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The incidence, clinical characteristics, and outcome of COVID-19 in a prospectively followed cohort of patients with Behçet's syndrome

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Abstract

Initial case series of small number of patients at the beginning of the pandemic reported a rather guarded prognosis for Behçet's syndrome (BS) patients infected with SARS-CoV-2. In this prospective study, we describe the incidence, clinical characteristics, disease course, management, and outcome in a large cohort of BS patients with laboratory-confirmed infection of SARS-CoV-2. We defined a cohort of 1047 registered BS patients who were aged between 16 and 60 years and seen routinely before the pandemic at the multidisciplinary outpatient clinic. We followed prospectively this cohort from beginning of April 2020 until the end of April 2021. During 13 months of follow-up, of the 1047 (599 M/448 F) patients, 592 (56.5%) were tested for SARS-CoV-2 PCR at least once and 215 (20.5%; 95% CI 0.18–0.23) were tested positive. We observed 2 peaks which took place in December 2020 and April 2021. Of the 215 PCR positive patients, complete information was available in 214. Of these 214, 14 (6.5%) were asymptomatic for COVID-19. In the remaining, the most common symptoms were anosmia, fatigue, fever, arthralgia, and headache. A total of 40 (18.7%) had lung involvement, 25 (11.7%) were hospitalized, 1 was admitted to the intensive care unit while none died. Favipiravir was the most prescribed drug (74.3%), followed by colchicine (40.2%), and hydroxychloroquine (20.1%) in the treatment of COVID-19. After COVID-19, 5 patients (2.3%) were given supplemental O_2 and 31 (14.5%) antiaggregant or anticoagulants. During COVID-19, of the 214 PCR positive patients, 116 (54.2%) decreased the dose of their immunosuppressives or stopped taking completely; 36 (16.8%) experienced a BS flare which was mostly oral ulcers (10.3%). None of the patients reported a thrombotic event. A total of 93 (43.5%) patients reported BS flares after a median 45 days of COVID-19 infection and this was found to be significantly associated with immunosuppressive drug discontinuation. Multiple regression analysis adjusted for age and gender indicated that smoking and using interferon-alpha decreased the likelihood of getting COVID-19. The incidence and severity of COVID-19 did not differ between those who were using colchicine or not. The cumulative incidence of COVID-19 in this prospectively followed cohort of BS patients was almost two folds of that estimated for the general population living in Istanbul, Turkey, however, the clinical outcome of COVID-19 was not severe and there was no mortality. The protective effect of smoking and interferon deserves further investigation. On the other hand, colchicine did not have any positive or negative effect against COVID-19. Significant number of patients flared after COVID-19, however, this was significantly associated with immunosuppressive discontinuation during the infection. Contrary to our previous observations, COVID-19 did not seem to exacerbate thrombotic events during or after the infection.

Keywords Outcome · COVID-19 · Behcet's disease · Colchicine · Smoking · Interferon-alpha

Introduction

Since it emerged in December 2019, the Coronavirus disease-2019 (COVID-19) pandemic has affected at least 223 million people and caused more than 4.6 million deaths worldwide [1]. The first case in Turkey was recorded on 11 March 2020 [2], and as of 8 November 2021, there have been

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8,231,679 confirmed cases and 72,127 deaths registered due to COVID-19 [1].

Patients with rheumatic diseases (RD) particularly those with autoimmune diseases (AD) have been reported to have a higher infection rate and a worse outcome for COVID-19 [3, 4]. Behçet's syndrome (BS), a complex inflammatory disorder of unknown etiology, is one of the most prevalent RD in Turkey, with a prevalence rate of 0.4% [5]. It is characterized by recurrent skin mucosa lesions and uveitis, but may also involve joints, vascular, gastrointestinal, and central nervous systems. Although BS cannot be classified as a typical AD [6], immunosuppressive agents including glucocorticoids (GC), TNF inhibitors, and conventional disease-modifying anti-rheumatic drugs (DMARDs) are the mainstay of treatment [6–11]. Colchicine, a much-debated promising drug for COVID-19, is also used frequently in BS, especially to treat skin-mucosa lesions [12, 13]. There have been conflicting reports about the outcome of BS patients who were diagnosed with COVID-19 at the beginning of the pandemic [14–17]. We have previously reported ten patients with severe outcome [14]. Of the ten patients, eight were hospitalized of whom two had to be taken care of in the ICU. Ultimately, one died due to pneumonia and one developed de-novo deep vein thrombosis [14]. On the other hand, two small case series one from Italy and another from Spain reported a mild outcome [16, 17]. Moreover, a consensus based on multinational experts' opinion suggested that the prevalence of COVID-19 in BS is apparently lower than that in the general population, and that BS appears not to be associated with a more severe COVID-19 course [18].

In this prospective study, we describe the incidence rate, clinical characteristics, disease course, management, and outcomes in a large cohort of patients with BS with laboratory-confirmed infection of SARS-CoV-2.

