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REVIEW

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Defining the short-term and long-term skin manifestations of COVID-19: insights after more than three years of the pandemic

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Abstract

Aim: This review aimed to assess the impact of coronavirus disease 2019 (COVID-19) on skin health to establish a classification of the skin lesions that occur most frequently during the disease and whether a particular category of skin damage is more likely to occur both in the short term and in the long term. *Methods*: We conducted a literature search of the *PubMed* database. Ultimately, 109 articles were included in this review. The exact phrases/syntax and connectors used for the database search/query were as follows: "Coronavirus and skin", "COVID-19 and skin", "SARS-CoV-2 and skin", "Coronavirus cutaneous manifestations", "COVID-19 cutaneous manifestations", "SARS-CoV-2 cutaneous manifestations", "Coronavirus dermatology", "SARS-CoV-2 and dermatology", "COVID-19 and dermatology", "COVID-19 and skin eruption", "Coronavirus and skin rash", "COVID-19 and hair", "Coronavirus and hair", "Coronavirus and nails", "SARS-CoV-2 and hair", and "SARS-CoV-2 and nails". Only articles with abstracts referring strictly to cutaneous manifestations of COVID-19 were chosen. Articles without abstracts were not considered. *Results*: We established six of the most frequently reported clinical patterns associated with COVID-19 and their probability of occurring during COVID-19 disease evolution based on the current literature reports. We did not identify the particular types of skin lesions that are most prone to long-term persistence; most such cases are rare, and no conclusion can be drawn based on them. *Conclusions*: Apart from classified COVID-19-related skin disorders, this pandemic has been a challenge for dermatologists and a wide range of cutaneous side effects related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) treatments have been reported. We are aware of other polymorphic clinical presentations, with novel data being reported periodically, but the pathophysiological mechanisms and evolution are largely unknown.

Keywords: coronavirus, COVID-19, SARS-CoV-2, skin lesions, long term, cutaneous manifestations.

Introduction

Coronavirus disease 2019 (COVID-19) is a multisystem disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first identified in Wuhan, China, in December 2019 [1–3]. COVID-19 has spread staggeringly, becoming a serious threat to public health. Since March 11th, 2020, the disease has been an ongoing global pandemic. SARS-CoV-2 infections have a wide spectrum of clinical presentations, ranging from no symptoms to acute respiratory distress syndrome (ARDS), multiple organ failure, and death [1–4].

SARS-CoV-2 is mainly transmitted through virus-containing respiratory droplets or by contaminated objects [5], although there is evidence of fecal–oral transmission in children [6]. The incubation period ranges from two to 14 days, with an average of five days [7]. The virus enters the cells by binding to angiotensin-converting enzyme 2 (ACE2). This binding hypothesis may provide a first clue in identifying the pathogenesis of COVID-19's skin manifestations, which might be caused by the virus's interactions with the skin, through the ACE2 receptor of the basal layer of the epidermis, or complement activation with microvascular injuries, causing a hyperactive immune response [2].

Since the beginning of the pandemic, the cutaneous afflictions of COVID-19 have been divided into six main clinical patterns: vesicular eruptions, petechial/purpuric rashes, acral lesions, livedoid lesions, urticarial rashes, and maculopapular–erythematous rashes [2].

Recent analyses describe a wide array of dermatological findings, with more than 30 different skin eruptions related to COVID-19 disease; moreover, new cutaneous patterns are expected to emerge because of novel virus variants and long COVID syndrome [8]. To date, maculopapular rashes, urticarial lesions, and chilblains are the most frequently reported skin manifestations of COVID-19.

Various cutaneous clinical patterns related to SARS-CoV-2 viral infections occur at different times throughout the disease course and may predict severity and prognosis. Moreover, some cutaneous patterns have been documented as prodromal signs of systemic symptoms or represent the only clinical features of COVID-19 infections, serving as early indicators of infection or revealing asymptomatic carriers of the virus [9–11]. The persistence of skin symptoms associated with COVID-19 months after the disease will be further referred to in this paper as "long COVID".

Aim

This study aimed to analyze the scientific literature on major dermatological manifestations associated with COVID-19 up to September 2022. We searched the *MEDLINE* (*PubMed*) electronic database for case reports and original and review articles written in English from November 2019 to September 2022.

