892 (0.8%) presented any type of systemic autoimmune diseases before COVID-19-related admission: Sjogren's syndrome constituted 25%, systemic vasculitis 21%, systemic lupus erythematosus 19%, Sarcoidosis 17%, systemic sclerosis 11%, mixed and undifferentiated connective tissue disease 4%, BD 4% and inflammatory myopathies 2%. The in-hospital mortality rate	The COVID-19 mortality rate in patients with systemic autoimmune diseases during 2020 was 20%, higher than other hospitalized patients. It was related to the higher burden of comorbidities, probably secondary to direct organ damage and sequelae of

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	for other illnesses, including infectious diseases and systemic autoimmune diseases, and have demonstrated its high value for producing estimates of current burden and time trends for different clinical conditions at a national level. Data regarding demographics and outcomes, including age, gender, ethnicity, length of admission, ICU admission or death were included, as well as baseline conditions, as well as the presence of respiratory insufficiency. Among other medical conditions, it included diabetes mellitus, heart failure, dementia, chronic kidney disease, liver disease, and cancer, most of which have been associated with severe COVID-19.	was higher in systemic autoimmune disease individuals (20% vs. 16%). After adjustment by baseline conditions, systemic autoimmune diseases were not associated with a higher mortality risk. Mortality in the systemic autoimmune disease patients was determined by age, heart failure, chronic kidney disease, and liver disease.	their condition, and not due to systemic autoimmune diseases themselves.

Espinosa and collaborators (2021) enrolled 2,135 patients with SARS-CoV-2 infection in Barcelona. Of all patients, four had BD, of whom three were admitted to the hospital. In that study, patients with BD had a COVID-19 clinical picture resembling the general population, and the severity of COVID-19 was mild in all cases [13]. In the same context, Eslambolchi and collaborators (2021) compared computed tomography scan findings in patients with systemic autoimmune diseases which enrolled only one case of BD exposing a patch of ground glass opacity in the left upper lobe, consistent with COVID-19 pneumonia and a nodular density in central lingula, which can be suggestive of nodular involvement of pulmonary parenchyma in BD [26].

Correa-Rodríguez and collaborators (2021) performed a retrospective study conducted among 244 patients with BD [10]. The authors found that the prevalence of COVID-19 among those patients seems to be higher than that among the general population in Spain [10]. The authors hypothesized that continuous tumor necrosis factor inhibitor therapy might increase the prevalence of worse clinical outcomes such as dyspnea; oral glucocorticoids and colchicine apparently did not protect COVID-19-related clinical outcomes in patients with BD [10]. In the same way, Den Otter and

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collaborators (2022) performed a cohort to investigate the cumulative incidence and the severity of COVID-19 in patients with BD (N = 185) [27] demonstrating a higher risk for COVID-19 without an increase of virus-related mortality [27]. The course of COVID-19 disease in this cohort was mild, with a lower admission rate than expected of patients using immunosuppressive medication [27].

Shahram and collaborators (2022) evaluated data from 61 episodes of COVID-19 in 59 patients with BD that demonstrated an equal incidence of COVID-19 in patients with BD and the general population in Iran [14]. In addition, the patients showed milder phenotypes with lower morbidity and mortality rates, and, most of the patients were on immunosuppressive drugs or had a comorbidity apart from BD [14]. The same results were obtained by Mattioli and collaborators (2021) who assessed the prevalence of SARS-CoV-2 infection among 335 patients with BD and, the authors, empathized that the disease did not cause a greater risk of COVID-19 or severe complications when compared with the general population [28].

Zouboulis and collaborators (2021) performed a telematic survey of 2,789 Spanish patients. The study concluded that the prevalence of COVID-19 in patients with Adamantiades-BD is lower than that in the general population [29] and, this fact, can be related to being careful with social shielding. Moreover, the authors concluded that Adamantiades-BD appears not to be associated with a more severe COVID-19 course [29]. Lim and collaborators (2023) described the characteristics of Adamantiates-BD in 14 patients with a positive SARS-CoV-2 infection test demonstrating a lower prevalence and a milder course of the disease [30]. Yet, Accorinti and collaborators (2022) described a higher prevalence of SARS-CoV-2 infection among those with BD and ocular involvement when compared with other inhabitants [12.3% (8/65) vs. 3.84% (220,349/5,730,588)] in Lazio, Italy [31].

Yurttaş and collaborators (2020) described the clinical profile of 10 patients with BD and COVID-19 concluding that none of the drugs used for BD treatment seemed to prevent COVID-19 since nine of 10 patients were using either an immunosuppressive drug or colchicine [32]. However, the authors also described a high frequency of pneumonia and thrombosis among the patients [32]. In contrast, a study published by Nas and collaborators (2022) investigated 7 cases and concluded that the use of colchicine may be effective in the treatment of COVID-19 and in managing the severity of the clinical phenotype [33].