Patients and methods

Our prospective cohort study was done during the first 13 months of the pandemic at Behçet Disease Research Center in Cerrahpasa Medical Faculty of Istanbul University-Cerrahpasa, Turkey. At the onset of the pandemic, we defined a cohort of 1047 registered BS patients who were aged between 16 and 60 years and seen between the beginning of August 2019 and the end of December 2019 at our multidisciplinary outpatient clinic. We followed prospectively this cohort from the beginning of April 2020 until the end of April 2021. The follow-up was terminated when the vaccination program for immune-compromised individuals started in Turkey [19]. We basically conducted a telephone survey using a standardized questionnaire which was composed of 3 parts. The first part included questions regarding socio-demographic variables such as age, gender,

occupation, marital status, educational status, and household size. In the second part, the participants were asked whether they were smokers and have been previously diagnosed with a comorbid disease (such as cardiovascular disease, chronic lung disease, hypertension, diabetes mellitus, or else). The third part included questions regarding COVID-19. Further information on clinical characteristics, disease duration, and prescribed medications were collected from patients' charts. We first tested the questionnaire on 26 patients to check its usability and to see whether there are unclear, unwelcome or unnecessary questions. After these pre-test evaluations, we were able to refine the survey.

The "Ministry of Health Public Health Data Management System" database has been established at the beginning of the SARS-CoV-2 pandemic in Turkey, on March 2020 to store COVID-19 related hospital records, PCR and other laboratory test results as well as radiological imaging of Turkish citizens. The database was accessed freely only by specialists of clinical infectious diseases (I.I.B. and F.T.). National identity and phone numbers of all study individuals had been stored in our hospital record system. After obtaining patients' consent, we used the database to screen all the study participants to see which ones were tested for PCR or reported as COVID-19 cases. We recorded how many PCR tests were done and when these tests were performed. We also examined the electronic notes of the family physicians who were responsible for the follow-up of patients if they were diagnosed or suspected with COVID-19 infection. For those who were living outside of Istanbul, we collected all these information through telephone interviews. We screened all patients periodically until the end of April 2021. All patients were called for the third part of the questionnaire between August–September 2020, December 2020-January 2021, and March–April 2021.

After we defined the subgroup of patients with positive PCR tests for COVID-19, we created a second questionnaire for the investigation of the following factors: current use/discontinuation or dose reduction of BS drugs during the pandemic and during the COVID-19 infection; medical treatment for COVID-19; COVID-19 related symptoms and findings; hospitalization, admission to the intensive care unit, BS exacerbation during or after the COVID-19 infection and any other complaints/symptoms developed after the infection. All these information was obtained from the Ministry of Health Public Health Data Management System database and through telephone interviews. For the hospitalized patients, we requested hospital files/records from the hospital staff or patients themselves. We had complete information in all patients with positive PCR test except one who refused to talk (Fig. 1). This part of the study was terminated by the end of June 2021, however, we continued to check those patients who had pneumonia and those who reported

Fig. 1 Flow chart of the study population selection according to the PCR test for COVID-19 (the chart breaks down initially into PCR tested vs non-tested then into PCR positive vs PCR negative)
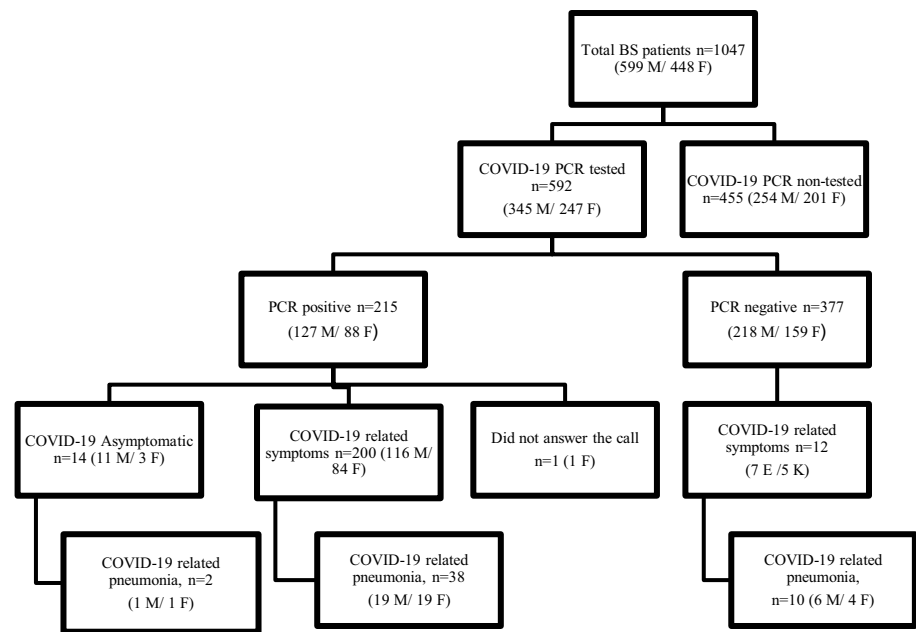
BS: Behçet's syndrome; M: male; F: female.

post-COVID symptoms with frequent telephone calls until the manuscript was prepared for submission.