Materials and Methods

This research used the following keywords: 'SARS-CoV-2', 'Coronavirus', and 'COVID-19' in combination with 'Cutaneous manifestations', 'Dermatologic', 'Exanthema', 'Maculopapular', 'Urticaria', 'Chilblain', 'Vascular lesions', 'Vesicular eruptions', 'Treatment', 'Hair', and 'Nails'. The bibliography lists scientific papers of interest. Thus, the number of articles was limited by eliminating those that lacked direct relevance to dermatological lesions. For each article, we extracted the following data: type of elementary lesions, number of cases reported, the clinical course, localization, early or late occurrence concerning other COVID-19 symptoms, age, associated symptoms, and the clinical outcome for the patient. This study is a literature review that was performed without a pre-existing registered protocol.

Exact phrases/syntax and connectors used for the database search/query were as follows: "Coronavirus and skin", "COVID-19 and skin", "SARS-CoV-2 and skin", "Coronavirus cutaneous manifestations", "COVID-19 cutaneous manifestations", "SARS-CoV-2 cutaneous manifestations", "Coronavirus dermatology", "SARS-CoV-2 and dermatology", "COVID-19 and dermatology", "COVID-19 and skin eruption", "Coronavirus and skin rash", "SARS-CoV-2 and skin eruption rash", "COVID-19 and hair", "Coronavirus and hair", "Coronavirus and nails", "COVID-19 and hair", "SARS-CoV-2 and hair", and "SARS-CoV-2 and nails".

First, articles were screened based on their titles, and duplicate records were removed. Article eligibility was evaluated based on titles and abstracts, and articles that were considered irrelevant were excluded. Articles without abstracts were not considered. Finally, full-text articles were screened for eligibility based on whether the articles referred strictly to cutaneous manifestations during COVID-19 infections. Each article was studied independently afterward for data extraction.

The initial search on the electronic database yielded 403 articles. After removing articles unrelated to skin manifestations during COVID-19 infections, 205 articles remained, which were then screened for relevance based on titles and abstracts. Out of these, 140 were screened for eligibility. Ultimately, 109 articles were included in this review after excluding articles in which skin rashes occurring during COVID-19 infections seemed to be coincidences given the very low number of reported cases (Figure 1).

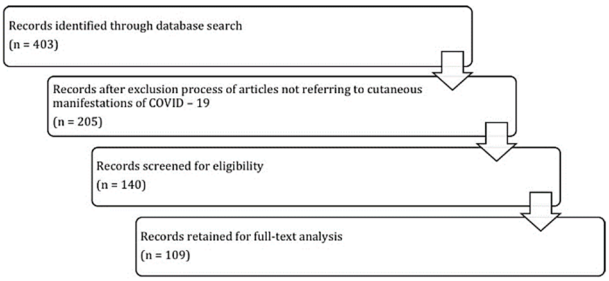

Figure 1 – ***Flowchart depicting the selection process for the inclusion of manuscripts in the article.***

Initially, the cutaneous features associated with SARS-CoV-2 were not reported [12] but evidence of dermatological manifestations has emerged since the pandemic began [13]. In Italy, Recalcati was the first to report skin afflictions related to SARS-CoV-2 infections, mentioning that around 20% of the inpatients developed urticaria, erythematous rashes, and chicken-pox-like vesicles [14]. Subsequent reports have shown a wide variety of skin issues related to COVID-19, and their cutaneous manifestations have been divided up according to their morphology: vesicular rashes, petechial/purpuric rashes, acral lesions, livedoid lesions, urticarial rashes, and maculopapular rashes [15–18].

In their review of 375 patients with suspected or confirmed SARS-CoV-2 infections, Galván Casas *et al.* [19] tried to correlate the pattern of the skin eruptions with disease severity and noted that livedoid lesions were associated with increased severity, whereas pseudo-chilblains were a late sign in mild cases or those without systemic symptoms. Perna *et al.* [4] noted the high prevalence of chilblain eruptions compared with all other skin manifestations, with almost half (46%) of the patients having this type of lesion.

Other authors have provided complex reports and searched for distinct associations between comorbidities, such as obesity, diabetes (7.4%), and hypertension (5.5%) and dermatological lesions related to COVID-19 [9].

