Impact of COVID-19 Pandemic on Hidradenitis Suppurativa Patients: a Cross-Sectional Study From Tertiary Referral Hospital

Ecem Bostan¹, Adam Jarbou¹, Aysen Karaduman¹, Duygu Gulseren¹, Basak Yalici-Armagan¹, Neslihan Akdogan¹

¹ Department of Dermatology and Venereology, Hacettepe University, Faculty of Medicine, Ankara, Turkey

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Corresponding author: Ecem Bostan, MD, Hacettepe University, Faculty of Medicine, Department of Dermatology and Venereology, Ankara, Turkey, Phone: 03123051704, Fax: 0 3123054127, E-mail: bostanecem@gmail.com

ABSTRACT

Introduction: Hidradenitis suppurativa (HS) is a chronic, disabling skin disorder which is characterized by recurrent attacks of nodule, abscess, sinus tract formation and scarring. Oral/topical antibiotics, oral retinoids and TNF-alpha inhibitors are used for the treatment of HS.

Objectives: In the present study, we aimed to determine the prevalence of coronavirus disease 2019 (COVID-19) real-time polymerase chain reaction (real-time PCR) positivity and the presence of COVID-19 related symptoms in relation to the age, gender, body mass index, disease duration, treatment used for HS, treatment duration and smoking.

Methods: We conducted a comparative, cross-sectional study of 178 patients diagnosed with HS in a referral hospital. Age, gender, smoking status, body mass index, treatment modalities used for HS, the presence of COVID-19 related symptoms, history of close contact to a person with COVID-19 and COVID-19 real time-PCR results were determined by a telephone questionnaire.

Results: Sixty-three patients were female, whereas 115 patients were male. During COVID-19 pandemic, 94 out of 178 patients had COVID-19 related symptoms; COVID-19 real time-PCR test was performed in 109 (61.2%) patients. Thirty (27.5%) cases tested positive for COVID-19 whereas 79 (72.5%) tested negative.
Introduction

Hidradenitis suppurativa (HS) is a chronic, inflammatory, debilitating skin disorder characterized by painful, deep-seated nodules and abscesses, draining sinus tracts and cicatrisation [1]. The disease is more likely to be seen in the intertriginous areas of the body including groin, gluteal area, axillae and inframammary region [1]. HS is staged according to the type, extent and severity of the skin lesions [2]. Single or multiple nodules or abscesses without sinus tracts and cicatrix formation refer to Hurley stage 1; recurrent nodules or abscesses with limited sinus tract formation and scarring refers to Hurley stage 2; whereas stage 3 disease is characterized by diffuse involvement of the affected area by nodules/abscesses, multiple interconnected sinus tracts and cicatrisation [2].

Genetic, environmental, endocrinologic, bacterial and host defense related immunologic factors as well as obesity, smoking have all been implicated in the etiology of HS [3]. Depression, inflammatory bowel disease, spondyloarthropathy, diabetes mellitus, hyperlipidemia and metabolic syndrome are among the common associated comorbidities in HS patients [4]. Low self-confidence, sexual dysfunction, impairment of daily functioning, chronic anxiety and depression all lead to poor life quality for HS patients [5,6].

In the early stages of the disease characterized by only a few nodules or abscess, only systemic antibiotics in combination with topical antibiotics or intralesional corticosteroids, are usually enough to control disease activity [7,8]. However, advanced stages require both surgical intervention and systemic treatment modalities. Tumor necrosis factor-alpha (TNF-α) inhibitors (especially adalimumab and infliximab) are the much-preferred agents used in the treatment of advanced stage HS, in combination with topical and systemic antibiotics [9].

During coronavirus disease 2019 (COVID-19) pandemic, the safety of biologic agents is one of the most frequently investigated issues in dermatology practice. The use of antibiotics and TNF-α inhibitors in the patients with HS does not seem to increase the risk for COVID-19 [10].

