
*Ministry of Higher Education*

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# Skin Manifestations Associated with COVID-19

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**Abstract:**

Coronavirus disease-19 (COVID-19) is an ongoing worldwide pandemic because of the “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2), which was firstly isolated in Wuhan (China) in December 2019. Common symptoms and signs include fever, cough, fatigue, dyspnea and Hypogeusia/hyposmia. Among extra-pulmonary signs related to COVID-19, dermatological manifestations have been increasingly reported in the last few months. The polymorphic nature of COVID-19 related cutaneous manifestations led our group to propose a classification, which distinguishes the following six important medical clinical patterns: (1)urticarial rash, (2)confluent erythematous /maculopapular /morbilliform rash, (3)papulovesicular exanthem, (4)chilblain- like acral pattern, (5)livedo reticularis /racemosa-like pattern, (6)purpuric “vasculitic” pattern.

**Objective:**

Since the onset of the 2019-nCoV disease (COVID-19), many skin manifestations have been reported in COVID-19 patients. This article aims to provide a systematic review of various skin manifestations among patients with COVID-19 .

**Keywords:** Coronavirus , SARS-CoV-2 , COVID-19 , skin manifestations.

## Introduction:

The first reviews of human beings infected with 2019 novel coronavirus (2019-nCoV) have been posted in December 2019 in Wuhan, China. Afterwards, the pandemic spread rapidly all over the world [1]. The symptoms of 2019-nCoV disease (COVID-19) differ from person to person, and it covers a wide range of clinical manifestations. However, most of the patients may presented mild or no symptoms [2]. Older people and those who suffer from underlying clinical situations such as hypertension, heart disease, or diabetes appear to be at higher risk for developing more serious complications of COVID-19 [3]. According to the studies, the most common symptoms of COVID-19 are fever, tiredness, and dry cough. Also, some patients may experience myalgia, runny or stuffy nose, sore throat, gastrointestinal symptoms, and lack of smell and taste [4]. In addition to these symptoms and according to the outcomes of studies on COVID- 19 patients, different types of skin manifestations have been noticed in a number of patients. The skin involvement in patients with COVID-19 was not seen at the early stages of this pandemic, however it has obtained much more attention recently. The most important skin manifestations in human being with COVID-19 are red spots on the hands, blisters at the trunk, and itchy hives [5]. In some COVID-19 patients, red patches of itchy skin, associated with skin inflammation, had been

determined as well. These lesions affect the hands and feet and may look like small, swollen, itchy blisters [6]. Despite the observation of skin manifestations in sufferers COVID-19, researchers are still looking for answers to the question of whether or not this skin presentations are directly associated to the virus itself or are complications of the infection. In addition, in many cases, skin problems in COVID-19 patients may be due to drug side effects and the virus won't be the cause [7]. Therefore, it noticed that finding out the potential relationship between COVID-19 and skin manifestations can help in better understanding the pathogenesis of the disease and adoption of better infection control policies.

From the pathogenic viewpoint, the immune response triggered by infection with SARS-CoV-2 may result in dangerous effects, such as endothelial cell dysfunction and activation of coagulation pathways; this can provide explanation for the cardiovascular and thrombotic complications that affect a subgroup of patients. [8]

The *corona* (or crown) of this virus is formed from protruding glycoproteins that shape spikes. These structures are what enables the virus to set up itself within side the host. The infection process takes place by binding to receptors of angiotensin converting enzyme 2 (ACE2), a membrane protein expressed within side the cardiovascular system, kidneys, gastrointestinal system, and lungs. This enzyme is implicated in activation of the renin-angiotensin-aldosterone system (RAAS). ACE2, in normal conditions,

counteracts the interest of the ACE enzyme by decreasing the quantity of angiotensin II (vasoconstrictor) and increasing the vasodilatory metabolites of the RAAS. According to initial data, when SARS-CoV-2 infection occurs, ACE2 seems to be down-regulated and this process is implicated in the development of acute lung lesions. [9]