Mehta and collaborators (2021) published a case report from a 54-year-old man with multiple pseudoaneurysms and COVID-19 that calls for attention to the challenges of diagnosing BD in patients with multiple symptoms [34]. El Hasbani and collaborators (2023) also published a case report of a 35-year-old woman with pre-existing BD in remission on colchicine presenting with new onset erythema nodosum-like lesions on her right shin being diagnosed with COVID-19 [35]. Despite treatment with a systemic corticosteroid, the lesions did not resolve, necessitating the initiation of anti-interleukin-6 therapy which highlighted the importance of correct diagnosis [35]. Finally, O'Kaeefe and collaborators (2021) described the case of a 22-year-old male with SARS-CoV-2 infection who presented to the emergency department with weakness and vision changes [36].

4. Discussion

BD is a chronic multisystem condition that is characterized by relapsing–remitting periods of a diverse spectrum of manifestations [3]. During the COVID-19 pandemic, concerns have been raised about whether patients with BD are at an increased risk of worse COVID-19 outcomes [14, 37]. As no specific guidelines for the treatment of COVID-19 were present for patients with BD, the management was done according to the general national guidelines defined by the Ministry of Health. In this context, we performed a cohort study using a national dataset that contained epidemiological information about those who were hospitalized due to COVID-19 in Brazil. In brief, our study data found that patients with BD were not at an increased risk of worse COVID-19 outcomes when compared to the general population in Brazil as published before [38, 39].

In Brazil, Sansone and collaborators (2022) published a study with 2,740,272 hospitalized patients due to severe acute respiratory infection to evaluate the epidemiologic profile of the patients during the COVID-19 pandemic [38]. The authors concluded that patients with a higher risk of death had a different epidemiological profile when compared with patients who recovered from the

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infection, like older age, Black, Indigenous, and multiracial background races, low educational level, residence in a flu outbreak region, need for intensive care unit and need for mechanical ventilatory support [38]. Moreover, the patients with COVID-19 in the general population presented a case fatality rate of 34.7% which was above the 26.1% observed for patients with BD. However, the case fatality rate for patients with BD was above other populations evaluated in that study, such as patients infected with a) Influenza virus (14.2%), b) another respiratory virus (4.6%), c) another known etiological agent, and d) undefined etiological agent (19.8%) [38]. The same research group published another study conducted with 585,655 hospitalized individuals with a positive result in the SARS-CoV-2 test to evaluate the characterization of demographic data, clinical signs, comorbidities, and outcomes according to the race in Brazil [39]. The study concluded that Black individuals, alongside multiracial background individuals and the Indigenous populations, were at increased risk of death in COVID-19 [39]. Curiously, for all races, the case fatality rate was higher than those described here for patients with BD observed the highest rate for Indigenous peoples followed by Black people (41.7%), multiracial background people (39.1%), White people (35.7%), and Asians (35.6%) [39]. Yet, for Indigenous peoples, in another study with 3,122 patients, 1,994 were diagnosed with COVID-19 and 730/1,816 (40.2%) of them died [40]. The study also concluded the Indigenous population is at a higher risk for death in COVID-19 when compared to the rest of the population [40].

Also, In Brazil, other studies were published using the same data set to evaluate the impact of the disease among those with genetic conditions, mainly the rare ones. For example, two studies evaluated if patients with Down syndrome were at higher risk for worse outcomes in COVID-19 [41, 42]. One study included 3,117,562 individuals with severe acute respiratory infections representing 2 years of the COVID-19 pandemic in Brazil. From these, 5,152 individuals were identified as individuals with Down syndrome and were positive for SARS-CoV-2 infection. In this study, the patients with Down syndrome presented a case fatality rate of 42.3% versus 35.5% from the general population with a relative risk of 1.193 [95%CI = 1.156 to 1.232] [41]. Also, another study accounted for three groups of individuals, patients with Down syndrome and COVID-19 (N = 1619), patients with Down syndrome without COVID-19 (N = 1431), and patients without Down syndrome and comorbidities (N = 222,181) that presented, respectively, the following case fatalities rates, 39.2%, 18.0%, and 14.0% [42]. Both studies showed higher case fatality rates in patients with Down syndrome when compared to the rest of the population, as well as, with patients with BD [41, 42]. Moreover, another study described the characteristics of 18 patients with COVID-19 and X-linked disorders [Hemophilia B (1 patient), Klinefelter syndrome (8 patients – 3 deaths occurred, 1 unrelated to SARS-CoV-2 infection), and Turner syndrome (9 patients – 2 patients died] in a cohort of 2,066,678 Brazilian patients hospitalized due to COVID-19 in Brazil. Nearly half of the patients needed intensive care unit (8/17), and a quarter required invasive mechanical ventilation (4/16) [43]. Importantly, even among the patients with X-linked disorders, the case fatality rate was above the rate of patients with BD in Brazil. Curiously, in Brazil, it was described that asthma among the chronic conditions, especially pulmonary ones, was not associated with a high chance of dying or needing mechanical ventilation in COVID-19 [44]. The data described for asthma apparently contradicts what was expected, and the same scenario may have occurred for BD, as we will describe below.

