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Original article

Prevalence and Pattern of Skin Manifestations in COVID-19 Patients; A Cross-Sectional Observational Study in Saudi Arabia

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Abstract

Background: Although COVID-19 is known to cause fever and an array of respiratory symptoms, the disease has recently been reported to be associated with dermatological symptoms. It is crucial to identify the frequency and the nature of these symptoms to facilitate the early detection and the efficient management of the disease. ***Methods:*** A cross-sectional observational survey study that was carried out in Saudi Arabia Previously-infected adult residents with COVID-19 were considered. Sociodemographic characteristics, concomitant medications, medical history, and the occurrence of skin manifestations while having COVID-19 infection were collected. Data were represented in the form of frequencies (number of responders) and valid percentages for categorical variables. ANOVA test was utilized to compare means between different subgroups. All P values < 0.05 were considered statistically significant. ***Result:*** A total of 464 participants were included. Gender distribution was almost equal. Out of them, 54.1% aged from 21 to 40 years old and 65.9% hold a university degree. Skin symptoms were reported in 9.1% respondents. The most common locations were all-over the body (1.5%), arms (1.3%), face or upper body (1.3%) and fingers (1.3%). Participants experienced morbilliform rash (3.5%), maculopapular rash (1.3%), urticaria (0.9%), livedo reticularis (0.2%) while 5.4% experienced miscellaneous skin symptoms. ***Conclusion:*** More research studies investigating the prevalence and patterns of skin symptoms accompanying COVID-19 infection are suggested.

Keywords: ***COVID-19, Skin Manifestations, Morbilliform Rash, Maculopapular Rash.***

Introduction

Since its emergence from Wuhan, China, in late 2019, coronavirus disease (COVID-19) has caused a global viral outbreak of respiratory illness [1]. On 11 March 2020, it was declared to be a pandemic [2].

The most common clinical presentations of COVID-19 are chills, cough, dyspnea, myalgia, sore throat, and fever. New and variant manifestations of the disease are being reported as time goes on [3]. COVID-19 is reported to be associated with different manifestations such as dermatological symptoms [4].

An Italian study has reported that 20% of patients had cutaneous lesions, described as rash or urticaria, and including one case of 'chickenpox-like' lesions [5]. Different case reports have described rash mistaken for dengue, acro-ischemia in children and critical patients, plaques on the heels, and urticaria [6-11].

In another study, dermatological characteristics of 132 acral lesions in suspected cases of COVID-19 were described. However, these cases have not been biopsied, and only 18.1% of the cases had a definite COVID-19 diagnosis [12].

Margo et al. hypothesized that perniosis associated with COVID-19 could be a representative of a virally-triggered exaggerated immune reaction with significant type I interferon signaling and that the vascular thrombosis in the skin and other organ systems in critically ill patients with COVID-19, is associated with a minor interferon response [13].

The frequency of COVID-19-related skin lesions varies greatly. The incidence was only 0.2% in a Chinese case series and 20.4% in an Italian case series [14]. In Spain, high frequency of male pattern hair loss among COVID-19 patients was observed, and it was suggested that androgen expression might be a determinant of the severity of COVID-19 infection [15].

The French Society of Dermatology has launched a national case call to confirm or dispute the correlation between COVID-19 infection and dermatological manifestations by documenting cases in terms of collection context, clinical signs and their evolution, photos, and possibly biopsies. The first progress reported detailing cases of COVID-19 having dermatological manifestations such as erythematous maculopapular lesions on the face and pseudo-frostbite [16].

A systematic review and meta-analysis of various skin manifestations among patients with COVID-19 has shown that skin manifestations in COVID-19 patients are diverse and can occur at any stage of the disease development or even after antibiotic treatment. Skin manifestations including rash, urticaria and erythematous lesions were the most commonly reported symptoms among patients with COVID-19 [17].

In the region of Murcia, the most common cutaneous reactions among COVID-19 patients in their series were hives (25%), rashes (19%), and chilblain-like lesions (12%) [18].

