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Dermatologic comorbidities of the patients with severe COVID-19: A case-control study

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Abstract

The current studies focus on the association between COVID-19 and certain comorbidities. To the best of our knowledge, the association between severe COVID-19 and dermatologic comorbidities has not been reported yet. In this study, we aimed to describe the dermatologic comorbidities of patients with severe COVID-19 and compare it with the control group. Patients who have died at Uşak Training and Research Hospital due to COVID-19 and other diseases in the COVID-19 Intensive Care Units and Internal Medicine Intensive Care Units were recruited into the study. Two groups were compared with each other regarding the most common dermatologic comorbidities. A total of 198 patients including 111 patients with COVID-19 and 87 age and sex-matched patients with other diseases were enrolled in the study. The most common dermatologic comorbidities were pruritus (8.1%), eczema (6.3%), skin infections (3.6%), leukocytoclastic vasculitis (1.8%), and urticaria (0.9%) in the COVID-19 group while they were skin infections (9.2%), eczema (3.4%), pruritus (2.3%), and urticaria (1.1%) in the control group. None of patients in the control group had leukocytoclastic vasculitis. There were no significant differences between COVID-19 and control groups in terms of pruritus, eczema, skin infections, and urticaria (*P values* were .117, .517, .181, .505, and 1.000, respectively). In conclusion, although it is not statistically significant, it appears that pruritus and leukocytoclastic vasculitis are more common in severe COVID-19 patients. These cytokines-related diseases in the immuno-cutaneous systems may give some clues on the COVID-19 severity. Further studies are required to elucidate the relationship between the immuno-cutaneous system and COVID-19 severity.

KEYWORDS

dermatologic comorbidities, eczema, leukocytoclastic vasculitis, pruritus, SARS-CoV2, severe COVID-19, skin infections, urticaria

1 | INTRODUCTION

Coronavirus is continuing its spread without slowing down and the number of confirmed cases has recently passed 71 million. As of 14 December 2020, the COVID-19 pandemic has resulted in over 1.6 million deaths across the world.[1]

The current studies focus on the association between COVID-19 and certain comorbidities. We have recently reported that the most common dermatologic comorbidities in patients infected with COVID-19 were superficial fungal infections, psoriasis, and eczema.[2] However, this cross-sectional study has investigated the presence of dermatologic comorbidities in COVID-19 patients, regardless of severity.

It has been reported that COVID-19 triggers an excessive immune response known as cytokine storms.[3,4] A cytokine storm which includes increasing levels of tumor necrosis factor (TNF)-α, IL-1, IL-6, IL-18, IFN gamma, and interestingly IL-10 is reported to be the

main factors for the severity and fatality of the disease.[4] There are numerous dermatologic diseases that have an immunological infrastructure that includes cytokine releases.[5,6] Therefore, certain dermatologic comorbidities may give hints about the COVID-19 severity. To the best of our knowledge, the association between severe COVID-19 and dermatologic comorbidities has not been reported yet.

In this study, we aimed to describe the dermatologic comorbidities of patients with severe COVID-19 and compare it with the control group.

2 | MATERIALS AND METHODS

Patients who have died at Uşak Training and Research Hospital due to COVID-19 and other diseases in the COVID-19 Intensive Care Units and Internal Medicine Intensive Care Units were recruited into the study. These patients were divided into two groups; COVID-19 and control group. The age and gender-matched control group was selected at random from among patients who have died at Internal Medicine Intensive Care Units. Severe COVID-19 cases have been admitted to the intensive care unit according to the following Turkish COVID-19 guideline criteria: respiratory failure necessitating mechanical ventilation, respiratory rate ≥30 breaths/min, PaO2/FiO2 < 300, multilobar infiltration, delirium or loss of consciousness, SpO2 < 90% or PaO2 < 70 mmHg despite 5 L/min oxygen therapy, high levels of troponin and arrhythmia, Lactate>2 mmol presence of livedo reticularis, and hypotension (systolic blood pressure < 90 mmHg and a decrease from usual SBP more than 40 mmHg and mean arterial pressure < 65 mmHg, tachycardia >100/min.[7,8]

Two groups were determined in terms of common dermatologic comorbidities. Dermatological comorbidities classified into five subgroups as follow: pruritus, leukocytoclastic vasculitis, urticaria, eczema, and skin infections. Two groups were compared with each other regarding the most common dermatologic comorbidities. The patients under 18 years of age and pregnant were excluded.

