Incidence and Prognosis of COVID-19 in Patients with Psoriasis: A Multicenter Prospective Study from the Eastern Black Sea Region of Turkey

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ABSTRACT: COVID-19 infection can have a poor prognosis, especially in patients with chronic diseases and those receiving immunosuppressive or immunomodulating therapies.

This study aimed to investigate the severity of COVID-19 infection in patients with psoriasis and compare the infection severity for systemic treatments and comorbidities.

We conducted a study in the dermatology clinics of five different centers in the Eastern Black Sea region of Turkey. Four hundred and eighty-eight patients were included, and 22.5% were confirmed as having COVID-19 infection.

In our study, the frequency of hospitalization rates due to COVID-19 infection were similar (15.4%, 25.9% respectively) in patients receiving biological treatment and receiving non-biological systemic treatment (*P*=0.344). Hospitalization rates were higher in patients with hypertension, androgenetic alopecia, and acitretin use (*P*=0.043, *P*=0.028, *P*=0.040).

In conclusion, current biologic treatments and non-biologic systemic treatments in patients with psoriasis did not appear to increase the risk of the severe form of COVID-19, except for acitretin.

KEY WORDS: COVID-19, psoriasis, comorbidity, biologic, non-biologic systemic drugs

INTRODUCTION

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected the whole world, and the possibility transmission causing severe disease is an important problem, especially in those with chronic diseases and those receiving immunosuppressive or immunomodulating therapies (1).

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Psoriasis vulgaris is a chronic inflammatory disease, with an incidence of 2-3% in the general population. 30% of the affected patients receive various systemic treatments such as immunosuppressive drugs: methotrexate, cyclosporine, and biologics including TNF-α, IL-17, IL-12/23, and IL-23 inhibitors. These drugs are associated with increased risk of infection, especially respiratory tract infection, so dermatologists and patients had serious concerns in the first wave of the pandemic about the drugs and tended to stop treatments. Contradictory results have been reported on the rates of hospitalization and intensive care unit admission due to severe Covid 19 infection in patients with psoriasis treated with biologics. Some studies showed that biologics were associated with lower risk of COVID-19-related hospitalization, compared with non-biologic systemic therapies in patients with psoriasis (2,3). Additionally, in a study with biologics, the authors found no significant number of hospitalizations or deaths from COVID-19 (5). Despite that, a study showed biologics resulted in greater risk to contract COVID-19 infection and to be hospitalized, but no increased risks of intensive care unit admission or death were reported (4).

Cardiovascular diseases, diabetes, chronic respiratory disease, older age, hypertension, and cancer were defined as risk factors for death associated with COVID-19 infection. Similarly, patients with psoriasis, especially with moderate to severe disease, and with psoriatic arthritis were affected with comorbidities, such as diabetes mellitus, arterial hypertension, and obesity. For that reason, most dermatologist have concerns about the probable increased risk of severe infections and death for patients with psoriasis on biologics. Some studies demonstrated that in addition to hypertension, diabetes mellitus, and cardiovascular disease, dark skin, chronic lung disease, old age, and being male are common risk factors for hospitalization and worse prognosis of COVID-19 pneumonia in patients with psoriasis (3).

In this study, we aimed to investigate the outcomes of COVID-19 infection in patients with psoriasis and compare the infection severity for systemic treatments and comorbidities in our region.

METHODS

We conducted a study in the dermatology clinics of four different tertiary centers and one state hospital in the Eastern Black Sea region of Turkey (Figure 1). All patients with psoriasis followed up between March 1, 2021 and June 1, 2021 were questioned in visits to dermatology clinics. The study was approved by the Local Ethics Committee of Karadeniz Technical University School of Medicine (protocol no: 2021/54, date:01.03.2021) and has been conducted in accordance with the guidelines for human studies and Declaration of Helsinki. Informed consent was obtained from all subjects.

Complete physical examination and evaluation of psoriasis severity was performed in all patients. We assessed psoriatic lesions using the Psoriasis Area Severity Index (PASI).

Patient demographic data including sex, age, body mass index (BMI), smoking, alcohol use, and disease characteristics including type, duration of disease, comorbidities, androgenetic alopecia, and psoriasis treatments were recorded. We also collected the date of diagnosis and methods, symptoms, pulmonary involvement, hospitalization, and intensive care unit stay duration, treatment for COVID-19, and prognosis of patients who were diagnosed with COVID-19. At the time we conducted our study, only inactivated vaccines had been administered to people over age of 65 in our country. 20% of participants had received at least one dose of vaccination one month earlier.