This cross-sectional observational study was conducted to investigate the prevalence of skin manifestations among adult COVID-19 patients in Saudi Arabia and the factors associated with a higher prevalence of skin symptoms.

Subjects and Methods

Study design

This cross-sectional, survey-based study was conducted in Saudi Arabia. All adult residents of Saudi Arabia who were previously infected with COVID-19 were considered eligible to take part in this study. Completed surveys were included in the statistical analysis.

Data collection

Data was collected using a self-administered designed questionnaire that was distributed to the Saudi population (as a link to Google form) through social media. The questionnaire was composed of 21 questions divided into four main sections. The first section included demographic variables such as age, gender, place of residence, educational level, and nationality. The second section was aimed to collect data about the occurrence of skin manifestations in COVID-19 patients, including the site of symptoms and a checklist containing pictures of the most common skin manifestations in COVID-19 patients. The third section was about concomitant medications. And the last part included questions about the presence of allergy or autoimmune diseases.

Statistical analyses and sample size calculation

Data were represented in the form of frequencies (number of responders) and valid percentages for categorical variables. Chi-square test was used to compare the prevalence of skin symptoms between the different subgroups. All P values < 0.05 were considered statistically significant. IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) was used to perform all statistical calculations, version 21 for Microsoft Windows.

Considering a confidence level of 95%, a marginal error of 5%, and a response distribution of 50% (maximum uncertainty), it was planned to include a sample of 377 participants in this study. A total of 464 eligible participants responded to the questionnaire and were included in the statistical analysis.

Ethical considerations

A statement was included at the beginning of the questionnaire clarifying that the collected data will be anonymous and will be used for research purposes only. All participants were asked if they agree or not to take part in the study. Only those who agreed to participate were included. Before conducting any study-related procedures, ethical approval was obtained from Research Ethics Committee at Taif University.

Results

Data was collected during the period from the 8th of February to the 24th of March, 2021. A total of 895 participants responded to the questionnaire. This included 431 participants who have not been infected with the COVID-19 virus before, and accordingly, they were excluded from the analysis. A total of 464 participants met the eligibility criteria and were included in the statistical analysis. The socio-demographic characteristics of the participants are shown in table 1.

Table 1: Socio-demographics characteristics of the study participants (n=464)

Socio-demographics characteristics		Count	Percent
Gender	Male	234	50.4%
	Female	230	49.6%
Age (Years)	Less than 20	88	18.9%
	21-40	251	54.1%
	41-60	103	22.2%
	More than 60	22	4.7%
Educational Level	Postgraduate studies	29	6.3%
	University degree	306	65.9%
	Secondary education	96	20.7%
	Diploma	2	0.4%
	Intermediate education	21	4.5%
	Primary education	4	0.9%
	Read and write	6	1.3%
Residence	Makkah	358	77.2
	Riyadh	28	6
	Bahaa	25	5.4
	Madinah	13	2.8
	Eastern region	12	2.6
	Assir	10	2.2
	Taif	9	1.9

Socio-demographics characteristics		Count	Percent
	Qassim	5	1.1
	Tabuk	3	0.6
	Jazan	1	0.2

Medical history and concomitant medications

Results have shown that 7.3% of the participants suffer from allergies to a specific food or drug, while only 1.1% of the participants suffer from autoimmune diseases.

The use of the following medications; corticosteroids, chloroquine/ hydroxychloroquine, azithromycin, tocilizumab, lopinavir/ ritonavir, and convalescent plasma was reported by 4.7%, 2.8%, 2.4%, 0.9%, 0.6%, and 0.6% of the participants, respectively.

COVID-19 disease characteristics

Almost one-half of the participants (47.4%) were infected with COVID-19 one to 6 months before participation in the study, 40.9% were infected more than six months before participation, while 11.6% were infected with COVID-19 less than one month before participation in the study. The vast majority (93.8%) reported that they have not suffered from any skin diseases before being infected with COVID-19

Locations and patterns of skin symptoms

A total of 42 responders (9.1%) reported that they developed skin symptoms while suffering from COVID-19, as shown in figure 1. Out of these 42 patients, 29 (69.0%) said that it was their first time to notice these symptoms. Responders were asked about the location and pattern of their skin symptoms, and the results are provided in table 2.