Genovese *et al.* [20] reviewed clinical and histopathological features, pathophysiological mechanisms, and the management of all six skin manifestation patterns associated with the virus. González González *et al.* [21] proposed a pathophysiological classification of these cutaneous afflictions based on a triggering pathogenic mechanism, dividing the manifestations into those related to the direct viral cytopathic effect on keratinocytes (including maculopapular, urticaria, and varicella-like eruptions) and those manifestations caused by the uncontrolled overexpression of cytokines (stage of cytokine storm) issued by white blood cells, T-lymphocytes, and macrophages. In turn, the latter was subdivided into (*a*) cutaneous lesions secondary to macrophage activation, including acral ischemia and petechiae/purpuric rashes; (*b*) livedoid lesions caused by

hypercoagulability, which are associated with high patient morbidity and mortality; and (*c*) cutaneous features caused by the overproduction of type I interferon (IFN-I), including chilblain-like lesions.

In their review article, Fernández-Lázaro & Garrosa [2] summarized all the dermatological manifestations associated with SARS-CoV-2 infections into three groups: (*a*) vesicular eruptions; (*b*) rashes that do not blanch with pressure, including petechiae/purpura rashes, acral lesions, and livedoid lesions; and (*c*) rashes that blanch and disappear with pressure, such as maculopapular eruptions and urticarial rashes.

Skin damage in the initial stages of COVID-19 infections

Vesicular exanthema (papular–vesicular rashes)

First described by Recalcati [14], this eruption consists of micropapules smaller than 1 cm in size, commonly filled with transparent liquid and located under the epidermis. In a recent worldwide review conducted by Tan *et al.* [12], vesicular lesions were found to usually occur at the onset of COVID-19 symptoms, typically in middle-aged patients and associated with mild- or medium-severity disease. The prevalence of vesicular exanthema varies. Fernandez-Nieto *et al.* [22] found that the prevalence of vesicular lesions in COVID-19 is 15%, identifying a diffuse pattern in 75% of cases (more common: polymorphic widespread eruptions consisting of small vesicles and pustules) and a localized pattern in 25% of patients (less prevalent: monomorphic lesions over the anterior and posterior trunk), while Singh *et al.* noted a prevalence of vesicular rashes that ranges from 3.77% to 15% [17]. Monomorphic, herpetiform, and varicella-zoster-like vesicles associated with COVID-19 have also been described in the literature [12].

On average, the onset of the vesicular exanthema occurs three days after general symptoms, as per the evidence reported by Jindal & Chauhan [23]; the eruption appears in the early stages of COVID-19 and lasts for about 10 days. On the other hand, Sameni *et al.* [11] discovered that lesions appeared later than other SARS-CoV-2 infection symptoms, with a latency time of 14 days. The pathophysiological basis of vesicular lesions resembles both the cytopathic effect of the virus on the endothelium of the dermal blood vessels and cytokine storms [24]. According to Tan *et al.*, the survival rate is 96.1% among patients with COVID-19-associated papulovesicular lesions [12], while Mawhirt *et al.* reported a mortality rate of 13.6% for these patients [25].

The differential diagnosis is of great importance and should consider infections caused by members of the *Herpesviridae* family (superinfections or the recurrence of herpes simplex and herpes zoster infections may complicate the course of COVID-19) [25], *erythema multiforme*, and autoimmune bullous diseases. Clinical features of vesicular COVID-19 exanthema, such as widespread distribution – mainly with trunk involvement and mild/absent pruritus – differentiate it from true varicella. No standardized therapy is available for COVID-19-related vesicular exanthema. Given that the lesions resolve spontaneously within about one week, expectant management is indicated [25–27]. There are also reports of varicella-like exanthema as a specific COVID-19-associated skin manifestation [28]. The results are summarized in Table 1. A graphical comparison of vesicular lesion prevalence between studies is shown in Figure 2.

Table 1 – ***Vesicular exanthema (papular-vesicular rashes)***

Author(s)	Year	Number of patients that developed non-specific skin lesions/total number of patients included in the study	Prevalence of vesicular lesions	Severity of COVID-19
Tan *et al.* [12]	2021	Approximately 133/1211 (10.98%) patients	11% of cases in a multicenter study	Not specified
Recalcati [14]	2020	18/88 (20.45%) patients	5% of cases	Not specified
Singh *et al.* [17]	2021	835/1688 (49.47%) patients	3.77% to 15% of cases in a multicenter study	Not specified
Fernandez-Nieto *et al.* [22]	2020	24/24 (100%) patients	75% (18) of cases developed the disseminated pattern, and 25% developed the localized pattern in a prospective observational study	Moderate