Objectives

In our study, we aimed to investigate the prevalence of COVID-19 real-time polymerase chain reaction (real

Conclusions: Patients having COVID-19 related symptoms were shown to have statistically significantly higher mean age compared to the ones who did not have any symptoms (P = 0.031). No statistically significant relationship was found COVID-19 real-time-PCR positivity and the type of treatment administered for HS when categorized as tumor necrosis factor-alpha inhibitor, oral retinoid, topical antibiotic and oral antibiotic group (P > 0.05).

Methods

We conducted a cross-sectional, descriptive study of 178 HS patients who were followed up in our dermatology outpatient clinic. All 178 participants were clinically diagnosed with HS and further receiving various treatment modalities according to disease stage in our center’s chronic dermatologic illnesses outpatient clinic between January 2018 and September 2021. Only patients who were under active-continuous treatment for HS during COVID-19 pandemic, were included. Local ethics committee approval was obtained for the present study (the date, project number, decision number: September 7, 2021, GO 21/934, 2021/14-66). An oral questionnaire composed of 15 questions related to the demographic data, HS disease and COVID-19, was formed (Supplementary File 1). The answers were obtained via a telephone survey and an oral informed consent was taken from all the patients before the start of the survey. The accuracy of questions related to COVID-19 status of the participants, characteristics of treatment given for HS and treatment duration, was also verified from the medical data records.

IBM SPSS for Windows Version 20.0 was used for the statistical analysis. Numerical variables were shown as mean ± standard deviation (range: minimum-maximum), whereas categorical variables were given as percentages and frequencies. Shapiro-Wilk test was used to determine if the numerical variables are distributed normally. Fisher’s exact test or Chi-Square test was used to compare the differences between patients receiving various different modalities for HS (divided into 4 groups as oral antibiotics± topical antibiotics, oral retinoids± topical antibiotics, TNF-α inhibitors± oral/topical antibiotics and only topical antibiotics). Logistic regression analyses (in which age, gender, BMI, the presence of any other systemic disease and smoking were included as independent variables) were also performed taking the presence of COVID-19 symptoms and COVID-19 real time-PCR results (positive or negative) as the dependent variables. P values less than 0.05 were considered statistically significant.
Results

A total number of 178 patients were included in the study. The mean age was 35.69 ± 11.21 years (range: 16-61). Sixty-three (35.4%) patients were female, whereas 115 (64.6%) patients were male. Fifty-two (29.2%) patients had Hurley stage 1 disease, 52 (29.2%) patients had Hurley stage 2 disease whereas 74 (41.6%) had stage 3 disease. The mean BMI was 27.55 ± 3.30 kg/m² (range: 17.09-43.25); one (0.6%) patient had a BMI of <18.5 kg/m² (underweight); 31 (17.4%) patients had a BMI in 18.5 to 24.9 kg/m² range (optimal). One hundred ten (61.8%) out of 178 cases were determined to fall within the overweight category (a BMI of 25-29.9 kg/m²) whereas 36 (20.2%) patients were within the obese category (a BMI of >30 kg/m²). One hundred nine out of 178 patients were current smokers, the mean pack-years of smoking was 21.06 ± 14.12 pack-years (range: 3-80). The mean duration of treatment for HS was 18.37 ± 18.90 months (1-108) whereas the average duration of the disease was 119.38 ± 91.97 months (2-552).

Forty-eight (27%) cases were on oral antibiotics (doxycycline, clindamycin and rifampicin, only clindamycin, tetracycline) treatment either alone or combination with topical treatment modalities. Thirty (16.9%) patients were on oral retinoid (isotretinoin or acitretin) treatment whereas 85 (47.8%) were using TNF-α inhibitors either alone or with oral/topical antibiotics. Out of 85 patients from anti-TNF-α group, 9 (10.58%) patients were under infliximab treatment, whereas 76 (89.41%) were under adalimumab treatment. Patients with stage 2 and 3 HS were additionally using colchicine. Out of 178 cases, 75 (42.1%) patients had at least one systemic disease. Nineteen (10.7%) patients had rheumatologic illnesses (most common ones being Familial Mediterranean Fever, Behçet disease and ankylosing spondylitis); 22 (12.4%) patients had cardiovascular diseases most frequently being hypertension, coronary artery disease and heart failure. Five (2.8%) case presented with nephrologic diseases whereas five other (2.8%) patients had prior history of malignancy. Endocrinologic disorders such as diabetes mellitus, hypothyroidism and hyperlipidemia were seen in 33 (18.5%) cases, whereas respiratory diseases (most commonly asthma, allergic rhinitis) were present in 11 (6.2%) patients.