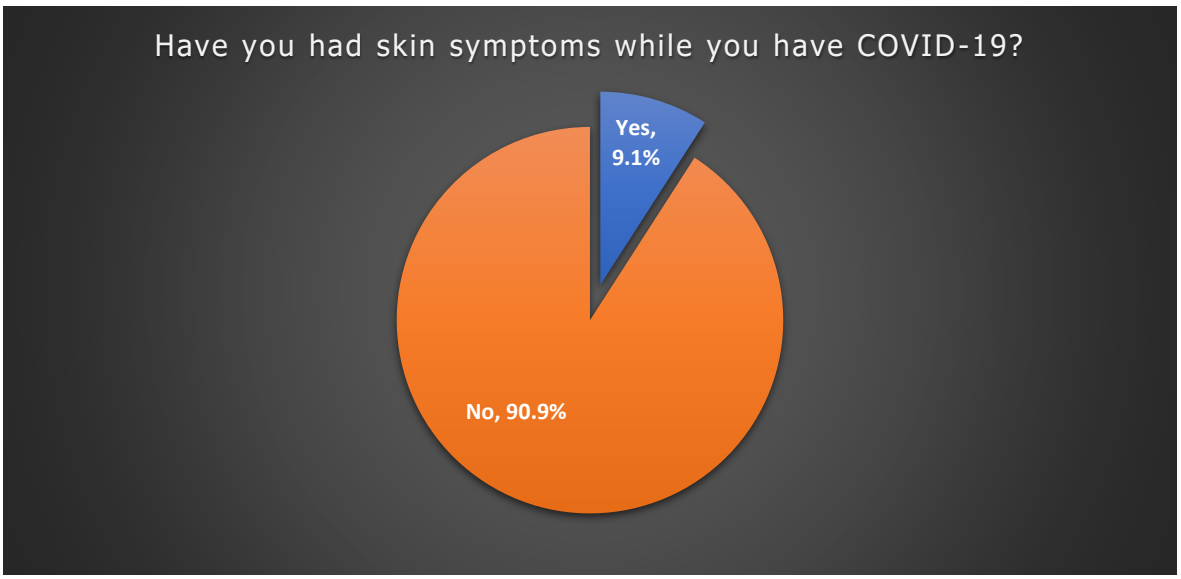

Figure 1: Percentage of patients who suffered from skin diseases before contracting COVID-19 then developed skin symptoms while contracting COVID-19

Table 2: Location and pattern of skin symptoms among COVID-19 patients

Location and pattern		Frequency	Percent out of the total population (n=464)	Percent out of patients who experienced skin symptoms (n=42)
Location	All over the body	7	1.50%	16.7%
	Arms	6	1.30%	14.3%
	Face or upper part of the body	6	1.30%	14.3%
	Fingers	6	1.30%	14.3%
	Chest, Arms, and Legs	4	0.90%	9.5%
	Chest and abdomen	3	0.60%	7.1%
	Back	2	0.40%	4.8%
	Chest	2	0.40%	4.8%
	Thigh	2	0.40%	4.8%
	Heels or toes	1	0.20%	2.4%
	In the elbow joint, knee, and under the eyes	1	0.20%	2.4%
	Mouth	1	0.20%	2.4%
Pattern**	Miscellaneous skin symptoms	25	5.40%	59.5%
	Morbilliform rash	16	3.40%	38.1%
	Maculopapular rash	6	1.30%	14.3%
	Urticaria	4	0.90%	9.5%
	Livedo reticularis	1	0.20%	2.4%

**One patient with missing data about the location of skin symptoms.*

*** Each patient may report more than one pattern of skin symptoms.*

Potential factors affecting the rate of developing skin symptoms while having COVID-19

The prevalence of skin symptoms was compared between the different subgroups of patients to investigate any significant difference. Based on collected data, gender (p=0.176), age (p=0.473), and educational level (p=0.960) showed no significant effect on the prevalence of skin symptoms among COVID-19 patients.