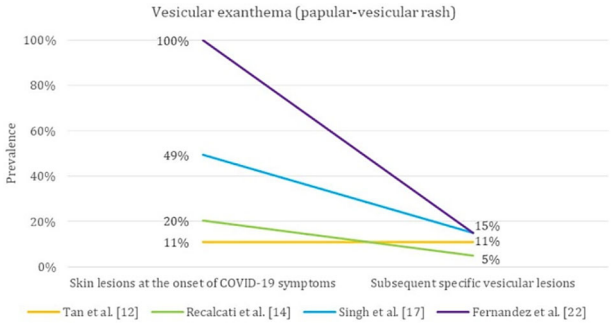

Figure 2 – ***Graphical comparison of the incidence of vesicular lesions in various studies.***

Erythematous/maculopapular/morbilliform rashes

Maculopapular rashes represent the most common pattern of skin damage [29–32] in up to 70% of cases [33]. Galván Casas *et al.* [19] found a 47% prevalence of maculopapular lesions, similar to the results of Freeman *et al.* (44%) [34]. In the study by Català *et al.* [35], seven maculopapular patterns were described: morbilliform, purpuric, *erythema multiforme*-like, pityriasis rosea, *erythema elevatum diutinum*-like, perifollicular, and other maculopapular eruptions, with the morbilliform pattern being the most frequent (45.5% of patients included). More commonly, this group of lesions is subdivided into morbilliform rashes, macular erythema, and papulosquamous lesions. Jindal & Chauhan [23] noted the distribution of lesions mainly on the trunk, similar to the Català *et al.* study where lesions began on the trunk and extended centrifugally, becoming generalized and symmetrical. Itching was reported in most patients. Mahé *et al.* [36] noted accentuated exanthema on the antecubital fossa and axillary folds. A graphical comparison of erythematous/maculopapular/morbilliform rash prevalence between studies is shown in Figure 3.

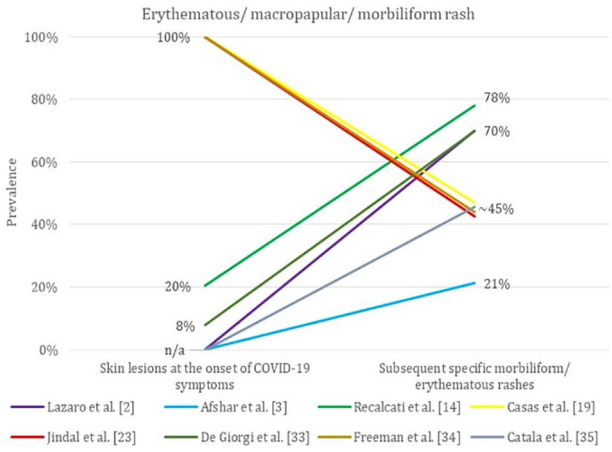

Figure 3 – ***Graphical comparison of the incidence of erythematous/maculopapular/morbilliform rashes in various studies. n/a: Not available.***

Most of the erythematous maculopapular rashes occurred in elderly patients after systemic COVID-19 symptoms appeared, with an average time of nine days. Exanthema is associated with severe disease in older patients, which varies according to different patterns. In patients with morbilliform lesions, hospitalization because of pneumonia is very frequent (80%) [19] and occurs in 76.5% of cases of those suffering from *erythema multiforme*-like rashes [35]. Two pathogenic mechanisms have been reported: the direct cytopathic effect of the virus on keratinocytes and cytokine overproduction because of immune responses to SARS-CoV-2. Differential diagnoses include other viral exanthemas and cutaneous adverse reactions to drugs.

Therapeutic options are consistent with the disease severity, with topical corticosteroids being recommended in most cases, but systemic therapy is reserved for generalized and severe exanthema [37]. The results are summarized in Table 2.