As shown in the flow chart (Fig. 1), we only evaluated those who had positive PCR test. The 10 patients whom we have previously reported at the beginning of the pandemic were not included either [14]. Those who had tested negative but had typical lesions on the thorax CT or who were ascribed as COVID-19 and medically treated as COVID-19 due to similarity of the symptoms were excluded from the study (Fig. 1).

The management of patients with COVID-19 diagnosis was done according to the Ministry of Health guidelines [20] and described in detail in the Supplement.

Ethical statement

This study was approved by the Ethics Committee of Istanbul University-Cerrahpasa, Cerrahpaşa Medical Faculty (12/10/2020–134022) and by the Ministry of Health (2020-08-18T15_54_13). During all the steps of the study, we obtained patients' consent and followed the ethical principles of the Helsinki declaration.

Statistical analysis

Descriptive data were presented as median and range for the continuous variables and frequency and percentages (%) for the categorical variables. Continuous variables were evaluated for normality distribution using Shapiro–Wilk test. PCR

(+) and PCR (−) group were compared with Mann–Whitney U test for non-normally distributed variables. Categorical variables were compared by using Chi-Square or Fisher's exact test for proportion. Survival analysis to express time to be PCR positive for COVID-19 was shown with Kaplan–Meier plots. Patients whose PCR test were not positive during the follow-up (0–13 months) were censored. Survival curves were compared with Log-Rank test with two-sided significance level of 0.05 for each group. We applied Univariate Logistic Regression Analysis to assess the association between independent factors and risk of COVID-19 and statistically significant independent factors were included Multivariate Logistic Regression model. Similar analyses were done to investigate variables associated with pneumonia due to COVID-19 as well hospitalization. All significance tests were 2-tailed, and values of $p < 0.05$ were considered statistically significant. Statistical analyses were performed using the RStudio version 4.0.2 software and IBM SPSS Statistics version 21.0.

Sample size calculation

The incidence of COVID-19 in the general population was reported as 0.2% at the beginning of the pandemic [21]. A sample size was calculated assuming the incidence of COVID-19 would be three times higher than that observed in the general population. We utilized simple sample size formula [22]. Minimum sample size was estimated as 916

patients with an absolute precision of 0.5% and 5% level of significance.

Results

Of the 1047 (599 M/448 F) patients, 592 (344 M/248 F) (56.5%) were tested for COVID-19 PCR at least once (median: 2, IQR: 1–5). Of these 592, 215 (127 M/88 F) were tested positive. The median number of PCR tests was significantly higher among those who were tested positive (median: 2, IQR: 1–3) compared to those who were tested negative (median: 1, IQR: 1–2), $p < 0.001$. Of the 377 (218 M/159 F) patients who were tested negative, 10 had pneumonia specific for COVID-19 and 5 were hospitalized. For the study purposes, we only considered those 215 (127 M/88 F) PCR positive patients as diagnosed with COVID-19 (Fig. 1). There were 92 patients (8.8%) who were living outside of Istanbul in the cohort and of these, 35 (38.0%) were tested positive.

Incidence of COVID-19 in the BS cohort

As shown in the Kaplan Meier plot (Fig. 2), the cumulative incidence of COVID-19 in the cohort rose from 0 to 20.5% (95% CI 18–23%) from April 1, 2020 to April 30, 2021. During 13 months of follow-up, there were two peaks. The first peak occurred in December 2020 in which 51 cases were recorded in a single month. The cumulative incidence surged from 9% (95% CI 10–12%) to 14% (95% CI 12–16%). The second peak occurred in April 2021 in which we observed 41 cases with COVID-19 in a single month. Hence, the cumulative incidence increased from 16% (95% CI 14–19%) to 20.5% (95% CI 18–23%). These two peaks coincided well with the peaks observed in the general population in Turkey [1]. Additional Kaplan–Meier plots stratified for age (16–40 years vs 41–60 years), gender and presence of comorbid disease did not show any significance, however, those who smoke were shown to have a lower probability for contracting COVID-19 as compared with those who do not smoke (Fig. 3, 4, 5 and 6 in the Supplement).

Socio-demographic and clinical characteristics of the patients with BS who tested positive for COVID-19

As shown in Table 1, those who were diagnosed as COVID-19 were significantly less likely to smoke and significantly less likely to use interferon-alpha compared to those who were not. Besides these parameters, there were no socio-demographic or clinical characteristics that were significantly different between the two groups. These were also confirmed in the univariate logistic regression analysis (Table 1).