The data were assessed in SPSS 20.0 (SPSS Inc., Chicago, Illinois) package program. Descriptive statistics are given by giving frequency and percentages. Student's *t*-test and Wilcoxon's test were used in terms of normal distribution in continuous variables while Pearson's Chi-square test and Fisher's exact test were used for categorical variables. The approval of the Institutional Review Board was received (IRB approval status [approval date and number: 24.07.2020/612.01.99]).

3 | RESULTS

A total of 198 patients including 111 patients with COVID-19 and 87 age and sex-matched patients with other diseases were enrolled in the study. The mean age of the patients with COVID-19 was 71.11 ± 14.30 years, while the mean age of the control group was 73.17 ± 15.73 years. There were 46 (41.4%) females and 65 (58.6%) males in the COVID-19 group, while 39 (44.8%) females and 48 (55.2%) males in the control group. No significant differences were found between two groups in terms of age and gender (P = .110 and P = .633, respectively). The cytokine related laboratory characteristics of the patients are seen in Table 1.

Twenty (18.0%) patients with the COVID-19 group and 14 (16.1%) patients with a control group had dermatologic comorbidities for the last 3 years. There was no statistically significant difference between two groups regarding the frequency of dermatologic comorbidities (P = .721)

The most common dermatologic comorbidities were pruritus (8.1%), eczema (6.3%), skin infections (3.6%), leukocytoclastic vasculitis (1.8%), and urticaria (0.9%) in the COVID-19 group while skin infections (9.2%), eczema (3.4%), pruritus (2.3%), and urticaria (1.1%) in the control group. None of the patients in the control group had leukocytoclastic vasculitis (Tables 2 and 3).

There were no significant differences between COVID-19 and control groups in terms of pruritus, eczema, skin infections, and urticaria (P values were .117, .517, .181, .505, and 1.000, respectively; Table 4). In the COVID-19 group, 4 (44.4%) out of 14 patients with pruritus presented in a year before COVID-19 while five (55.6%) presented in between 1 and 3 years.

4 | DISCUSSION

Severe COVID-19 is mainly associated with increased certain inflammatory cytokines and mediators. It shares many common aspects regarding cytokine storms with other infectious and non-infectious diseases including dengue viruses, Ebola virus infection, multiple sclerosis, pancreatitis, graft-vs-host disease, or multiple organ dysfunction syndromes.[9-13]

Siddiqia et al reported there is a significant increasing number of inflammatory cytokines along with biomarkers including IL6, IL-7, macrophage inflammatory protein 1-α, TNF-α, CRP, D-dimer, ferritin, and procalcitonin in the hyperinflammation stage of COVID-19.[14,15] In our study, inflammatory markers such as CRP, D-dimer, procalcitonin levels increased in patients with COVID-19. There are many dermatologic diseases that are associated with increased certain inflammatory cytokines and mediators. These cytokines and mediators may lead to an increased risk of getting and severity of certain systemic diseases. The relationship between psoriasis and cardiovascular diseases, atopic dermatitis and asthma, or pityriasis versicolor and *Helicobacter pylori* infection can be discussed in this context.[16] Therefore, previous inflammatory dermatologic diseases may give some hints about the immunological basis of patients.[17] In our study, despite the similar frequency of previous dermatologic comorbidities in both groups, we found some what different dermatological comorbidities profiles. These differences existed more prominent in cytokine related diseases such as pruritus, leukocytoclastic vasculitis, and skin infections.