When compared to the existing published literature, there are conflicting results. There are published papers that highlight that patients with BD are at higher risk for severe cases of COVID-19, while others concluded that these patients are not at higher risk than the ordinary population. However, several factors may interfere with these results. For example, medication non-adherence and disrupted continuity of medical care are associated with rheumatologic disease fares and worsening disease activity and can play a key role in exacerbations for patients with BD.

Some studies evaluated patients with BD among those with other clinical conditions, for example, other autoimmune diseases, mainly for rheumatic disease [15–19, 21]. Those studies demonstrated that autoimmune diseases could affect the COVID-19 course based on their peculiarities [15] being, for example, systemic autoimmune diseases such as rheumatic ones predictors of a poor outcome during the SARS-CoV-2 infection [16, 17, 19]. In contrast, individuals

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with uveitis associated with autoimmune disease did not present worse clinical outcomes and had similarly received immunosuppressive treatment when it was compared to asymptomatic and symptomatic patients with COVID-19 [18].

Regarding the treatment of systemic autoimmune diseases, the results in the literature had conflicting information about their impact on protection from COVID-19 or developing less severe disease; for example, in one study colchicine or hydroxychloroquine were ineffective in preventing COVID-19 and ameliorating its manifestations [20], but, other study demonstrated that the patients in use of corticosteroids and with multiple comorbidities were prone to develop more severe COVID-19 phenotypes [21]. Among those with BD, the literature is scarce about the response of therapy in preventing COVID-19 or attenuating its severity. In this context, it is postulated that some treatments, such as the use of colchicine had no link with COVID-19 among those with BD [10, 22]. In this context, it is postulated that some treatments, such as the use of colchicine had no link with COVID-19 among those with BD [10, 22, 32], except in one study that investigated 7 cases and concluded that the use of colchicine may be effective in the treatment of COVID-19 and in managing the severity of the clinical phenotype [33].

Most of the studies about BD and COVID-19 demonstrated that the patients were not at a higher chance of death or severity phenotype when compared with the general population, even, in some study populations there is a low chance of SARS-CoV-2 infection or the presence of high proportion of asymptomatic patient [11, 13, 14, 24, 25, 25, 28–30], maybe due social shielding [29]. Importantly, despite the absence of increased severity or mortality rates, some data in the literature showed that patients with BD suffered from an increased exacerbation rate related to COVID-19 or had some clinical manifestations such as pneumonia and thrombosis [24, 32]. Even, in the literature, some studies demonstrated only a higher prevalence of COVID-19 among patients with BD without impact on severity [10, 27, 31]. Moreover, it is important to highlight the need for a correct diagnosis even among those with a rare COVID-19 phenotype [35, 36, 45]. In brief, in Brazil, Boschiero et al. (2022) evaluated a population of 1,851,592 hospitalized individuals due to COVID-19 with the data for COVID-19 and outcomes, among these individuals, 632,101/ (34.1%) deaths were observed [41]. This data demonstrated the higher impact of COVID-19 among the general population in Brazil when compared with patients with BD.

Elmas and collaborators (2020) published a narrative review regarding treatment considerations for BD in the COVID-19 era [46]. The study concluded that topical treatments, colchicine, and non-steroidal anti-inflammatory drugs should not be discontinued for pandemic-related causes [46]. It suggests that systemic steroids can be used at the lowest possible dose if needed. The study also encourages ongoing treatments in patients with no suspected or confirmed COVID-19 [46]. In cases with COVID-19 symptoms, immunosuppressive and biological agents can be temporarily stopped but the decision should be made individually for each patient [46]. For example, the reduction in intravenous treatment adherence of patients with chronic inflammatory rheumatic diseases during the COVID-19 pandemic was associated with fear of COVID-19 and SARS-CoV-2 positivity seemed to be the major reasons for discontinuing/postponing intravenous treatments [47]. Also, patients with long disease duration and less systemic involvement may be more prone to discontinuing their treatments [47]. In addition, patients with neuro-BD had neurological and psychiatric issues with COVID-19 causing negative effects on an individual's mental health and increasing rates of stress, anxiety, and depression [48]. Besides that, no complications related to treatments were encountered in any of the patients that were followed during the pandemic period in a cohort study [49], as we showed and the literature review also demonstrated, patients with BD are not at higher risk of infection or severity due to COVID-19.