Table 2 – ***Erythematous/maculopapular/morbilliform rashes***

Author(s)	Year	Number of patients that developed non-specific skin lesions/total number of patients included in the study	Prevalence of morbilliform/erythematous rashes	Severity of COVID-19
Fernández-Lázaro & Garrosa [2]	2021	Not specified	40–70% of cases, including erythematous eruptions (38.5%), maculopapular eruptions (18.3%), macular erythema (6.8%), papulosquamous eruptions (2%) in a narrative literature review	Not specified
Mohseni Afshar *et al.* [3]	2021	Not specified	21.3% of reported cases from an evidence-based review	Not specified
Recalcati [14]	2020	18/88 (20.45%) patients	78% of cases	Not specified
Galván Casas *et al.* [19]	2020	375/375 (100%) patients	47% of reported cases in a nationwide case study	Not specified
Jindal & Chauhan [23]	2020	458/458 (100%) patients	42.5% in a registry-based study	Not specified
De Giorgi *et al.* [33]	2020	53/678 (7.82%) patients	Up to 70% (macular, papular, maculopapular, and *erythema multiforme*-like eruptions) of reported cases in a multicenter prospective study	Not specified
Freeman *et al.* [34]	2020	716/716 (100%) patients	44% of cases (morbilliform, 22%; macular, 13%; papulosquamous, 9.9%) in a large registry-based study	Moderate severity
Català *et al.* [35]	2020	Not specified/176 patients	Subanalysis of maculopapular cases found in a cross-sectional study describing seven major patterns: morbilliform (45.5%), other maculopapular (20.0%), purpuric (14.2%), *erythema multiforme*-like (9.7%), pityriasis rosea-like (5.7%), *erythema elevatum diutinum*-like (2.3%), and perifollicular (2.3%)	Not specified

Vascular cutaneous manifestations: petechiae/purpura rashes

Purpuric rashes have a high prevalence in hospitalized patients (25.7%) [37], the cutaneous feature associated with the highest rate of COVID-19-disease-related mortality. Purpuric manifestations may evolve into hemorrhagic blisters [38], and in most severe clinical presentations, acute extensive gangrene with disseminated intravascular coagulation may occur. In their case study, Bouaziz *et al.* [39] reported two patients with purpuric lesions evolving into necrotic lesions, and Del Giudice *et al.* documented catastrophic acute bilateral lower-limb necrosis associated with COVID-19 [40].

Freeman *et al.* reported that 82% of patients had purpura and ARDS [16], and Rekhtman *et al.* [37] noted that 66.7% of patients with vasculitic lesions required mechanical ventilation. Clinical features include the occurrence of red spots that do not blanch when applying pressure [41], with a diameter of less than 4 mm (petechiae) or between 4 mm to 10 mm (purpura). This is the result of severe microvascular injuries (severe damage of endothelial cells) caused by the overproduction of cytokines or mediated by complement activation (or an exaggerated inflammatory reaction) [42]. Purpuric and petechial lesions can occur in elderly patients with severe disease at any time during the COVID-19 disease course [27, 42]. Vasculitic macules may be distributed on acral regions [43], intertriginous areas [44], or in a generalized manner [45], and they are associated with a burning sensation.

Purpuric lesions may cause differential diagnosis difficulties. The first COVID-19-related skin rash with petechiae was reported by Joob & Wiwanitkit [46] and was initially misdiagnosed as a Dengue virus eruption. Jimenez-Cauhe *et al.* [47] reported a millimetric purpuric rash located on flexural regions that was related to Hydroxychloroquine and Lopinavir/Ritonavir therapy. Viral hemorrhagic fever should also be considered as a differential diagnosis. Mild cases can be treated with topical corticosteroids, while generalized rashes or more severe cases require systemic corticosteroids. The results are summarized in Table 3. A graphical comparison of petechiae/purpura rash prevalence between studies is shown in Figure 4.

Table 3 – ***Petechiae/purpura rashes***

Author(s)	Year	Number of patients that developed non-specific skin lesions/total number of patients included in the study	Prevalence of petechiae/purpura rashes	Severity of COVID-19
Fernández-Lázaro & Garrosa [2]	2021	Not specified	4% of cases with purpura did not require hospitalization; 96% needed hospitalization	Not specified
Freeman *et al.* [16]	2020	Not specified	100% of patients with purpura required hospitalization	Not specified
Freeman *et al.* [34]	2020	716/716 (100%) patients	3–8% of cases in a large registry-based study	Not specified
Rekhtman *et al.* [37]	2021	35/296 (11.82%) patients	25.7% of cases in hospitalized patients in a cohort study	Not specified
Bouaziz *et al.* [39]	2020	14/14 (100%) patients	14% in a cohort study	Severe

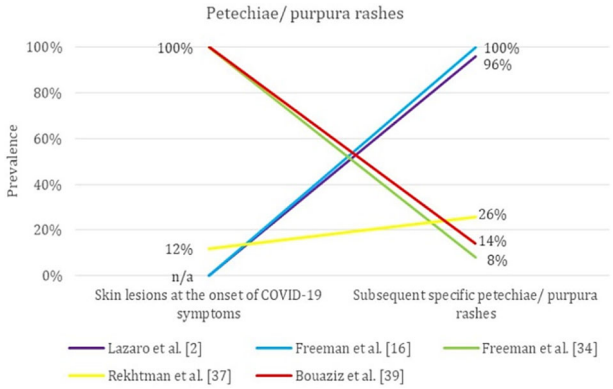

Figure 4 – ***Graphical comparison of the incidence of petechiae/purpura rashes in various studies. n/a: Not available.***