During COVID-19 pandemic, 94 (52.8%) out of 178 patients had COVID-19 related symptoms such as fever, anosmia, ageusia, malaise, sore throat, dry cough, diarrhea and myalgia. COVID-19 real time-PCR test was performed in one hundred nine (61.2%) out of 178 patients. Thirty (27.5%) cases tested positive for COVID-19 whereas 79 (72.5%) tested negative. Forty-seven (26.4%) cases had a history of close contact to someone with a confirmed diagnosis of COVID-19. Of 109 patients with COVID-19 real-time PCR test, 30 (27.5%) had positive test result whereas 79 (72.5%) were tested negative. The average age of patients with positive real-time PCR was statistically significantly higher compared to the patients with negative result (p=0.007) (Table 1). There was no statistically significant relationship between gender versus COVID-19 real-time PCR positivity (P = 0.275) and BMI vs COVID-19 real-time PCR positivity (P = 0.873) (Table 1). There was no statistically significant difference in COVID-19 real-time PCR positivity between smokers and non-smokers (P = 0.111) (Table 2). There was no statistically significant relationship between the mean pack-years of smoking of patients who tested positive and negative for COVID-19 (P = 0.222) (Table 2). We found a statistically significant relationship between COVID-19 real-time PCR results and the mean disease duration for HS (P = 0.031) (Table 3). The patients with positive real-time PCR results have a higher mean disease duration compared to the ones with negative COVID-19 real-time PCR results. However, no statistically significant relationship was found between the positive results of COVID-19 real-time PCR and the mean duration of treatment for HS (P = 0.716) (Table 3).

<p>| Table 1: Covid-19 Real Time-PCR results in relation to the age, gender and body-mass index. |
|--------------------------------------|------------------|------------------|------------------|</p>
<table>
<thead>
<tr>
<th>COVID-19 real time-PCR results</th>
<th>Number of patients (n)</th>
<th>Age (years)</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Minimum</td>
</tr>
<tr>
<td>Negative</td>
<td>79</td>
<td>35.65</td>
<td>9.94</td>
</tr>
<tr>
<td>Positive</td>
<td>30</td>
<td>42.07</td>
<td>11.75</td>
</tr>
<tr>
<td>Total</td>
<td>109</td>
<td>37.41</td>
<td>10.80</td>
</tr>
</tbody>
</table>

SD = standard deviation.
The average age of patients with positive COVID real time-PCR was statistically significantly higher compared to the patients with negative result (P < 0.007). There was no statistically significant relationship between the gender vs COVID-19 real time-PCR results (P = 0.275). Additionally, there was also no statistically significant relationship between the body-mass index versus COVID-19 real time-PCR results (P = 0.873).
There was no statistically significant difference in COVID-19 real-time PCR positivity between smokers and non-smokers (P = 0.111). Among smokers, no statistically significant relationship was found between the mean pack-years of smoking of patients who tested positive and negative for COVID-19 (P = 0.222).

Statistically significant relationship was present between COVID-19 real-time PCR results and the mean disease duration for HS (P = 0.031). The patients with positive real-time PCR results have a higher mean disease duration compared to the ones with negative COVID-PCR results. However, no statistically significant relationship was found between the positive results of COVID-19 real-time PCR and the mean duration of treatment for HS (P = 0.716).