Regarding the COVID-19 pandemic control, Apaydin and collaborators (2022) investigated the side effects and post-vaccine disease exacerbation rates of COVID-19 vaccines in a BD cohort comprising 450 patients that demonstrated that the vaccines were well tolerated, and side effects were more common after mRNA vaccines [50]. Curiously, exacerbations after the COVID-19 vaccine were common, predominantly mucocutaneous and articular involvement, and exacerbations in the form of other organ involvement were rare [50]. In this context, special attention must be paid to

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phase IV clinical studies on vaccines in order to facilitate better management of the pandemic, including for specific populations that should not be neglected [51].

Finally, Zhao and collaborators (2023) analyzed the potential relationship between COVID-19 and BD using transcriptome data [37]. The study found that patients with BD are at an increased risk of developing severe COVID-19, and the effectiveness of conventional drugs for BD may be reduced, making the treatment of patients with both diseases more difficult [37]. In contrast, the epidemiological studies demonstrated, the majority of them, a contrary response with a low chance of infection and severity.

Although this was a large national study, it has limitations including possible errors in coding/data entry, which are inherent limitations of studies using electronic health records. The literature provides an insight on how the disease relates to COVID-19 in other countries. However, mixed results and the lack of deeper investigation with a larger number of patients make it difficult to establish a pattern. Furthermore, the disease is less prevalent in Brazil when compared to endemic areas, therefore results may not be generalizable to regions where BD is endemic and more severe. Further studies are encouraged for better understanding and to establish better healthcare propositions and policies for this population, mainly in Brazil, where the COVID-19 pandemic has had a major impact on all sectors of society and was linked with a high rate of underreporting [52–56].

5. Conclusions

Patients with BD were not at an increased risk of worse COVID-19 outcomes when compared to the general population in Brazil and the literature.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of São Francisco University protocol code 36628020.0.0000.5514, February 27, 2023.

Informed Consent Statement: The requirement for obtaining a free and informed consent form was waived by the Ethics Committee. This decision was based on the fact that participant information was collected from a public database provided by the Brazilian Ministry of Health. This database does not contain personal identifying information such as names, addresses, personal documents, telephone numbers, or email addresses of the patients, which could be used to identify them. Everyone included in the research has a unique code in the original database. The complete dataset can be obtained at the following address: https://opendatasus.saude.gov.br/dataset/srag-2021-a-2023.

Data Availability Statement: The complete dataset can be obtained at the following address: https://opendatasus.saude.gov.br/dataset/srag-2021-a-2023.