As shown in Table 2, multiple regression analysis adjusted for age and gender indicated that smoking (OR 0.65; 95% CI 0.46–0.92, $p = 0.014$) and using interferon-alpha (OR 0.13; 95% CI 0.02–1.00) decreased the risk of getting COVID-19.

Fig. 2 Cumulative incidence plot indicating patients who developed positive PCR test for COVID-19 during the first 13 months of the pandemic in the whole cohort including 1047 patients with Behçet's syndrome
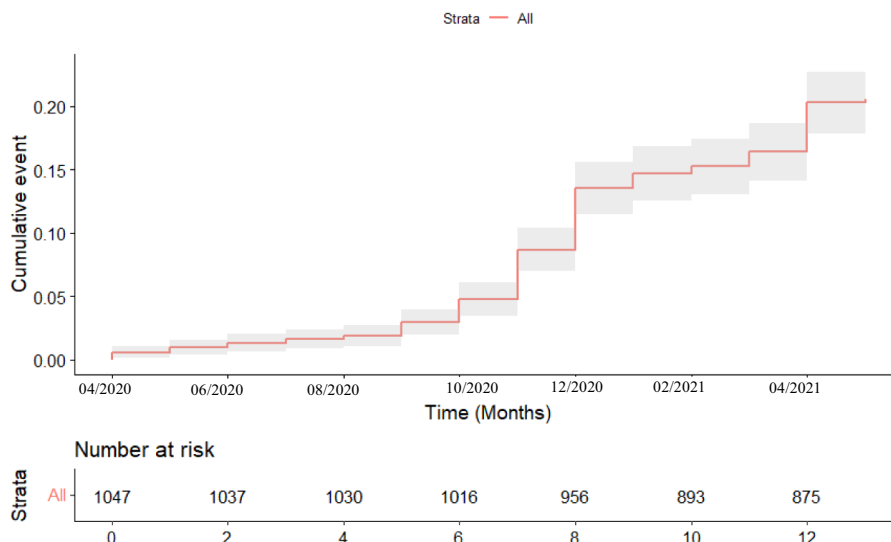
Grey area indicates 95% confidence interval.

Table 1 Socio-demographic and clinical characteristics and drugs used among the study groups (univariate comparison and univariate logistic regression analysis)

	Diagnosed with COVID-19, N=215	Not diagnosed with COVID-19, N=822[a]	p*	Odds Ratio (95% Confidence Interval)	p**
PCR tested for COVID-19, n (%)	215 (100)	367 (44.6)	NA	NA	NA
Male, n (%)	127 (59.1)	465 (56.6)	0.510	1.08 (0.91–1.50)	0.510
Age, median (range), years	40 (16–60)	41 (16- 60)	0.740	0.99 (0.98–1.02)	0.829
Married, n (%)	177 (82.3)	648 (78.8)	0.520	1.15 (0.43–3.09)	0.786
Household, median (range), n	4 (1–10)	4 (1–11)	0.907	1.01 (0.91–1.12)	0.875
Being educated in primary school or less, n (%)	106 (49.3)	391 (47.6)	0.650	0.82 (0.26–2.57)	0.730
Employed during the pandemic, n (%)	147 (68.4)	520 (63.3)	0.164	0.80 (0.58–1.09)	0.164
Continued to go out for work during the pandemic, n (%)	44 (20.6)	162 (19.8)	0.908	0.90 (0.51–1.59)	0.724
Being smoker, n (%)	57 (26.5)	290 (35.3)	0.015	0.66 (0.47–0.93)	0.016
Disease duration, mean ± SD, years	10 (1–33)	10 (1–50)	0.501	0.99 (0.97–1.01)	0.345
Types of organ involvement					
Skin-mucosa, alone, n (%)	38 (17.7)	150 (18.2)	0.846	1.04 (0.70–1.54)	0.846
Joint, n (%)	73 (34.0)	328 (39.9)	0.111	0.77 (0.57–1.06)	0.111
Vascular, n (%)	58 (27.0)	230 (28.0)	0.770	1.05 (0.75–1.47)	0.770
Eye, n (%)	121 (56.3)	448 (54.5)	0.641	0.93 (0.69–1.26)	0.641
Neurological, n (%)	14 (6.6)	60 (7.3)	0.690	1.13 (0.62–2.06)	0.690
Gastrointestinal, n (%)	2 (0.9)	17 (2.1)	0.268	2.25 (0.52–9.81)	0.281
Additional rheumatologic disease, n (%)	8 (3.7)	45 (5.5)	0.299	1.50 (0.69–3.23)	0.302
Comorbid disease, n (%)	43 (20.1)	146 (17.8)	0.436	0.86 (0.59–1.26)	0.436
Any drug, n (%)	187 (87.0)	724 (88.1)	0.660	0.90 (0.58–1.42)	0.660
Colchicine, n (%)	130 (60.5)	486 (59.1)	0.721	0.95 (0.70–1.29)	0.721
Glucocorticoids, n (%)	26 (12.1)	113 (13.7)	0.526	1.15 (0.74–1.83)	0.527
Azathioprine, n (%)	85 (39.5)	271 (33.0)	0.071	0.75 (0.55–1.02)	0.072
Conventional DMARDs other than azathioprine, n (%)	5 (2.3)	37 (4.5)	0.176	0.51 (0.19–1.30)	0.157
Anti-TNF, n (%)	37 (17.2)	119 (14.3)	0.286	0.80 (0.53–1.20)	0.275
Interferon, n (%)	1 (0.5)	30 (3.6)	0.012	0.12 (0.01–0.90)	0.040