In addition, the pattern of tissue damage noticed in lung samples and some skin samples taken from patients with severe COVID-19 suggest occlusive microvascular damage mediated by complement activation of both the alternative pathway and the lectin-associated pathway. Capillary damage has been determined with extensive deposition of the C5b-9 membrane attack complex, C4d, and mannosebinding lectin-associated serine protease 2 (MASP2) in the lungs. There have additionally been reports of a pattern of microvascular thrombotic disease mediated by complement in the skin of patients similar to that seen in livedo racemosa lesions and retiform purpura, with C5b-9 and C4d deposition. Activation of those mechanisms and interference in ACE2 function in target tissues because of viral action leads to an increase in angiotensin II, associated with greater inflammation and oxidative stress. The release of these reactive oxygen species and interference in antioxidant activity may also increase complement activation. [10]

In this regard, there are six essential clinical patterns of COVID-19 associated cutaneous manifestations:

1. urticarial rash
2. confluent erythematous / maculopapular / morbilliform rash
3. papulovesicular exanthem
4. chilblainlike acral pattern
5. livedo reticularis / racemosa-like pattern
6. purpuric “vasculitic” pattern [11]

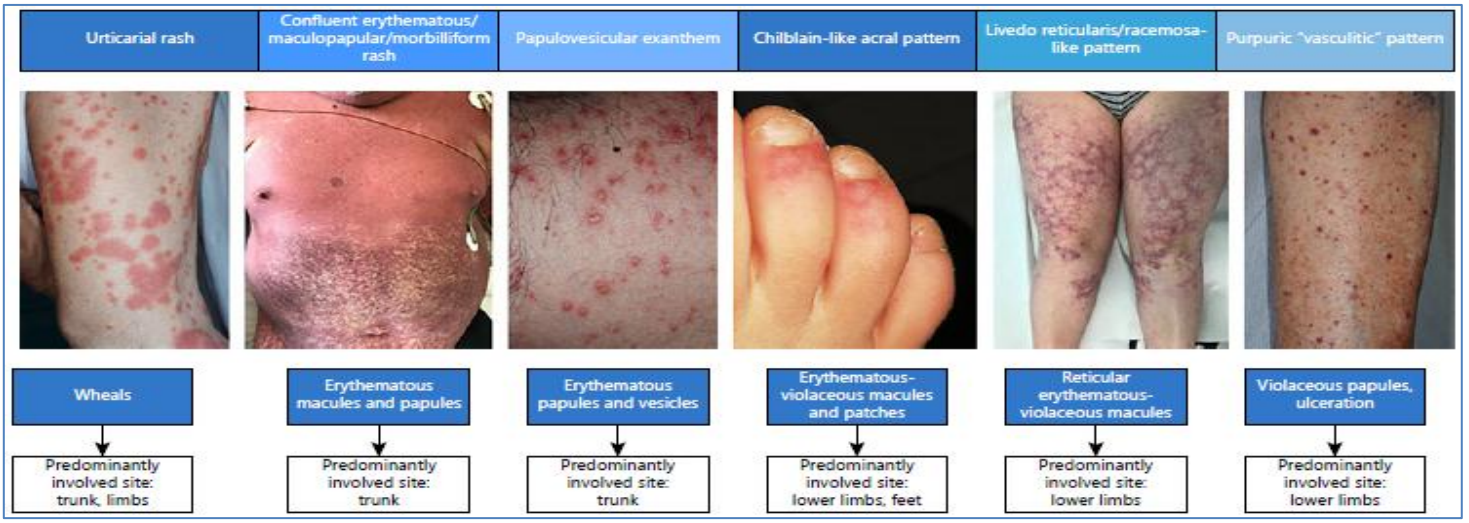


**Figure (1):** Clinical features of COVID-19-associated cutaneous manifestations.

**Table (1):** Summary of clinical features, histopathological findings, severity of COVID-19 systemic symptoms and therapeutic options of COVID-19-related skin manifestations. [12]