In our study, COVID-19 was diagnosed as probable/confirmed COVID-19 as defined by the WHO (4). COVID-19-associated mortality was defined as cause of death with COVID-19 or its complications.

Figure 1. Tertiary centers in the Eastern Black Sea region of Turkey

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Table 1. Demographics and characteristics of patients with psoriasis with COVID-19 infection

demographics n (%)	
Age	
0-20	6 (5.5%)
20-40	43 (39.1%)
40-65	48 (43.6%)
>65	13 (11.8%)
Gender	
Female	54 (49.1%)
Male	56 (50.9%)
Comorbidities n (%)	
Smoking	
Active smoker	22 (20.2%)17
Former smoker	(15.6%)
None	70 (64.2%)
Alcohol	
Current use	6 (5.5%)
Previous use	8 (7.3%)
None	95 (87.2%)
Obesity	24 (22.0%)
Diabetes mellitus	16 (14.5%)
Hypertension	24 (21.8%)
Inflammatory bowel disease	0(0%)
Chronic obstructive lung disease	1 (0.9%)
Chronic renal disease	0 (0%)
Malignancy	2 (1.8%)
Hepatosteatosis	4 (3.6%)
Coronary disease	4 (3.6%)
Androgenetic alopecia	27(29%)
Covid related symptoms	
Fever	43 (39.1%)
Weakness	75 (68.2%)
Cough	50 (45.5%)
Headache	60 (54.5%)
Throat ache	37 (33.6%)
Muscle pain	65 (59.1%)
Skin rash	3 (2.7%)
Diarrhea	11 (10.0%)
Taste/smell loss	37 (33.6%)
Shortness of breath	25 (22.7%)
Lung involvement	25 (22.7%)
COVID-19 outcome	
Oxygen requirement	12 (10.9%)
Hospitalization	16 (14.5%)
İntensive care unit	1 (0.9%)
Death	1(0.9%)

Statistical analysis

The SPSS 26.0 program was used in the analyses. The mean, SD, median lowest and highest, frequency, and ratio values were used to measure the descriptive statistics. The distribution of variables was measured with the Kolmogorov Smirnov test. The Mann-Whitney test was used to analyze the independent quantitative data. Chi-square analysis was used to compare descriptive data and the frequencies of different methods. The level of statistical significance was set to $P<0.05$

RESULTS

Four hundred and eighty-eight patients were included. One hundred and ten (22.5%) were confirmed as COVID-19 infection with compatible lung imaging and/or positive serology. Clinical characteristics of patients with psoriasis and with COVID-19 infection are shown in Table 1. Eighty-eight percent of the patients had chronic plaque psoriasis, 15% had active psoriatic arthritis, and 44% of the patients were treated with topical treatment, 29% with non-biologic systemic drugs, 26% with biological drugs, and 1% with phototherapy.

Among the comorbidities that increased the risk of severe course of COVID-19, 98 patients (20.1%) were obese, 85 patients (17.4%) had arterial hypertension, 55 patients (11.3%) had type 2 diabetes, and 15 patients (3.1%) had chronic pulmonary disease.

After COVID-19 infection, the disease was stable in 73 (71.6%) of the patients, exacerbation was observed in 23 (22.5%) patients, and recovery in 6 (5.9%). The rate of treatment discontinuation after COVID-19 infection was 38.2% (42 patients), and the mean duration of interruption of treatment was 26.05±17.9 days.

Nineteen of the patients were healthcare workers, and 14 (73.6%) of them had COVID-19 infection; this rate was determined as 20.5% in non-health workers, the difference being significantly higher ($P<0.0001$).

Comparison of psoriasis severity, comorbidities, and treatments in patients with and without COVID-19 are shown in Table 2. There were no statistically significant differences in sex, duration of treatment, PASI, prevalence of psoriatic arthritis, or comorbidity indicators of an increased risk of a severe course of COVID-19 between patients who tested positive and negative for anti-SARS-CoV-2 antibodies. COVID-19 frequency was significantly higher in those with mild disease ($P=0.011$)

The frequency of COVID-19 was found to be 20.5% in those receiving biological treatment and 19.1% in those receiving non-biological systemic treatment, but the difference was not statistically significant ($P=0.878$); additionally, hospitalization rates were similar (15.4% and 25.9% respectively) ($P=0.344$).