A previous study reported from China has revealed that severe COVID-19 cases had common comorbidities such as hypertension, cardiovascular diseases, cerebrovascular diseases, diabetes mellitus,

TABLE 1 The cytokine-related laboratory characteristic of patients

Parameters	COVID-19 group	Control group	Normal value	*P* values
WBC ($\times 10^3/\mu l$)	11.84 ± 8.69	13.52 ± 9.64	4-10.5	.036
Eosinophils ($\times 10^3/\mu l$)	0.27 ± 0.13	0.46 ± 0.14	00.2-0.5	.001
MPV (fl)	9.84 ± 1.30	9.89 ± 1.34	6.5-12	.900
CRP (mg/L)	135.76 ± 84.36	126.45 ± 91.83	0.1-5	.255
Procalcitonin (ng/ml)	5.70 ± 15.58	9.07 ± 16.09	<0.01	.001
D-dimer (μg/L)	2441.63 ± 1547.77	3417.43 ± 1232.91	0-550	.006
Fibrinogen (mg/dl)	510.53 ± 162.97	379.15 ± 125.87	180-350	.037

Abbreviations: CRP, C-reactive protein; MPV, mean platelet volume; WBC, white blood cells.

TABLE 2 The dermatologic comorbidities of the severe COVID-19 patients for the last 3 years

Number	Age	Gender	Diagnosis	Admission time
1	77	Male	Pruritus	In a year/3 years
2	86	Male	Pruritus	In a year
3	93	Female	Pruritus/Contact dermatitis	In a year/3 years
4	73	Female	Contact dermatitis and pruritus	In 3 years
5	63	Female	Urticaria and pruritus/LCV	In a year/3 years
6	73	Female	Actinic keratosis/pruritus	In a year/3 years
7	57	Male	Pruritus	In 3 years
8	69	Male	Pruritus	In 3 years
9	82	Male	Pruritus	In 3 years
10	76	Female	Tinea pedis/Actinic keratosis	In a year/3 years
11	59	Male	Skin tag, solar lentigo	In a year
12	52	Male	Tinea corporis	In a year
13	68	Male	Seborrheic dermatitis	In a year/3 years
14	72	Male	Bacterial infection/LCV	In a year
15	62	Male	Actinic keratosis/seborheic dermaitits	In a year/3 years
16	67	Male	Seborrheic dermatits	In 3 years
17	60	Male	Psoriasis vulgaris	In 3 years
18	82	Female	Molluscum contagiosum	In 3 years
19	64	Male	Contact dermatitis	In 3 years
20	81	Female	Contact dermatitis	In 3 years

Abbreviation: LCV, leukocytoclastic vasculitis.

hepatitis B infections, chronic obstructive pulmonary diseases, chronic kidney diseases, and malignancy, respectively.[3] In our previous study, we reported that the infection risk of COVID-19 may be related to fungal infections and using immunosuppressive agents in certain diseases such as psoriasis. However, this study did not address the association between severe COVID-19 and dermatologic comorbidities. To the best of our knowledge, this is the first study on the association between severe and fatal COVID-19 and dermatologic comorbidities. In this study, although there was no statistically significant relationship between pruritus and severe COVID-19, we found patients who have presented to dermatology outpatient clinics for pruritus in the last 3 years were 3.5 times more common in severe COVID-19 patients when compared to control group. IL-31 is one of the main cytokines in the pruritus that is produced by CD4 + T helper cells in the setting of IL-4 secretion. Numerous dermatologic diseases including chronic urticaria, prurigo nodularis, atopic dermatitis, etc. are related to the increased serum IL-31 levels. Although it mainly secreted from Th2 cells, it has recently been reported that secretion of IL-31 is crucial to inhibit Th2-type response in the lung.[18,19] In addition, IL-31 is known as the part of the IL-6 family that has both inflammation and neuropathic properties.[20] Meanwhile, previous studies have supposed that IL-2 and IFN gamma that are secreted from T1 cells can be related to the TRP channels resulted in chronic itching. IL-2 is a strong itch-related cytokine in both healthy people and patients. Injection of IL-2 into healthy people or patients with atopic dermatitis stimulates 2 to 3 days lasting itch.[21-23] It is known