[a]10 patients who tested PCR negative but having either thorax CT findings or symptoms compatible with COVID-19 were excluded. *NA* not applicable

*Univariate comparison

**Univariate logistic regression analysis

Table 2 Multiple regression analysis of variables associated with the risk of PCR positivity, pneumonia and hospitalization

	PCR (+) for COVID-19		COVID-19 pneumonia		Hospitalization	
	Odds ratio (95% confidence interval)	p	Odds ratio (95% confidence interval)	p	Odds ratio (95% confidence interval)	p
Age, per 1 year increase	1.00 (1.00–1.01)	0.521	1.01 (0.97–1.05)	0.588	1.01 (1.00–1.06)	0.629
Being male vs female	1.24 (0.90–1.70)	0.182	0.86 (0.44–1.65)	0.639	0.76 (0.34–1.72)	0.515
Smoking vs not smoking	0.65 (0.46–0.92)	0.014	0.25 (0.10–0.66)	0.005	0.32 (0.11–0.95)	0.040
Having a comorbid disease vs having not	1.25 (0.84–1.87)	0.270	2.78 (1.36–5.67)	0.005	2.70 (1.13- 6.43)	0.011
Using glucocorticoids vs using not	0.85 (0.54–1.36)	0.509	1.86 (0.81–4.28)	0.147	3.44 (1.40- 8.47)	0.007
Using interferon vs not[a]	0.13 (0.02–1.00)	0.050	NA	NA	NA	NA

[a]Using interferon was not included in the analyses because of the low number in the groups in the analysis of COVID-19 pneumonia and hospitalization

NA not applicable

Presenting symptoms, treatment, and outcome associated with COVID-19 among PCR positive BS patients (Table 3)

There were 215 patients who were tested positive of whom complete information was available in all except one. Of these 214 patients, 14 (6.5%) were asymptomatic

Table 3 Presenting symptoms, treatment and outcome associated with COVID-19 infection among PCR positive BS patients ($n = 214$[a])

Symptoms, n (%)	
Anosmia	117 (54.7)
Fatigue	114 (53.3)
Fever	112 (52.3)
Joint pain	112 (52.3)
Headache	103 (48.1)
Coughing	89 (41.6)
Myalgia	79 (36.9)
Dyspnea	63 (29.4)
Sore throat	52 (24.3)
Nausea/vomiting	44 (20.6)
Diarrhea	41 (19.2)
Backpain	37 (17.3)
Rhinorrhea	37 (17.3)
Ageusia or loss of appetite	29 (13.6)
Other symptoms[b]	27 (12.6)
Asymptomatic	14 (6.5)
Thorax CT findings compatible with covid-19 pneumonia, n (%)	40 (18.7)
Hospitalization, n (%)	25 (11.7)
Admission to the intensive care unit, n (%)	1 (0.5)
Treatment during COVID-19 infection, n (%)	
Favipiravir	159 (74.3)
Colchicine	86 (40.2)
Hydroxychloroquine	43 (20.1)
Oseltamivir	7 (3.3)
Azithromycin	6 (2.8)
Dexamethasone	9 (4.2)
Tocilizumab	2 (0.9)
Aspirin	42 (19.6)
Low molecular weight heparin	27 (12.6)
Supplemental O_2	14 (6.5)
No treatment	23 (10.7)
Treatment after COVID-19 infection, n (%)	
Supplemental O_2 need	5 (2.3)
Anti-aggregant or anticoagulant use	31 (14.5)

[a]1 patient who could not be reached out was excluded

[b]Chest pain ($n = 8$), redness/itchiness/watering/burning of eyes ($n = 5$), somnolence ($n = 3$), abdominal pain ($n = 2$), vertigo ($n = 1$), neck pain ($n = 1$), sneezing ($n = 1$), jaw pain ($n = 1$), hypertension ($n = 1$), burning sensation in nose ($n = 1$), weakness in eyelids ($n = 1$), swelling of libs ($n = 1$), postnasal drip ($n = 1$)