| | Urticarial rash | Confluent erythematous/ Maculopapular/morbilliform rash | Papulovesicular exanthem | Chilblain-like acral pattern | Livedo reticularis/ racemosa-like pattern | Purpuric "vasculitic" pattern |
|---|---|---|---|---|---|---|
| **Clinical features** | Itching urticarial rash predominantly involving the trunk and limbs; angioedema may also rarely occur | Generalized, symmetrical lesions starting from the trunk with centrifugal progression; purpuric lesions may coexist from the onset or develop during the course of the skin eruption | (i) Widespread polymorphic pattern consisting of small papules, vesicles and pustules of different sizes; (ii) localized pattern consisting of papulovesicular lesions, usually involving the mid chest/upper abdominal region or the back | Erythematous-violaceous patches or plaques predominantly involving the feet or, to a lesser extent, hands. Pain/burning sensation as well as pruritus were commonly reported symptoms | Livedo reticularis-like lesions: mild, transient, symmetrical, lace-like, dusky patches forming complete rings surrounding a pale center. Livedo racemosa-like lesions: large, irregular and asymmetrical violaceous annular lesions frequently described in patients with severe coagulopathy | Purpuric lesions may be generalized, arranged in an acral distribution or localized in the intertriginous regions. Purpuric elements may evolve into hemorrhagic blisters, possibly leading to necrotic-ulcerative lesions |
| **COVID-19 Severity** | Intermediate severity | Intermediate severity | Intermediate Severity | Asymptomatic status | Livedo reticularislike lesions: intermediate severity; livedo racemosa-like lesions: high severity | High severity |
| **Histopathological Findings** | Vacuolar interface dermatitis associated with superficial perivascular lymphocytic infiltrate | Superficial perivascular lymphocytic and/or neutrophilic infiltrate | Prominent acantholysis and dyskeratosis associated with unilocular intraepidermal vesicles in a suprabasal location | Perivascular and periadnexal dermal lymphocytic infiltrates | Pauci-inflammatory microthrombotic vasculopathy | Leukocytoclastic vasculitis, severe perivascular neutrophilic and lymphocytic infiltrate, presence of fibrin and endothelial swelling |
| **Therapeutic Options** | Low-dose systemic corticosteroids combined with nonsedating antihistamines | Topical corticosteroids for mild cases; systemic corticosteroids for severe cases | Wait and see | Wait and see | Wait and see | Topical corticosteroids for mild cases; systemic corticosteroids for severe cases |

Other ordinary uncommon COVID-19 associated cutaneous manifestations include, among others, the erythema multiforme-like eruption, pityriasis rosea-like rash , multi-system inflammatory syndrome in children, anagen effluvium and a pseudoherpetic variant of Grover disease. However, the spectrum of possible COVID-19-associated skin manifestations is likely to be still incomplete, and it is expected that new entities related to this infection might be described. [13]

## Literature review:

Given that millions of patients have been infected with COVID-19 and no related pathognomonic dermatologic phenomenon has been identified, it is unlikely that one exists. Nevertheless, literature review of documented dermatologic manifestations sufferers with COVID-19 infection, as well as our own experience of the ongoing dynamic observations of the patients suffering from this devastating viral illness, lets in us to conclude that skin manifestations are sometimes the first manifestations of COVID-19 infection. Thus, even as the data on dermatologic involvement in COVID-19 infection continue to accumulate, it is important to try and categorize the already documented findings.

Because of the increasing emergence of skin manifestations of COVID-19 worldwide, the study research **(Skin manifestations of**

**COVID-19: A worldwide review)** that published in 2021, which investigated the published reports of these lesions.

The study conducted a literature search for original and review articles published from November 11, 2019 to September 30, 2020.

The results of this study: Identified 5 skin lesions common in patients with COVID-19: pseudo-chilblains, rashes containing macules and papules, and urticarial, vesicular, and vaso-occlusive lesions. These lesions manifested at various times in relation to the COVID-19 symptoms, which may indicate whether the lesions are virus-induced or are delayed immunological responses to the infection. Skin lesions were more prevalent among Europeans and United States residents than among Asians, as was pseudo-chilblain, and the morphology of the skin lesions varied among continents. Pseudo-chilblains were the most common COVID-19 skin manifestation in Europe and the United States, but there was only 1 reported case from Asian populations. Additionally, patients with vaso-occlusive lesions were more likely than those with pseudo-chilblains to be admitted to the intensive care unit and to die.