Pulmonary involvement was detected in 25 (22.7%) patients. The rate of comorbidities (34.0%) in those with pulmonary involvement was statistically significantly higher than those without (12.3%) ($P=0.011$); in addition, the rate of hypertension (45.8%) was significantly higher in those with pulmonary involvement ($P=0.005$). Lung involvement was detected in 16 patients over 65 years and 9 patients younger than 65 years. The rate of lung involvement

Table 2. Comparison of psoriasis severity, comorbidities, and treatments regarding COVID-19 positivity

	COVİD-19 positive n=110	COVID-19 negative n=378	p value
Gender n (%)			
Female	54 (49.1%)	179 (47.4%)	0.748
Male	56 (50.9%)	199 (52.6%)	
Severity of Psoriasis			
Mild	84 (77.1%)	242 (64.0%)	0,011
Moderate/severe	25 (22.9%)	136 (36.0%)	
Drugs, n (%)			
Metotrexate	21 (19.1%)	64 (16.9%)	0,702
Acitretin	6 (5.5%)	48 (12.7%)	0,050
TNF inhibitors	5(4.5%)	16 (4.2%)	0,796
Ustekinumab	9 (8.2%)	21 (5.6%)	0,433
Secukinumab	5 (4.5%)	40 (10.6%)	0,082
İxekizumab	7 (6.4%)	25 (6.6%)	1,000
PASI, mean ± SD	4,73 ± 4,71	6,94 ± 9,36	0,273
Comorbidities, n (%)			
Obesity	24(22.0%)	74 (19.6%)	0,680
Diabetes type 2	16 (14.5%)	39 (10.3%)	0,288
Hypertension	24 (21.8%)	61 (16.1%)	0,215
Coronary artery disease	4 (3.6%)	18 (4.8%)	0,788
Androgenetic alopecia	32(29.4%)	112 (31.3%)	0,724
Psoriatic arthritis	23 (20.9%)	50 (13.2%)	0,066

was significantly higher in patients over 65 years of age (69.2% and 16.5%, respectively) (*P*<0.0001).

Factors associated with hospitalization in patients with psoriasis and COVID-19 are shown in Table 3. Hospitalization rates were higher in patients with hypertension, androgenetic alopecia, and acitretin use (*P*=0.043, *P*=0.028, *P*=0.040, respectively).

Hospitalization frequency due to COVID-19 infection was not different in those with androgenetic alopecia with Hamilton Norwood classification stage 4 and above (27.3% and 23.1%, respectively) (*P*=0.813).

DISCUSSION

In our study, we found that 22.5% of patients with psoriasis developed COVID-19 infection, while the rate of general hospitalization was 14.5% and the rate of hospitalization in the intensive care unit was 0.9%. We found that the hospitalization rates were higher in patients with hypertension, androgenetic alopecia, and those using acitretin.

Several studies evaluated the incidence of COVID-19 prognosis (hospitalization and death) in patients using systemic therapies for psoriasis during the pandemic. A reduced / delayed type I IFN response was related to poor COVID-19 prognosis; thus, immune dysregulation in psoriasis may be advantageous. The second phase of COVID-19 comprises the cytokine storm, with increased proinflammatory cytokines (TNF, IL-1b, IL-6, IL-8, and IL-17 / IL-23) – these cytokines are also implicated in psoriasis development. While not yet fully clarified, in this phase COVID-19 infection is expected to be severe and progress in patients with psoriasis, ~~but~~ treatments targeting these cytokines are thought prevent this (3,6).

In a study by Kridin *et al.*, it was reported that COVID-19-associated mortality was lower in patients treated by TNF inhibitors (7). IL-17A in viral infections may contribute to secondary inflammatory injury, and IL-17A levels were elevated in patients with severe COVID-19 pneumonia (8). Reports showed high plasma levels of TNF and IL-17 in patients with severe COVID-19 and low hospitalization rates in patients using TNF inhibitors or IL-17 inhibitors compared with IL-23 inhibitors (9).[9] Similar to the literature, the hospitalization rates in our study of patients using TNF inhibitors and IL-17 inhibitors were similar to those who did not receive them.