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References

1. Suzuki Kurokawa, M.; Suzuki, N. Behcet's Disease. *Clin Exp Med* **2004**, *4*, 10–20, doi:10.1007/s10238-004-0033-4.
2. Sakane, T.; Takeno, M.; Suzuki, N.; Inaba, G. Behçet's Disease. *N Engl J Med* **1999**, *341*, 1284–1291, doi:10.1056/NEJM199910213411707.
3. Nair, J.R.; Moots, R.J. Behcet's Disease. *Clin Med (Lond)* **2017**, *17*, 71–77, doi:10.7861/clinmedicine.17-1-71.
4. Tong, B.; Liu, X.; Xiao, J.; Su, G. Immunopathogenesis of Behcet's Disease. *Front Immunol* **2019**, *10*, 665, doi:10.3389/fimmu.2019.00665.
5. Nakamura, K.; Tsunemi, Y.; Kaneko, F.; Alpsoy, E. Mucocutaneous Manifestations of Behçet's Disease. *Front Med (Lausanne)* **2020**, *7*, 613432, doi:10.3389/fmed.2020.613432.
6. Kiafar, M.; Faezi, S.T.; Kasaeian, A.; Baghdadi, A.; Kakaei, S.; Mousavi, S.A.; Nejadhosseinian, M.; Shahram, F.; Ghodsi, S.Z.; Shams, H.; et al. Diagnosis of Behçet's Disease: Clinical Characteristics, Diagnostic Criteria, and Differential Diagnoses. *BMC Rheumatol* **2021**, *5*, 2, doi:10.1186/s41927-020-00172-1.
7. Watanabe, K.; Tanida, S.; Inoue, N.; Kunisaki, R.; Kobayashi, K.; Nagahori, M.; Arai, K.; Uchino, M.; Koganei, K.; Kobayashi, T.; et al. Evidence-Based Diagnosis and Clinical Practice Guidelines for Intestinal Behçet's Disease 2020 Edited by Intractable Diseases, the Health and Labour Sciences Research Grants. *J Gastroenterol* **2020**, *55*, 679–700, doi:10.1007/s00535-020-01690-y.
8. Alibaz-Oner, F.; Direskeneli, H. Advances in the Treatment of Behcet's Disease. *Curr Rheumatol Rep* **2021**, *23*, 47, doi:10.1007/s11926-021-01011-z.
9. Ciotti, M.; Ciccozzi, M.; Terrinoni, A.; Jiang, W.-C.; Wang, C.-B.; Bernardini, S. The COVID-19 Pandemic. *Crit Rev Clin Lab Sci* **2020**, *57*, 365–388, doi:10.1080/10408363.2020.1783198.
10. Correa-Rodríguez, M.; Callejas-Rubio, J.-L.; Rueda-Medina, B.; Ríos-Fernández, R.; Hera-Fernández, J. de la; Ortego-Centeno, N. Clinical Course of Covid-19 in a Cohort of Patients with Behçet Disease. *Med Clin (Engl Ed)* **2022**, *159*, 262–267, doi:10.1016/j.medcle.2022.08.009.
11. Pakhchanian, H.; Raiker, R.; Kardeş, S. COVID-19 among Patients with Behçet Syndrome in the United States. *Clin Rheumatol* **2022**, *41*, 317–319, doi:10.1007/s10067-021-05936-9.
12. Hyrich, K.L.; Machado, P.M. Rheumatic Disease and COVID-19: Epidemiology and Outcomes. *Nat Rev Rheumatol* **2021**, *17*, 71–72, doi:10.1038/s41584-020-00562-2.
13. Espinosa, G.; Araujo, O.; Amaro, S.; Bodro, M.; Moreno, P.J.; Moreno, R.; Ugarte, A.; Cervera, R. COVID-19 and Behçet's Disease: Clinical Case Series. *Ann Rheum Dis* **2021**, *80*, e41, doi:10.1136/annrheumdis-2020-217778.