The spectrum of manifestations of symptomatic infection ranges from mild to critical. An increasing number of reports worldwide concern the cutaneous manifestations of COVID-19 that precede

common acute respiratory symptoms. The most generally described cutaneous manifestation that precedes other COVID-19 symptoms is vesicular lesions, but they are not well characterized.2 For this literature review, we tested the published reports of the cutaneous manifestations of COVID-19, and we described these manifestations in relation to clinical practice. We report the geographical variations in the morphology of rashes, the onset of the rash eruption almost about the illness progression, and the relationship of the rash to disease severity. [14]

According to another study research **(Cutaneous Manifestations of COVID-19: A Systematic Review)** that published in 2020, which reveal reporting items for systematic reviews and meta-analyses (PRISMA)-compliant review focuses on cutaneous manifestations reported in COVID-19 patients.

Literature review was conducted using the PubMed database to examine various cutaneous manifestations related to the SARS-CoV-2 infection. Published articles (n = 56) related to search criteria from the onset of the COVID-19 pandemic to June 30, 2020, were included. The primary literature articles included in this study were mainly from France, Spain, Italy, and the United Kingdom.

The results of this study: Unique to many other symptoms of COVID-19, its cutaneous manifestations have been found in people of all age groups, including children. The cutaneous manifestations of COVID-19 are varied and include maculopapular, chilblain-like, urticarial, vesicular, livedoid, and petechial lesions. In addition, rashes are common in multisystem inflammatory syndrome in children, a new and serious health condition that shares symptoms with Kawasaki disease and is likely related to COVID-19. In addition, personal protective equipment-related skin wounds are of serious concern since broken cutaneous barriers can create an opening for potential COVID-19 infections.

COVID-19's cutaneous symptoms appear in patients of all ages with differing ranges of severity. Currently, the importance of these symptoms remains relatively unknown by many health care personnel because of a shortage of literature reviews. This review consolidates available data and summarizes information of each skin manifestation, along with their incidence, susceptible age groups, site of lesions, severity, and time of onset relative to other COVID-19 clinical symptoms. An increase in awareness and identification of these cutaneous manifestations with the aid of using physicians may be vital to an earlier and more accurate

diagnosis, possibly resulting in better prognosis in COVID-19 patients. [15]

## Conclusion:

According to the researches of included studies, skin manifestations in COVID-19 patients are very diverse and maybe occur at the beginning of the disease or after treatment. Based on many results, skin manifestations including erythematous lesions, rash, and urticaria have been the most commonly reported among patients with COVID-19. Identifying those skin manifestations can be a quick way to diagnose some COVID-19 patients. As a result, the significance of this issue is to help stop the spread of COVID-19 and protect other people. In addition to the importance of the side effects of COVID-19, the importance of drug interactions during supportive therapy have to additionally be considered. Physicians can consider skin manifestations as important clinical features in the diagnosis of sufferers with COVID-19. However, further study and investigation is needed to confirm and explain an understanding of COVID-19 associated skin manifestations.

Different cutaneous manifestations in patients suffering with COVID-19 could reflect an extensive spectrum of viral interactions with the skin, though reporting bias might also additionally play a role as well.

The mere occurrence of skin manifestations in COVID-19 patients is not always an indicator for the disease severity, and it highly depends on the type of skin lesions. Chilblain-like and vascular lesions are the ends of a spectrum in which from chilblain-like to vascular lesions, the severity of the disease increases, and the patient's prognosis worsens. Those with vascular lesions have to additionally be considered as high-priority patients for further medical care.

Albeit numerous hypotheses on pathophysiological mechanisms at the basis of these skin findings are present within side the literature, none of them is substantiated by strong evidence, and this field needs to be largely elucidated. Moreover, cutaneous eruptions because of viruses other than SARS-CoV-2 or drugs prescribed for the management of this infection always need to be ruled out. Experimental pathophysiological researches and clinical data derived from large case series are still needed for shedding light onto this novel, underexplored and fascinating topic.

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