and were tested because of the history of COVID-19 in a close contact (Table 3). The remaining 200 patients had one or more symptoms as shown in Table 3. The most common symptoms were anosmia (54.7%), fatigue (53.3%), fever (52.3%), arthralgia (52.3%), and headache (48.1%). A total of 40 (18.7%) had pneumonia, 25 (11.7%) were hospitalized, 1 was admitted to the intensive care unit while none died. Univariate analysis found that smoking and having a comorbid disease were associated with COVID-19 pneumonia (data not shown). Variables associated with hospitalization were smoking, having a comorbid disease, and using GC (data not shown). Age and gender-adjusted multivariate regression analysis revealed that smoking decreased the risk of getting COVID-19 pneumonia (OR 0.25, 95% CI 10–66%; $p = 0.005$) and hospitalization (OR 0.32, 95% CI 0.11–0.95; $p = 0.040$). On the other hand, having a comorbid disease was associated with increased risk for both COVID-19 pneumonia (OR 2.78, 95% CI 1.36–5.67; $p = 0.005$) and hospitalization (OR 2.70, 95% CI 1.13–6.43; $p = 0.011$). Similarly using prednisolone was found to be associated with increased risk of hospitalization (OR 3.44, 95% CI 1.40–8.47; $p = 0.007$) (Table 2).

While 23 (10.7) did not receive any COVID-19 related treatment, the remaining received one or more drugs. Favipiravir (74.3%, 159/214) was the most prescribed drug, followed by colchicine (40.2%, 86/214), and hydroxychloroquine (20.1%, 43/214). None of the patients used remdesivir. Oseltamivir and azithromycin were given to a few patients at the beginning of the pandemic. Tocilizumab and dexamethasone were given to 2 and 9 patients, respectively. A total of 27 (12.6%) patients used low-molecular-weight heparin and 42 (19.6%) aspirin. Supplemental O_2 was given to 14 (6.5%) patients. After COVID-19 infection, 5 (2.3%) patients were given supplemental O_2 and 31 (14.5%) anti-aggregants or anti-coagulants.

BS flare during and after COVID-19 (Table 4)

During the pandemic, a total of 39 (18.2%) patients of 214 PCR positive BS patients decreased ($n = 18$) or stopped ($n = 21$) the dose of their medications associated with BS. After having being diagnosed with COVID-19 infection, a total of 116 (54.2%) either discontinued ($n = 106$) or decreased the dose of their medications ($n = 10$). During COVID-19 infection, 36 (16.8%) experienced a BS flare which was mostly oral ulcers (10.3%), genital ulcers (3.3%), skin lesions (6.5%), and uveitis (4.7%). None of

Table 4 BS flare during COVID-19 and after COVID-19 infection among BS patients

	All patients (n=214[a])	Decreased or stopped using drugs during COVID-19 (n=116)	Continued using drugs during COVID-19 (n=98)	p
Any lesion during COVID-19, n (%)	36 (16.8)	25 (21.6)	11 (11.2)	0.044
Oral ulcers	22 (10.3)	16 (13.8)	6 (6.1)	0.066
Genital ulcers	7 (3.3)	7 (6.0)	0	0.016
Uveitis	10 (4.7)	7 (6.0)	3 (3.1)	0.350
Thrombosis	0	0	0	
Skin lesions	14 (6.5)	10 (8.6)	4 (4.1)	0.181
Any lesion after COVID-19, n (%)	93 (43.5)	61 (52.6)	32 (32.7)	0.003
Oral ulcers	56 (26.2)	36 (31.0)	20 (20.4)	0.078
Genital ulcers	9 (4.2)	8 (6.9)	1 (1.0)	0.041
Uveitis	29 (13.6)	20 (17.2)	9 (9.2)	0.086
Thrombotic events	8 (3.7)	4 (3.4)	4 (4.1)	1.0
Skin lesions	24 (11.2)	17 (14.7)	7 (7.1)	0.083
Other lesions[b]	60 (28.0)	35 (30.2)	25 (25.5)	0.449

[a] 1 patient in whom information was not available was excluded from the analyses

[b] Joint pain (n=50); epistaxis (n=1), hemoptysis (n=1), epididymitis (n=1), GIS symptoms (n=4), neurologic flare (n=1), oral pain (n=2), genital itchiness (n=1), leg swelling (n=1), back pain (n=1), leg pain (n=1)

the patients reported a thrombotic event. BS flares during COVID-19 infection were significantly more likely to be frequent among those who discontinued or decreased the dose of their immunosuppressives (Table 4).

A total of 93 (43.5%) patients reported having an exacerbation associated with BS after a median 45 days [IQR: 21–90] of COVID-19 infection. These were oral ulcers (26.2%), uveitis (13.6%) and skin lesions (11.2%). Genital ulcers (4.2%) and lower extremity vein thrombosis (3.7%) were observed rarely. BS flares that occurred after COVID-19 infection were significantly more common among those who reduced the dose of their medications or stopped taking them (52.6%) compared to those who continued to take their drugs regularly (32.7%), (p=0.003) (Table 4).