14. Shahram, F.; Esalatmanesh, K.; Khabbazi, A.; Rezaieyazdi, Z.; Mirfeizi, Z.; Sadeghi, A.; Soroosh, M.; Kavosi, H.; Alikhani, M.; Mostafaei, S. Coronavirus Disease 2019 in Patients with Behcet's Disease: A Report of 59 Cases in Iran. *Clin Rheumatol* **2022**, *41*, 1177–1183, doi:10.1007/s10067-021-06004-y.
15. Chang, R.; Yen-Ting Chen, T.; Wang, S.-I.; Hung, Y.-M.; Chen, H.-Y.; Wei, C.-C.J. Risk of Autoimmune Diseases in Patients with COVID-19: A Retrospective Cohort Study. *EClinicalMedicine* **2023**, *56*, 101783, doi:10.1016/j.eclinm.2022.101783.
16. Moreno-Torres, V.; de Mendoza, C.; Mellor-Pita, S.; Martínez-Urbistondo, M.; Durán-del Campo, P.; Tutor-Ureta, P.; Vázquez-Comendador, J.-M.; Calderón-Parra, J.; Múñez-Rubio, E.; Ramos-Martínez, A.; et al. Systemic Autoimmune Diseases in Patients Hospitalized with COVID-19 in Spain: A Nation-Wide Registry Study. *Viruses* **2022**, *14*, 1631, doi:10.3390/v14081631.
17. Al-Adhoubi, N.K.; Ali, M.; Wahshi, H.A.; Salmi, I.A.; Al-Balushi, F.; Lawati, T.A.; Mohammed, A.; Muqbali, A.A.; Kalbani, H.A.; Al-Abrawi, S.; et al. COVID-19 Mortality in Patients with Rheumatic Diseases: A Real Concern. *Curr Rheumatol Rev* **2022**, *18*, 234–242, doi:10.2174/1573397118666220412114514.
18. Fanlo, P.; Espinosa, G.; Adán, A.; Arnáez, R.; Fonollosa, A.; Heras, H.; Oteiza, J.; Del Carmelo Gracia Tello, B.; Sáez Comet, L.; Pallarés, L. Impact of Novel Coronavirus Infection in Patients with Uveitis Associated with an Autoimmune Disease: Result of the COVID-19-GEAS Patient Survey. *Arch Soc Esp Oftalmol (Engl Ed)* **2021**, *96*, 347–352, doi:10.1016/j.oftale.2020.12.007.
19. Sattui, S.E.; Conway, R.; Putman, M.S.; Seet, A.M.; Gianfrancesco, M.A.; Beins, K.; Hill, C.; Liew, D.; Mackie, S.L.; Mehta, P.; et al. Outcomes of COVID-19 in Patients with Primary Systemic Vasculitis or Polymyalgia Rheumatica from the COVID-19 Global Rheumatology Alliance Physician Registry: A Retrospective Cohort Study. *Lancet Rheumatol* **2021**, *3*, e855–e864, doi:10.1016/S2665-9913(21)00316-7.
20. Oztas, M.; Bektas, M.; Karacan, I.; Aliyeva, N.; Dag, A.; Aghamuradov, S.; Cevirgen, S.B.; Sari, S.; Bolayirli, M.; Can, G.; et al. Frequency and Severity of COVID-19 in Patients with Various Rheumatic Diseases Treated Regularly with Colchicine or Hydroxychloroquine. *J Med Virol* **2022**, *94*, 3431–3437, doi:10.1002/jmv.27731.
21. Bourguiba, R.; Kyheng, M.; Koné-Paut, I.; Rouzaud, D.; Avouac, J.; Devaux, M.; Abdallah, N.A.; Fautrel, B.; Ferreira-Maldent, N.; Langlois, V.; et al. COVID-19 Infection among Patients with Autoinflammatory