No statistically significant relationship was found between COVID-19 real-time PCR positivity and the type of treatment administered for HS when the treatment modalities are divided into four categories as oral antibiotics ± topical antibiotics, oral retinoids ± topical antibiotics, TNF-α inhibitors ± oral/topical antibiotics and only topical antibiotics (P = 0.657).
Patients having COVID-19 related symptoms were shown to have statistically significantly higher mean age compared to the ones who did not have any symptoms (P = 0.031). The percentage of patients with COVID-19 related symptoms according to the treatment type was shown in Figure 2. We found no statistically significant relationship between the presence of COVID-19 symptoms and the gender (P = 0.241), BMI (P = 0.472), cigarette smoking (P = 0.272), treatment duration (P = 0.353), disease duration (P = 0.850) and given treatment type when grouped as oral antibiotics ± topical antibiotics, oral retinoids, TNF-α inhibitors ± oral/topical antibiotics, colchicine and topical antibiotics (P = 0.124). Patients with cardiovascular disease were shown to present with COVID-19 related symptoms compared to the ones with no accompanying cardiovascular disease (P = 0.035). Additionally, patients who had at least one systemic disease (classified as respiratory, nephrologic, cardiovascular, rheumatologic, gastroenterologic, endocrinologic disorders) had higher probability to exhibit COVID-19 symptoms (Figure 3). Lastly, patients who reported to have COVID-19 related symptoms were shown to present with significantly higher pack-years of smoking compared to the ones with no symptoms (P = 0.024) (Figure 4).

As expected, there seems to be a statistically significant relationship between the presence of COVID-19 symptoms and COVID-19 RT-PCR positivity (P < 0.001) (Table 5). Of 109 patients who were tested for COVID-19, 75 (68.8 %) had COVID-19 related symptoms; 30 (40%) cases out of 75 cases with COVID-19 related symptoms, were tested positive for COVID. Thirty-four patients who did not demonstrate any symptoms still gave COVID-19 PCR test, were all tested negative. Of 109 patients who were tested for COVID-19, 43 (39.45 %) had close contact to someone with a confirmed diagnosis of COVID-19; whereas 66 (60.55%) did not have any close contact. Twenty-seven (62.8%) cases out of 43 with close contact to a person diagnosed with COVID-19 had positive RT-PCR result. We found a statistically significant relationship between the history of close contact to someone with a confirmed COVID-19 diagnosis and COVID-19 RT-PCR positivity (P < 0.001) (Table 5). No patient was hospitalized for severe COVID-19 infection.

Binary logistic regression analyses (in which age, gender, BMI, the presence of any other systemic disease and smoking were included as independent variables) were performed...
the presence of any other systemic disease were considered as independent variables) were also carried out by taking COVID-19 RT-PCR result (positive or negative) as the dependent variable. As a result, it was found that age, gender, BMI and the presence of at least one systemic illness did not contribute significantly to the outcome of COVID-19 test result.

Taking the presence of COVID-19 symptoms as the dependent variable. Smoking (odds ratio [OR] 2.595; 95% confidence interval: 1.009-6.674; P = 0.048) and the presence of any other systemic illness (OR 6.968; 95% interval: 2.754-17.631; P < 0.001) were associated with an increased risk of developing COVID-19 related symptoms. In addition, logistic regression analyses (in which age, gender, BMI and the presence of any other systemic disease were considered as independent variables) were also carried out by taking COVID-19 RT-PCR result (positive or negative) as the dependent variable. As a result, it was found that age, gender, BMI and the presence of at least one systemic illness did not contribute significantly to the outcome of COVID-19 test result.

Figure 2. The percentage of the patients with COVID-19 related symptoms according to the treatment type.

Figure 3. The distribution of the percentages of the patients with absent and present COVID-19 related symptoms among the participants without any systematic disease (A) and among the participants with at least one systematic disease (B)
females compared to males with a ratio of 3:1 [6,14]. Since patients with HS suffer from acute (bacterial superinfection, lymphadenopathy) and chronic complications of the disease (amyloidosis, chronic disease anemia, lymphedema, lymphatic obstruction, significant scarring, chronic pain, malodor and fistula formation) [15]; early diagnosis and adequate treatment of this debilitating disease are quite essential.