On the other hand, the place of residence and previous history of skin disease were found to significantly affect the prevalence of skin symptoms among COVID-19 patients.

The rate of skin symptoms was significantly higher (p=0.027) in the Eastern region (33.3%), Madinah (30.8%), compared to Taif (11.1%), Riyadh (10.7%), Bahaa (8.0%), Makkah (7.8%), Assir (0.0%), Jazan (0.0%), Qassim (0.0%), and Tabuk (0.0%).

Patients with a previous history of skin diseases showed a significantly higher rate of skin symptoms (p<0.001) compared to those who have no history of skin diseases (37.9% vs. 7.1%).

The use of some medications was associated with a higher risk of developing skin symptoms during COVID-19 infection. These medications included hydroxychloroquine, azithromycin, corticosteroids, and convalescent plasma (p<0.05).

Patients suffering from an allergy to a specific food or drug showed a significantly higher rate (p<0.001%) of skin symptoms compared to those who have no history of allergy to foods or drugs (44.1% vs. 6.3%). On the other hand, autoimmune diseases showed no significant effect on the rate of skin symptoms (p=0.478). More details are provided in table 3.

Table 3: Potential effect of different factors on developing skin diseases while having COVID-19 (n=464)

Have you had skin symptoms while you have COVID-19?		Yes	No	P-value*
Gender	Male	7.3%	92.7%	0.176
	Female	10.9%	89.1%	
Age	Less than 20	11.8%	88.2%	0.473
	21-40	9.6%	90.4%	
	41-60	7.8%	92.2%	
	More than 60	0%	100%	
Residence	Assir	0.0%	100.0%	0.027
	Bahaa	8.0%	92.0%	
	Eastern region	33.3%	66.7%	
	Jazan	0.0%	100.0%	
	Madinah	30.8%	69.2%	
	Makkah	7.8%	92.2%	
	Qassim	0.0%	100.0%	
	Riyadh	10.7%	89.3%	
	Tabuk	0.0%	100.0%	
	Taif	11.1%	88.9%	
Educational Level	Postgraduate studies	10.3%	89.7%	0.960
	University degree	8.8%	91.2%	
	Secondary education	10.4%	89.6%	
	Diploma	0.0%	100.0%	
	Intermediate education	9.5%	90.5%	
	Primary education	0.0%	100.0%	
	Read and write	0.0%	100.0%	
Did you suffer from skin diseases before you contracted COVID-19?	Yes	37.9%	62.1%	<0.001
	No	7.1%	92.9%	
Do you use hydroxychloroquine?	Yes	38.5%	91.80%	<0.001
	No	8.2%	72.70%	
Do you use azithromycin?	Yes	27.3%	91.40%	0.033
	No	8.6%	66.70%	
Do you use Lopinavir / Ritonavir?	Yes	33.3%	91.10%	0.141
	No	8.9%	50.00%	
Do you use Corticosteroids?	Yes	50.0%	93.00%	<0.001
	No	7.0%	75.00%	
Do you use tocilizumab?	Yes	25.0%	91.10%	0.264
	No	8.9%	33.30%	
Do you use Convalescent Plasma?	Yes	66.7%	91.30%	<0.001
	No	8.7%	55.90%	
Do you suffer from an allergy to a specific food or drug?	Yes	44.1%	93.70%	<0.001
	No	6.3%	100.00%	
Do you have an autoimmune disease?	Yes	0.0%	90.80%	0.478
	No	9.2%	91.80%	

**P-value at a level of significance <0.05.*

Discussion

Throughout the past decades, there was growing evidence about the relationship between respiratory tract infections and dermatological disorders. In spite of the continuously increasing reporting pattern of COVID-19-related skin manifestations, the exact incidence rate and the most common skin symptoms have yet to be defined. Identifying the occurrence rate and the most common patterns of skin symptoms accompanying COVID-19 infection can significantly enhance the early detection, especially in the absence of more traditional symptoms, and, accordingly, the efficient management of the disease in addition to controlling its spread among the population [19].