Diseases: A Study on 117 French Patients Compared with 1545 from the French RMD COVID-19 Cohort: COVIMAI - the French Cohort Study of SARS-CoV-2 Infection in Patient with Systemic Autoinflammatory Diseases. *RMD Open* **2022**, *8*, e002063, doi:10.1136/rmdopen-2021-002063.

22. Oz, Y.; Qoraan, I.; Oz, A.; Balta, I. Prevalence and Epidemiology of Tinea Pedis and Toenail Onychomycosis and Antifungal Susceptibility of the Causative Agents in Patients with Type 2 Diabetes in Turkey. *Int J Dermatol* **2017**, *56*, 68–74, doi:10.1111/ijd.13402.
23. AlBloushi, A.F.; Alfawaz, A.M.; Abu El Asrar, A.M. Implications of COVID-19 Infection on Patients with Uveitis under Biologic Treatment. *Br J Ophthalmol* **2022**, *106*, 1538–1541, doi:10.1136/bjophthalmol-2020-318577.
24. Accorinti, M.; Manni, P.; Sampalmieri, L.; Saturno, M.C. Ocular Behçet Disease and COVID-19. *Eur J Ophthalmol* **2022**, *32*, 11206721221074437, doi:10.1177/11206721221074437.
25. Polat, B.; Erden, A.; Güven, S.C.; Armağan, B.; Karakaş, Ö.; Özdemir, B.; Apaydın, H.; Usul, E.; Ateş, İ.; Küçükşahin, O.; et al. COVID-19 in Patients with Behçet's Disease: Outcomes and Rate of Behçet's Exacerbations in a Retrospective Cohort. *Mod Rheumatol* **2022**, *32*, 455–459, doi:10.1093/mr/roab016.
26. Zouboulis, C.C.; van Laar, J. a. M.; Schirmer, M.; Emmi, G.; Fortune, F.; Gül, A.; Kirino, Y.; Lee, E.-S.; Sfikakis, P.P.; Shahram, F.; et al. Adamantiades-Behçet's Disease (Behçet's Disease) and COVID-19. *J Eur Acad Dermatol Venereol* **2021**, *35*, e541–e543, doi:10.1111/jdv.17325.
27. Enginar, A.U.; Gundogdu, M. The Course of COVID-19 in Patients with Behçet's Disease. *Reumatologia* **2021**, *59*, 356–361, doi:10.5114/reum.2021.112347.
28. den Otter, A.A.S.; van der Houwen, T.B.; van Hagen, P.M.; van Laar, J.A.M. Clinical Course of COVID-19 Infections in Patients with Behçet's Disease in The Netherlands. *Clin Exp Rheumatol* **2022**, *40*, 1504–1509, doi:10.55563/clinexprheumatol/xdx09v.
29. Yurttaş, B.; Oztas, M.; Tunc, A.; Balkan, İ.İ.; Tabak, O.F.; Hamuryudan, V.; Seyahi, E. Characteristics and Outcomes of Behçet's Syndrome Patients with Coronavirus Disease 2019: A Case Series of 10 Patients. *Intern Emerg Med* **2020**, *15*, 1567–1571, doi:10.1007/s11739-020-02427-8.
30. Eslambolchi, A.; Aghaghazvini, L.; Gholamrezanezhad, A.; Kavosi, H.; Radmard, A.R. Coronavirus Disease 2019 (COVID-19) in Patients with Systemic Autoimmune Diseases or Vasculitis: Radiologic Presentation. *J Thromb Thrombolysis* **2021**, *51*, 339–348, doi:10.1007/s11239-020-02289-z.
31. Mattioli, I.; Bettiol, A.; Silvestri, E.; Urban, M.L.; Palermo, A.; Fagni, F.; Malandrino, D.; Del Bianco, A.; Prisco, D.; Emmi, G. Prevalence and Clinical Course of SARS-CoV-2 Infection in Patients with Behçet's Syndrome. *Clin Exp Rheumatol* **2021**, *39 Suppl 132*, 47–50, doi:10.55563/clinexprheumatol/pmnqmf.
32. Mehta, A.; Shakarchi, J.A.; Meecham, L.; Vijay, S.; Downing, R. Undiagnosed Behçet's Disease Complicated by Multiple Pseudoaneurysms and COVID-19 Infection. *Int J Angiol* **2023**, *32*, 71–74, doi:10.1055/s-0041-1735208.
33. Nas, K.; Dilek, G.; Unan, M.K.; Tekeoğlu, İ.; Kamanlı, A. The Clinical Outcomes of COVID-19 in Patients with Behçet's Disease: A Series of 7 Cases and Brief Review of the Literature. *Eurasian J Med* **2022**, *54*, 305–309, doi:10.5152/eurasianjmed.2021.21203.
34. Ozcifci, G.; Aydin, T.; Atli, Z.; Balkan, I.I.; Tabak, F.; Oztas, M.; Ozguler, Y.; Ugurlu, S.; Hatemi, G.; Melikoglu, M.; et al. The Incidence, Clinical Characteristics, and Outcome of COVID-19 in a Prospectively Followed Cohort of Patients with Behçet's Syndrome. *Rheumatol Int* **2022**, *42*, 101–113, doi:10.1007/s00296-021-05056-2.
35. El Hasbani, G.; Jawad, A.S.; Uthman, I. Erythema Nodosum in Behçet's Disease in Remission: Think COVID-19? *SAGE Open Med Case Rep* **2023**, *11*, 2050313X231154316, doi:10.1177/2050313X231154316.
36. Lim, A.; Altenburg, A.; Zouboulis, C.C. Interplay between Adamantiades-Behçet's Disease and COVID-19 – a Case Series from the German Registry of Adamantiades-Behçet's Disease. *Journal of the European Academy of Dermatology and Venereology* **2023**, *37*, e581–e585, doi:10.1111/jdv.18939.
37. O'Keefe, J.M.; Grall, K.J.H. Profound Weakness and Blurry Vision in a Pandemic: A Case Report. *Clin Pract Cases Emerg Med* **2021**, *5*, 230–233, doi:10.5811/cpcem.2021.3.51104.
38. Zhao, Z.; Zhou, C.; Zhang, M.; Qian, L.; Xia, W.; Fan, Y. Analysis of the Potential Relationship between COVID-19 and Behcet's Disease Using Transcriptome Data. *Medicine (Baltimore)* **2023**, *102*, e33821, doi:10.1097/MD.0000000000033821.
39. Sansone, N.M.S.; Boschiero, M.N.; Marson, F.A.L. Epidemiologic Profile of Severe Acute Respiratory Infection in Brazil During the COVID-19 Pandemic: An Epidemiological Study. *Front Microbiol* **2022**, *13*, 911036, doi:10.3389/fmicb.2022.911036.
40. Sansone, N.M.; Boschiero, M.N.; Valencise, F.E.; Palamim, C.V.; Marson, F.A. Characterization of Demographic Data, Clinical Signs, Comorbidities, and Outcomes According to the Race in Hospitalized Individuals with COVID-19 in Brazil: An Observational Study. *J Glob Health* **2022**, *12*, 05027, doi:10.7189/jogh.12.05027.