Topical and systemic antibiotics, anti-inflammatory agents, anti-androgens, oral retinoids, immunosuppressive treatments, TNF-α inhibitors (especially adalimumab and infliximab), apremilast, surgical intervention and laser excision repair are among the miscellaneous therapeutic interventions used for HS [16]. Generally, Hurley stage 1 HS is treated

**Table 5. Covid-19 Real-Time PCR results with respect to the presence of Covid-19-related symptoms and close contact to someone with a diagnosis of Covid-19.**

<table>
<thead>
<tr>
<th>Covid-19 Real Time-PCR Results</th>
<th>Covid-19 related symptoms N (%)</th>
<th>Close contact to someone with a diagnosis of Covid-19 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not present</td>
<td>Present</td>
</tr>
<tr>
<td>Negative</td>
<td>34 (100)</td>
<td>45 (60)</td>
</tr>
<tr>
<td>Positive</td>
<td>0 (0)</td>
<td>30 (40)</td>
</tr>
<tr>
<td>Total</td>
<td>34 (100)</td>
<td>75 (100)</td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

Statistically significant relationships were found between COVID-19 real-time-PCR positivity versus history of close contact to someone with a confirmed COVID-19 diagnosis (P < 0.001) and between COVID-19 real-time-PCR positivity versus the presence of COVID-19 related symptoms (P < 0.001).

**Figure 4.** The Pack-years of smoking according to the absence and presence of COVID-19 symptoms: Boxplot representing median values, 25-75% range (box) and minimum-maximum range (bars) of the pack-years of smoking with respect to the patients with COVID-19-related symptoms and patients without any COVID-19-related symptoms.

**Conclusions**

HS is one of the most challenging diseases of dermatology, which has a great impact on patients quality of life and presents with various associated comorbidities. The disease is characterized by deep-seated, tender, inflamed, draining nodules and abscesses subsequently leading to sinus tract and scar formation mainly in the flexural areas of the body [11]. HS is most commonly seen in the third and fourth decades of life [12]. Since different clinical entities including furunculosis, nodulocystic acne, epidermoid cyst, cutaneous Crohn disease may be considered in the differential diagnoses of HS, a mean diagnostic delay of 7.2 years has been reported in a study [13]. The disease is more commonly observed in
with topical and systemic antibiotics, surgical procedures; systemic antibiotics, oral retinoids, anti-TNF-α agents, surgical deroofing or laser excision are used for stage 2 and 3 disease [16].

From the start of COVID-19 outbreak in December 2019, the effect of immunosuppressive agents on the clinical course of COVID-19 is gradually being questioned by both physicians and patients [17]. COVID-19 infection is a multiphasic viral disease which commences with an antiviral response phase followed by an hyperinflammatory state [17,18]. The main cytokines that dominate the first (antiviral) phase differ from the cytokines which prevail the hyperinflammatory phase [18]. Interleukin (IL)-15, interferon-α, interferon-β and interferon-γ are the major cytokines responsible for viral clearance whereas TNF-α, IL-17, IL-6 and granulocyte-monocyte colony stimulating factor preponderate during the hyperinflammatory phase [17,18]. Therefore, it seems reasonable to use anti-TNF-α and anti-IL-17 agents during the hyperinflammatory state of COVID-19 since these agents do not seem to affect the course of the antiviral phase [18]. In phase 3 trials of adalimumab for HS, it was shown that there is a slightly escalated risk for total infections and nasopharyngitis by 2.5% but there was no significant difference between adalimumab and placebo group in terms of upper respiratory tract infections [19]. In line with this observation, in our study we found that no statistically significant relationship exists between COVID-19 real-time PCR positivity and the therapeutic interventions used for HS when the treatment modalities are divided into four categories as oral antibiotics ± topical antibiotics, oral retinoids ± topical antibiotics, TNF-α inhibitors ± oral/topical antibiotics and only topical antibiotics ($P = 0.657$). Also, similar to our study, Marasca et al [20] reported their experience with 93 HS patients during COVID-19 pandemic. In this study, 75 patients were on adalimumab treatment, 15 patients were using oral antibiotics and 3 patients were not on any treatment [20]. Only one patient reported COVID-19 related symptoms which subsided immediately and three patients (one under rifampicin+clindamycin treatment, the two others under adalimumab treatment) had been isolated due to a close contact to someone with a suspected diagnosis of COVID-19, without having positive real-time PCR test result [20]. Furthermore, Molinelli et al [21] declared that none of the 35 patients treated with adalimumab for HS in their cohort group had any symptoms related to COVID-19 and the ongoing biologic treatment was not discontinued in any patient. Supporting the findings of this study, we also did not find any statistically significant difference between the presence of COVID-19 symptoms and the given treatment modalities when categorized as oral antibiotics ± topical antibiotics, oral retinoid, TNF-α inhibitors ± oral/topical antibiotics and topical antibiotics ($P = 0.124$).