Methotrexate is associated with increased risk of infection; Dávila-Seijo *et al.* demonstrated 40%

Table 3. Factors associated with hospitalization in patients with COVID-19

	Hospitalization + (n=16)	**Hospitalization –** (n=94)	**P value**
Gender n %			
Female	5 (31.1%)	49 (52.1%)	0,203
Male	11 (68.8%)	45 (47.9%)	
Age >65 years	4 (25.0%)	12 (9.6%)	0,077
Disease duration, mean ± sd	12,14 ± 10,30	11,76 ± 9,72	0,746
Psoriatic arthritis	2 (12.5%)	21(22.3%)	0,515
Comorbidities n (%)			
Obesity	3 (20.0%)	21 (22.3%)	1,000
Diabetes type 2	4 (25.0%)	12 (12.8%)	0,246
Hypertension	7 (43.8%)	17 (18.1%)	**0,043**
Coronary artery disease	1 (6.2%)	3 (3.2%)	0,472
Malignancy	0 (0%)	2 (%2.1)	1.000
COLD*	1 (%6.2)	0 (0%)	1.000
Androgenetic alopecia	8 (53%)	24 (25%)	**0,028**
Drugs n %			
Metotrexate	3 (18.8%)	18 (19.1%)	1,000
Acitretin	4 (25.0%)	2 (2.1%)	**0,004**
TNF inhibitors,	0 (0%)	5 (5.3%)	1,000
Ustekinumab	1 (6.2%)	8 (8.5%)	1,000

higher risk of infection compared with acitretin. Acitretin does not appear to cause immunosuppressive adverse events and showed the lowest risk of infection (10). In our study, the frequency of COVID-19 was found to be similar in those receiving acitretin, but when compared with other drugs, the hospitalization rate was found to be higher in patients using acitretin. We think that the hospitalization rates were increased due to the fact that 80% of patients using acitretin were over 65 years of age. Contrary to the literature, the hospitalization rate did not increase with methotrexate compared with biologics.

Mahil et al. investigated probable factors associated with hospitalization rates of psoriasis for COVID-19, and reported that the patients on non-biologic systemic therapy were more frequently affected than those on biologics (3). In a multicenter study of 374 patients with psoriasis (71% on biologics, 18% on non-biologic systemics, and 10% topical treatment), 21% were hospitalized and 2% died, and biologic therapies were additionally associated with lower risk of hospitalization (11). In a study from France, Penso *et al.* showed increased risk of hospitalization for COVID-19 for patients with psoriasis receiving any systemic treatment (12). In a study from Lombardy with 1193 patients with psoriasis treated with biologics or immunosuppressive agents, no death was reported for COVID-19, but hospitalization was increased relative to the general population. Another study showed no cases of COVID-19-associated intensive care unit admission or mortality (13). In our study, general hospitalization rates were 14% and the rate of death was 1%. We did not find any difference in hospitalization between biologic therapies and non-biologic systemic treatments.

In general, treatment with biologics during the pandemic did not impact the development of complications SARS-CoV-2 infection. Thus, discontinuation of biologics to prevent any negative outcomes of COVID-19 infection is not required. Similarly, the frequency of complications of COVID-19 infection in patients with psoriasis did not appear to be increased both in studies in the literature and in our study, which may be due to the fact that these patients pay more attention to the use of face masks, isolation, and social distancing (14).

COVID-19-associated comorbidities have been reported with several chronic diseases, leading to poor prognosis. Diabetes, cardiovascular disease, and renal and pulmonary diseases are frequently observed comorbidities that increase the mortality rate of SARS-CoV-2 (2). Comorbidities including hypertension, diabetes mellitus, and cardiovascular disease are more prevalent in patients with psoriasis (3). Mahil *et al.* reported that the rate of hospitalization due to COVID-19 in patients with psoriasis was increased in the male gender, in advanced age, and in those with chronic lung disease and dark skin, and the authors also reported that comorbidities such as hypertension, cardiovascular disease, and chronic liver disease were more prevalent in hospitalized patients (3).

In our study, there was no increase in the frequency of COVID-19 in patients with psoriasis with androgenetic alopecia, but hospitalization rates were significantly higher than in those without androgenetic alopecia. We found that the severity of hair loss in androgenic alopecia did not change the frequency of hospitalization. There are studies in the literature showing that androgenic alopecia increases the severity of COVID-19, and the data we have obtained support these results (15).

STUDY LIMITATIONS

The major limitation of our study was the small sample size. In our study, only 12% of those who had COVID-19 were over the age of 65, as patients were randomized. The distribution of patients into age groups was not homogeneous.