TABLE 3 The dermatologic comorbidities of the control group for the last 3 years

Number	Age	Gender	Diagnosis	Admission time
1	84	Male	Pruritus	In a year/3 years
2	74	Male	Pruritus	In 3 years
3	61	Male	Zoster	In 3 years
4	83	Female	Candidiyasis	In a year/3 years
5	92	Female	Callus	In a year/3 years
6	46	Female	Herpes simplex	In a year/3 years
7	54	Male	Eczema/Tinea pedis	In a year/3 years
8	39	Female	Eczema	In a year/3 years
9	77	Male	Actinic keratosis	In a year/3 years
10	73	Female	Urticaria	In 3 years
11	88	Female	Tine pedis and Zoster	In 3 years
12	59	Male	Folliculitis	In 3 years
13	60	Male	Eritema intertrigo	In 3 years
14	76	Male	Dermatitis/Tinea pedis	In 3 years

TABLE 4 The differences between dermatologic comorbidities between severe COVID-19 and control group in the last 3 years

Diseases	COVID-19 group	Control group	*P* values
Pruritus	9 (8.1%)	2 (2.3%)	.117
Urticaria	1 (0.9%)	1 (1.1%)	1.000
Eczema	7 (6.3%)	3 (3.4%)	.517
Skin infection	4 (3.6%)	8 (9.2%)	.181
Leukocytoclastic vasculitis	2 (1.8%)	0 (0.0%)	.505

that itch-related cytokines such as IL-2, IFN gamma, IL 6 are increasing in the cytokine storms. Considering the increasing high numbers of patients with pruritus in the COVID-19 group, it can be speculated that patients who have idiopathic pruritus history may prone the more severe COVID-19 diseases. Therefore, we believe that elderly patients who have pruritus should be warned to avoid unnecessary applying for pandemic hospitals unless there are serious grounds. Nevertheless, large-sample-based further studies are needed in order to see the exact effect of pruritus on severe COVID-19.

In this study, we found that eczema and urticaria had approximately the same incidences in both groups. Furthermore, two patients with COVID-19 had leukocytoclastic vasculitis while none of the control group had leukocytoclastic vasculitis. It has been shown that IL-1, IL-6, IL-8, and TNF factors are increased in circulation in leukocytoclastic vasculitis.[24,25] There are also numerous reports that proposed the association between leukocytoclastic vasculitis and COVID-19.[26-29] Moreover, it has been reported that livedoid and necrotic lesions mostly appear in elderly patients and those with severe COVID-19.[30] In concordance with previous studies, our result suggests that a history of leukocytoclastic vasculitis may be an indicator of severe COVID-19.

It is well established that the main cause of death in COVID-19 patients is due to hyperactivation of the immune system rather than immunosuppression. SARS-CoV-2 can promptly activate pathogenic Th1 cells to produce pro-inflammatory cytokines including IL 6, IL 2, and TNF-α in severe COVID-19 cases.[4] This increased immune status may be one of the causes of less skin infections in patients with severe COVID-19. Given results from our previous and current study, it can be concluded that patients who have the immunosuppressive condition may be more vulnerable to become infected with COVID-19 while patients whose immune system hyperactive may be more vulnerable to getting severe COVID-19.[2,31-34]

In conclusion, although it is not statistically significant, it appears that pruritus and leukocytoclastic vasculitis are more common in severe COVID-19 patients. These cytokines-related diseases in the immuno-cutaneous systems may give some clues on the COVID-19 severity. Further studies are required to elucidate the relationship between the immuno-cutaneous system and COVID-19 severity.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are not publicly available due to privacy and ethical restrictions but are available from the corresponding author on reasonable request.

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