41. Sansone, N.M.S.; Boschiero, M.N.; Ortega, M.M.; Ribeiro, I.A.; Peixoto, A.O.; Mendes, R.T.; Marson, F.A.L. Severe Acute Respiratory Syndrome by SARS-CoV-2 Infection or Other Etiologic Agents Among Brazilian Indigenous Population: An Observational Study from the First Year of Coronavirus Disease (COVID)-19 Pandemic. *Lancet Reg Health Am* **2022**, *8*, 100177, doi:10.1016/j.lana.2021.100177.
42. Boschiero, M.N.; Lutti Filho, J.R.; Ortega, M.M.; Marson, F.A.L. High Case Fatality Rate in Individuals with Down Syndrome and COVID-19 in Brazil: A Two-Year Report. *J Clin Pathol* **2022**, *75*, 717–720, doi:10.1136/jcp-2021-207802.
43. Boschiero, M.N.; Palamim, C.V.C.; Ortega, M.M.; Marson, F.A.L. Clinical Characteristics and Comorbidities of COVID-19 in Unvaccinated Patients with Down Syndrome: First Year Report in Brazil. *Hum Genet* **2022**, *141*, 1887–1904, doi:10.1007/s00439-022-02468-3.
44. Boschiero, M.N.; Sansone, N.M.S.; Marson, F.A.L. Hospitalized Patients with X-Linked Disease and Infected with SARS-CoV-2 in Brazil: A Serial Case Report from the First Two Years of the Pandemic. *Respir Investig* **2023**, *61*, 460–466, doi:10.1016/j.resinv.2023.04.001.
45. Sansone, N.M.S.; Valencise, F.E.; Bredariol, R.F.; Peixoto, A.O.; Marson, F.A.L. Profile of Coronavirus Disease Enlightened Asthma as a Protective Factor against Death: An Epidemiology Study from Brazil during the Pandemic. *Front Med (Lausanne)* **2022**, *9*, 953084, doi:10.3389/fmed.2022.953084.
46. Mehta, V.; Vasanth, V.; Balachandran, C. Yellow Nails Following Hemodialysis in Chronic Renal Failure: Is It Yellow Nail Syndrome or a Variant? *Dermatol Online J* **2008**, *14*, 19.
47. Elmas, Ö.F.; Demirbaş, A.; Bağcıer, F.; Türsen, Ü.; Atasoy, M.; Dursun, R.; Lotti, T. Treatment Considerations for Behçet Disease in the Era of COVID-19: A Narrative Review. *Dermatol Ther* **2021**, *34*, e14507, doi:10.1111/dth.14507.
48. Konak, H.E.; Armağan, B.; Güven, S.C.; Atalar, E.; Karakaş, Ö.; Esmer, S.; Eksin, M.A.; Polat, B.; Apaydin, H.; Gök, K.; et al. Intravenous Treatment Adherence of Patients with Chronic Inflammatory Rheumatic Diseases during the COVID-19 Pandemic: Experience of a Single Center. *Rom J Intern Med* **2022**, *60*, 173–181, doi:10.2478/rjim-2022-0010.
49. Midi, I.; Gencel, A.; Sahin, H.; Mertoglu, F.; Bicer, F.B.; Akbas, Z.; Irmak, S. Perceived Stress Associated With COVID-19 in Patients With Neuro-Behcet's Disease. *Prim Care Companion CNS Disord* **2023**, *25*, 22br03476, doi:10.4088/PCC.22br03476.
50. Dursun, R.; Temiz, S.A.; Özer, İ.; Daye, M.; Ataseven, A. Management of Patients with Behçet's Disease during the COVID-19 Pandemic. *Dermatol Ther* **2020**, *33*, e14063, doi:10.1111/dth.14063.
51. Apaydin, H.; Erden, A.; Güven, S.C.; Armağan, B.; Konak, H.E.; Polat, B.; Afşin, Y.; Kaygisiz, M.; Omma, A.; Kucuksahin, O. Effects of Anti-SARS-CoV-2 Vaccination on Safety and Disease Exacerbation in Patients with Behçet Syndrome in a Monocentric Cohort. *Int J Rheum Dis* **2022**, *25*, 1068–1077, doi:10.1111/1756-185X.14387.
52. Ralise, A.E.G.; Camargo, T.M.; Marson, F.A.L. Phase 4 Clinical Trials in the Era of the Coronavirus Disease (COVID-19) Pandemic and Their Importance to Optimize the COVID-19 Vaccination. *Hum Vaccin Immunother* **2023**, *19*, 2234784, doi:10.1080/21645515.2023.2234784.
53. Marson, F. a. L.; Ortega, M.M. COVID-19 in Brazil. *Pulmonology* **2020**, *26*, 241–244, doi:10.1016/j.pulmoe.2020.04.008.
54. Boschiero, M.N.; Palamim, C.V.C.; Ortega, M.M.; Mauch, R.M.; Marson, F.A.L. One Year of Coronavirus Disease 2019 (COVID-19) in Brazil: A Political and Social Overview. *Ann Glob Health* **2021**, *87*, 44, doi:10.5334/aogh.3182.
55. Carvalho, T.A.; Boschiero, M.N.; Marson, F.A.L. COVID-19 in Brazil: 150,000 Deaths and the Brazilian Underreporting. *Diagn Microbiol Infect Dis* **2021**, *99*, 115258, doi:10.1016/j.diagmicrobio.2020.115258.
56. Martins, J.P.; Siqueira, B.A.; Sansone, N.M.S.; Marson, F.A.L. COVID-19 in Brazil: A 3-Year Update. *Diagnostic Microbiology and Infectious Disease* **2023**, *107*, 116074, doi:10.1016/j.diagmicrobio.2023.116074.
57. Palamim, C.V.C.; Siqueira, B.A.; Boschiero, M.N.; Marson, F.A.L. Increase in COVID-19 Underreporting among 3,282,337 Brazilian Hospitalized Patients Due to SARS: A 3-Year Report and a Major Concern for Health Authorities. *Travel Med Infect Dis* **2023**, *54*, 102616, doi:10.1016/j.tmaid.2023.102616.
58. Marson, F.A.L. COVID-19 – 6 Million Cases Worldwide and an Overview of the Diagnosis in Brazil: A Tragedy to Be Announced. *Diagn Microbiol Infect Dis* **2020**, *98*, 115113, doi:10.1016/j.diagmicrobio.2020.115113.