Patients with HS have multiple associated comorbidities including metabolic syndrome, obesity, diabetes mellitus, dyslipidemia, polycystic ovarian syndrome, thyroidal dysfunction, axial spondyloarthropathy and cardiovascular-associated adverse events [22]. A recent meta-analysis revealed that cardiovascular diseases, obesity, hypertension, history of smoking, old age are also risk factors for critical and mortal cases of COVID-19 infection [23]. Being male, smoking and being at an age greater than 65 years were shown to be associated with COVID-19 disease progression [23]. Critical COVID-19 cases had higher rates of having underlying diseases such as hypertension, cardiovascular disease and diabetes mellitus compared to the non-critical COVID-19 patients [23]. Even though, in our cohort no patient was needed to be hospitalized for severe COVID-19, we found that the mean age of the patients with positive results of COVID RT-PCR was statistically significantly higher compared to the ones with negative results ($P < 0.007$). Additionally, patients who demonstrated COVID-19 related symptoms were shown to have statistically significantly higher average age compared to the ones who did not demonstrate any symptoms ($P = 0.031$).

In line with the data in the literature, patients who had any cardiovascular disease (most common one being hypertension) were shown to have COVID-19 related symptoms at a higher rate compared to the ones with no accompanying cardiovascular disease ($P = 0.035$). Wang et al [24] showed that hypertension prevalence was higher in COVID-19 patients admitted to intensive care unit compared to ones who did not. In our study, we have also showed that patients who had at least one systemic disease had higher proportions of demonstrating COVID-19 symptoms compared to the ones who did not have any known systemic comorbidity. A recent study by Lowe et al [25] revealed that patients with > 30 pack-years of smoking were 2.25 times more likely to be hospitalized. Even though, we did not have any patient who was hospitalized for COVID-19, our study disclosed that patients with COVID-19 symptoms were shown to have statistically significantly higher pack-years of smoking compared to the ones without any symptoms ($P = 0.024$). Lastly, we found no statistically significant relationship between the presence of COVID-19 symptoms/COVID-19 RT-PCR positivity and gender, BMI, smoking status (current smoker vs non-smoker) and treatment duration ($P > 0.05$). In contrast, a study which investigated the relationship between COVID-19 and metabolic associated fatty liver disease, showed that obesity significantly increases the risk of having severe COVID-19 disease [26]. Since in our cohort population, not all the patients with COVID-19 related symptoms and with a history of close contact to someone with a confirmed diagnosis of COVID-19, were tested for COVID-19 we might have missed some real positive COVID-19 cases which might have limited our findings.
All in all, we would like underline once again that HS patients have multiple associated comorbidities some of which are also risk factors for critical/mortal COVID-19 disease. In our study, older age, higher pack-years of smoking, having at least one systemic disease, having a cardiovascular disease, were associated with increased risks of having COVID-19 related symptoms whereas higher disease duration of HS and older age were correlated with significantly higher levels of COVID-19 RT-PCR positivity. Treatment type did not seem to contribute significantly to the outcome of COVID-19 RT-PCR test and the incidence of COVID-19 associated symptoms. We suggest the ongoing TNF-α inhibitor treatment should be continued in patients with HS, unless a definitive diagnosis of COVID-19 is established.

Our study has some limitations since it was a single center study and no control group was present. Further multicenter, prospective studies with large number of patients are required to support our findings.

References