Post-COVID-19 symptoms

A total of 80 (37.4%) patients out of 214, developed at least one miscellaneous symptom after COVID-19. These were mostly dyspnea/chest pain (n=26), neuropsychiatric complaints (n=22), and cardio-pulmonary problems such as blood pressure dysregulations, arrhythmia, and cough (n=16). Further follow-up of these patients revealed that none of the patients has been diagnosed with myocardial infarction, stroke or cerebrovascular event.

Discussion

In this prospective large cohort study, the cumulative incidence of COVID-19 among BS patients was found to be 20.5% by the end of 13 months of the pandemic in Turkey. The clinical outcome seemed not to be severe, with no mortality or thrombotic events associated with COVID-19. Smoking and using interferon seemed to exert protective effects against COVID-19. On the other hand, colchicine was not found to have any protective or worsening effect against COVID-19. BS flares during or after COVID-19 infection were not infrequent but seemed to be associated with discontinuation or dose reduction of the immunosuppressive drugs.

As reported by the Turkish Ministry of Health, there have been overall 47,261,999 (56.2%) who were tested, 4,820,591 confirmed cases (5.77%; 95% CI 4.3–7.2%) and 40,131 (0.83%; 95% CI 0.67-0.99%) deaths registered due to COVID-19 in Turkey (population: 83,614,362) by the end of April 2021 [23]. When only those who were living in Istanbul (the largest city with a population [24] of 15,462,452) are considered, the cumulative incidence of PCR confirmed cases was estimated as 11.27% (95% CI 1.9–13.2%). It has to be noted that the great majority (91.2%) of the BS cohort in our study was residing

in Istanbul. The fact that the statistics provided by the government were not categorized by age and gender precludes the ability for direct comparisons with our findings. It would be as well to acknowledge that with only just over half of the BS and general populations having been PCR tested, there may well be ascertainment biases that would make confidence in the comparison between the groups rather weak. Nevertheless, the incidence among BS patients as found in the current survey seems to be roughly two folds of that estimated for the general population living in Istanbul. In line with our findings, a multicentre retrospective study done among patients with RD found an increased infection rate compared to family members with no RD (OR 2.68, 95% CI 1.14–6.27%; $p = 0.023$) [25]. A meta-analysis of seven case–controlled studies demonstrated that the risk of COVID-19 in AD was significantly higher than in control patients (OR 2.19, 95% CI 1.05–4.58%, $p = 0.038$) [26]. Similarly, a nation-wide study from South Korea recently reported that patients with inflammatory arthritis had an increased risk of testing positive for SARS-CoV-2 (OR 1.20, 95% CI 1.03–1.40%; $p = 0.020$) compared to those without inflammatory arthritis [27]. Finally, the high incidence rate of COVID-19 in the BS cohort may be due to the ascertainment bias as we mentioned earlier. BS patients could be more likely to pay frequent visits to places with high risk such as hospitals, outpatients, emergency departments, family physicians or pharmacies. It could be also due to the fact that BS patients could have been less likely to 'shield themselves from infection' during the pandemic because of the obligation to go out for work or due to lower educational and socioeconomical status, as we have previously reported [28].

Despite our first report [14] with relatively small sample size ($n = 10$), we found a favorable outcome in this large prospective cohort of BS patients. Our current observations are also in contrast with a number of studies who reported increased risk for severe COVID-19 infection and COVID-19 related death among patients with RD [4, 26, 27]. In our study, while 18.7% had lung involvement, none of the patients died or had a thrombotic event. We are unable to explain the exact mechanisms responsible for the favorable outcome. High frequency of immunosuppressive use, meticulous follow-up, and better handling of the pandemic during the course could be possible explanations. It has to be noted that colchicine was used by almost 60% of the study population for many years, therefore, while it was not found to have any effect on contracting COVID-19 infection, it may still have an effect for the better outcome. Finally, as we said earlier, the fact that BS is not a typical AD, hence exerting a different immune dysregulation with mostly intact adaptive response might also contribute to the better outcome.

Our results show clearly that the COVID-19 infection did not provoke thrombotic events in BS. This is most probably due to different prothrombotic mechanisms operating in BS and COVID-19, despite the fact that both conditions are associated with substantial arterial and venous thrombotic risk [6, 10, 11, 29, 30]. Mehta et al. suggested that the pathogenesis of thrombosis in patients with COVID-19 pneumonia shares similarities with that in patients with BS [30]. Our study demonstrates that this hypothesis is quite unlikely. In BS, vascular wall inflammation, rather than a hypercoagulable state, seem to play major role in the background of thromboses [6, 30]. In COVID-19 on the other hand, direct viral effects, sepsis-induced hyperinflammatory state, the high levels of D- dimer and many other factors can trigger a coagulopathy [29].