CONCLUSIONS

In conclusion, ongoing biologic treatments and non-biologic systemic treatments in patients with psoriasis did not appear to greatly increase the risk of severe form of COVID-19. In our study, we only found that hospitalization rates were higher in patients using acitretin, probably due to older age. Hypertension, which is one of the comorbidities that increase the severity of COVID-19 infection, was also a risk factor for hospitalization beside pulmonary involvement in patients with psoriasis. We also showed that androgenetic alopecia was associated with increased hospitalization rates of the patients regardless of the severity of alopecia.

References:

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;232:1239-42.
2. Singh MK, Mobeen A, Chandra A, Joshi S, Ramachandran S. A meta-analysis of comorbidities in COVID-19: Which diseases increase the susceptibility of SARS-CoV-2 infection? Comput Biol Med. 2021;130:104219.

3. Mahil SK, Dand N, Mason KJ, Yiu ZZN, Tsakok T, Meynell F, *et al.* PsoProtect study group. Factors associated with adverse COVID-19 outcomes in patients with psoriasis-insights from a global registry-based study. J Allergy Clin Immunol. 2021;147:60-71.
4. Gisondi P, Facheris P, Dapavo P, Piaserico S, Conti A, Naldi L, *et al.* The impact of the COVID-19 pandemic on patients with chronic plaque psoriasis being treated with biological therapy: the Northern Italy experience. Br J Dermatol. 2020;183:373-4.
5. Damiani G, Pacifico A, Bragazzi NL, Malagoli P. Biologics increase the risk of SARS-CoV-2 infection and hospitalization, but not ICU admission and death: Real-life data from a large cohort during red-zone declaration. Dermatol Ther. 2020;33:e13475.
6. Seo SH, Webster RG. Tumor necrosis factor alpha exerts powerful anti-influenza virus effects in lung epithelial cells. J Virol. 2002;76:1071-6.
7. Kridin K, Schonmann Y, Damiani G, Peretz A, Onn E, Bitan DT, *et al.* Tumor necrosis factor inhibitors are associated with a decreased risk of COVID-19-associated hospitalization in patients with psoriasis-A population-based cohort study. Dermatol Ther. 2021;34:e15003.
8. Pacha O, Sallman MA, Evans SE. COVID-19: a case for inhibiting IL-17? Nat Rev Immunol. 2020;20:345-6.
9. Haberman R, Axelrad J, Chen A, Castillo R, Yan D, Izmirly P, *et al.* Covid-19 in immune-mediated inflammatory diseases - case series from New York. N Engl J Med. 2020;38:85-8.
10. Dávila-Seijo P, Dauden E, Descalzo MA, Carretero G, Carrascosa JM, Vanaclocha F, *et al.* BIOBADADERM Study Group. Infections in Moderate to Severe Psoriasis Patients Treated with Biological Drugs Compared to Classic Systemic Drugs: Findings from the BIOBADADERM Registry. J Invest Dermatol. 2017;137:313-21.
11. Gisondi P, Bellinato F, Chiricozzi A, Girolomoni G. The Risk of COVID-19 Pandemic in Patients with Moderate to Severe Plaque Psoriasis Receiving Systemic Treatments. Vaccines (Basel). 2020;8:728.
12. Penso L, Dray-Spira R, Weill A, Zureik M, Sbidian E. Psoriasis-related treatment exposure and hospitalization or in-hospital mortality due to COVID-19 during the first and second wave of the pandemic: cohort study of 1 326 312 patients in France. Br J Dermatol. 2022;186:59-68.
13. Damiani G, Pacifico A, Bragazzi NL, Malagoli P. Biologics increase the risk of SARS-CoV-2 infection and hospitalization, but not ICU admission and death: Real-life data from a large cohort during red-zone declaration. Dermatol Ther. 2020;33:e13475.
14. Wan MT, Shin DB, Winthrop KL, Gelfand JM. The risk of respiratory tract infections and symptoms in psoriasis patients treated with interleukin 17 pathway-inhibiting biologics: A meta-estimate of pivotal trials relevant to decision making during the COVID-19 pandemic. J Am Acad Dermatol. 2020;83:677-9.
15. Wambier CG, Vaño-Galván S, McCoy J, Gomez-Zubiaur A, Herrera S, Hermosa-Gelbard Á, *et al.* Androgenetic alopecia present in the majority of patients hospitalized with COVID-19: The "Gabrin sign". J Am Acad Dermatol. 2020;83:680-2.