This cross-sectional observational study included a total of 464 Saudi residents who were previously infected with COVID-19 to investigate the prevalence of skin symptoms during COVID-19 infection. Our results showed that 9.1% of the study population experienced skin symptoms during their COVID-19 infection.

The most commonly identified skin symptoms in our population were morbilliform (3.4%), maculopapular (1.3%), urticaria (0.9%), and livedo reticularis (0.2%). This is in accordance with the findings by Freeman et al., where morbilliform rash was the most common skin manifestation of COVID-19, accounting for 22.0% of all skin manifestations [20]. In addition to morbilliform rash, other skin symptoms reported in our study were consistent with those symptoms proposed by Genovese et al. to be a guide for dermatologists and other healthcare providers during the examination of suspected COVID-19 patients. Genovese et al. proposed a classification of six clinical patterns of COVID-19-related skin manifestations, namely, urticarial rash, confluent erythematous/ maculopapular/ morbilliform rash, papulovesicular exanthem, chilblain-like acral pattern, livedo reticularis/ racemosa-like pattern, and purpuric "vasculitic" pattern [21].

Although the association between COVID-19 and dermatological manifestations is still unclear, it cannot be excluded as the observed skin findings may represent cutaneous reactions to the numerous treatments used for COVID-19. A variety of repurposed drugs as well as investigational drugs including remdesivir, lopinavir, hydroxychloroquine, ritonavir, chloroquine, interferon-beta, and others have been used for COVID-19 treatment. All of these drugs have potential dermatological side effects [22]. We investigated the prevalence of skin symptoms among the subgroups of patients receiving certain medications. Our results showed that the use of hydroxychloroquine, azithromycin, corticosteroids, and convalescent plasma was associated with significantly higher rates of skin symptoms, while lopinavir/ ritonavir and tocilizumab showed no significant effect on the occurrence of skin symptoms.

Corticosteroids have also been reported to cause an array of side effects in the form of skin pathologies that can be divided into local side effects (the most common include perioral dermatitis, atrophy, striae, acne, rosacea, and purpura. Less frequent reactions include pigment alteration, delayed wound healing, hypertrichosis, and exacerbation of skin infections) and systemic side effects [23]. Posttransfusion purpura (skin hemorrhages/lesions) has been described to be a side effect of convalescent plasma [24]. This explains our findings that highlighted that patients receiving hydroxychloroquine, corticosteroids, and convalescent plasma developed skin disease while contracting COVID-19 (P values 0.004, 0.000, and 0.023, respectively).

In addition to medications, it has to be considered that dermatological symptoms during the COVID-19 pandemic can be caused by other factors related to strict hygiene measures. A population-based study conducted to determine the prevalence of hand dermatitis in Saudi Arabia during the ongoing COVID-19 pandemic has shown that skin changes were common among the general population as well as healthcare workers due to excessive handwashing, use of alcohol-based sanitizers as well as excessive use of face masks and PPE [25].

The main limitations of our study are that, like all survey studies, the present study's findings depend mainly on the honesty as well as the memory of the responders, which may be affected by the recall bias. In addition, the whole population of our study can read and write and can use technology which may not be representative of the total population. Another limitation was the sampling method. Due to the electronic nature of the data collection process, cluster sampling was not applicable, which may affect the generalizability of the results to the whole Saudi population.

More studies that actively capture and document the occurrence of cutaneous manifestations in patients with COVID-19 are needed to help gain more information and inform the evidence-based practice of COVID-19 diagnosis and management. In addition, these studies will help identify the mechanisms, pattern, and onset of such findings.

Conclusion

Although our study presented significant factors that could be the causative of developing skin disease while contracting COVID-19, more research is needed to establish a solid correlation between COVID-19 and skin symptoms.

Ethics approval

Institutional research ethics board approval was acquired before conducting any study-related procedures. A statement was included at the beginning of the questionnaire clarifying that the participation in this study is voluntary and that collected data will be anonymous and will only be used for this study.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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