There has been a lot of controversy about the association between the COVID-19 infection and the smoking status. Several cross-sectional studies and one meta-analyses showed that current smokers were less likely to have positive SARS-CoV-2 PCR test results whereas more likely to undergo SARS-CoV-2 PCR tests [31–33]. Several studies have shown lower prevalence of smoker status amongst COVID-19 patients and found a negative association between being a smoker and having COVID-19 [34, 35]. Similarly, a low prevalence of current smoker status among hospitalized COVID-19 patients was also observed [36]. Authors suggested that nicotine might be protective against the SARS-CoV-2 infection and once the infection is acquired, nicotinic stimulation might protect against severe forms of the disease by anti-inflammatory actions. These results should be taken with caution due to potential unreported cases of smokers and the fact that elderly population who has the greatest risk against COVID-19 has a lower prevalence of smokers than the general population [37]. On the other hand, many studies and analyses represented higher mortality and complications as well as the severe progression of the disease and worsening conditions among smoker COVID-19 patients [38, 39]. Smoking is reported to be a predisposal factor for various viral and bacterial respiratory tract infections supposedly by disrupting the epithelium, impairing the mucociliary clearance and diminishing the immune protections [40]. Among several theories about how smoking affects SARS-CoV2 infection, the interaction with a nicotinic acetylcholine receptor which is known to be expressed in airway cells is most frequently suggested [41]. While further studies are needed to elucidate the association between the nicotine exposure and COVID-19, we suggest that our findings should be interpreted with caution.

Interferon-alpha (IFNα) is known to have complex immunomodulatory as well as anti-viral actions. It has been shown to be effective in the BS management and in the treatment of virus-related diseases, particularly acute and chronic hepatitis B, and hepatitis C [42–44]. IFNα was tested for the

treatment of COVID-19 and yielded promising results in line with our results [45, 46]. Recent studies also confirmed that patients having inborn errors of type 1 IFN-related genes and disrupted type 1 IFN response are susceptible to severe COVID-19 infection [47, 48].

Colchicine, an alkaloid, plant-derived secondary metabolite with anti-inflammatory effects, has been used in the treatment of BS, familial Mediterranean fever (FMF), gout, and several inflammatory disorders for decades [49, 50]. It exerts its actions mainly by inhibiting microtubule polymerization which has impacts on several cellular procedures such as signaling, proliferation, formation of the cellular shape, cellular movement, transfer, and migration [49]. It intervenes inflammatory pathways by inhibiting neutrophil adherence and recruitment to the site of inflammation, interfering with inflammasome activation which controls IL-1β-induced pathways [49]. It was also suggested to have some antiviral actions [51]. Throughout the COVID-19 pandemic, the use and efficacy of colchicine for the treatment of COVID-19 has been investigated in several studies. A number of them found a decreased rate of clinical worsening, hospitalization, and mortality [52–54]. Although rates of COVID-19 related hospital admissions and death did not show a significant decrease in the whole group in the COLCORONA study, these two parameters were significantly reduced in COVID-19 PCR confirmed colchicine-receiving group [55]. In two cohort studies, colchicine prescription was not found to have a significant protective or hazardous effect on COVID-19 related hospital admissions [56, 57]. Colchicine and COVID-19 association was reported in two case series with FMF [58, 59]. While the Turkish study [58] suggested that colchicine may decrease the symptoms of COVID-19, the French study [59] concluded that neither colchicine usage nor dysfunction of innate immunity composed a risk factor for COVID-19. In our study, we could not find any ameliorating or worsening effect of colchicine associated with COVID-19.

In line with the literature, we showed that chronic use of GC showed an adverse effect on COVID-19-related clinical outcomes [15, 26, 60]. On the other hand, both conventional DMARDs and anti-TNF agents were not found to be associated with an increased risk of getting COVID-19 or severe COVID-19 infection, similar to what have been previously reported [26, 60]. Additionally, we found that having comorbidities was associated with worse clinical outcome for COVID-19 as reported previously in several studies [61].

This study has several limitations. Lack of a diseased control group is an important one. Also, we were not able to compare our results directly with that found in the age and gender-matched general population. Our results may not be generalized for overall Turkey as 91.2% of the study cohort were living in Istanbul. We identified COVID-19 infection based on PCR test results. Therefore, we may have omitted some BS patients who may not have had a PCR test despite symptoms of COVID-19, especially when symptoms are mild. In addition, there is a small probability that PCR testing may have false-negative results.

Conclusions

Patients with BS have an increased risk of testing positive for SARS-CoV-2 suggesting caution during the follow-up these patients. Despite increased incidence, the clinical outcome of COVID-19 was not severe and there was no mortality. The protective effect of smoking and interferon should be investigated. Treatment with conventional DMARDs or anti-TNF agents was not associated with an increased risk of worse clinical outcomes. On the other hand, colchicine did not have any positive or negative effect against COVID-19. Considerable number of patients flared after COVID-19 however, this was significantly associated with immunosuppressive discontinuation during the infection. COVID-19 did not seem to exacerbate thrombotic events during or after the infection. Finally, the favorable outcome may suggest a possible role of a protective effect of BS itself or immune-modulating drugs.

Declarations

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