Vascular cutaneous manifestations: *livedo reticularis*/*livedo racemosa*-like patterns

The livedoid/necrosis pattern appears as cross-linked bluish discoloration lesions caused by desaturation secondary to slow blood flow and has been described as a typical *livedo reticularis* or *livedo racemosa* [48]. *Livedo racemosa*-like lesions are more associated with severe coagulopathies [49–54] and have been documented in 0.6% of cases [27], consisting of large, irregular, and discontinuous circles widespread over the body. With a total prevalence of 6% [19], livedoid eruptions are common in the elderly with more severe COVID-19 disease courses, equally affecting both men and women [55]. As hypercoagulability with microthrombi formation and complex immunological alterations [55] are described as underlying morpho-pathogenic mechanisms, livedoid manifestations, along with purpuric eruptions, have the highest mortality rates, approximately 10% [2]. Genovese *et al.* distinguish the purpuric pattern as a true vasculitic phenomenon from the *livedo reticularis*/*livedo racemosa* pattern, which involves the formation of microthrombi that generate small blood vessel occlusions [20]. According to some authors, *livedo reticularis* lesions require anticoagulant therapy, while others advise an expectant strategy [19, 25, 27, 43]. The results are summarized in Table 4. A graphical comparison of *livedo reticularis*/*livedo racemosa*-like eruption prevalence between studies is shown in Figure 5.

Table 4 – ***Livedo reticularis/livedo racemosa-like patterns***

Author(s)	Year	Number of patients that developed non-specific skin lesions/total number of patients included in the study	Prevalence of *livedo reticularis*/*livedo racemosa*-like eruptions	Severity of COVID-19
Galván Casas *et al.* [19]	2020	375/375 (100%) patients	6% of reported cases with *livedo reticularis* in a nationwide case study	Severe
Conforti *et al.* [27]	2020	655/655 (100%) patients	0.6% of reported cases with *livedo racemosa* and 3.5% of cases with *livedo reticularis* in a systematic review	Not specified

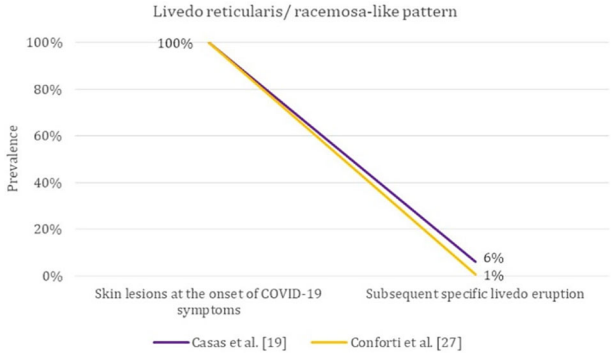

Figure 5 – ***Graphical comparison of the incidence of livedo reticularis/livedo racemosa-like eruptions in various studies. n/a: Not available.***

Vascular cutaneous manifestations: acral lesions

Acral eruptions, referred to as COVID fingers, were the second most frequent COVID-19-related cutaneous feature, with variable prevalence: 15% [23], 19% [19], and 62% [34]. The acral pattern resembles chilblain-like lesions, perniosiform eruptions, or acroischemia [2, 21, 22], but their occurrence is not related to cold exposure. However, Bouaziz *et al.* noted acral eruptions in two patients, one also presenting with Raynaud's syndrome [39]. Chilblain-like acral lesions are described as asymptomatic erythematous–edematous patches sometimes accompanied by a burning sensation and/or pruritus [56–58], with possible blister evolution [59]. They typically affect young patients with less severe disease or without systemic symptoms, occurring in both men and women equally [9]. An interesting finding is the diminished proportion of SARS-CoV-2-positive patients with acral lesions; this phenomenon is explained by a low viral load or the late onset of these cutaneous lesions in the disease course [60–62]. However, the hypothesis that these lesions are potentially related to COVID-19 infections is highly contested by Hébert *et al.* in

their study of 33 patients. After histological and serological examinations, the authors highlighted the lack of association between chilblain-like lesions and SARS-CoV-2 infections. The clinical and histological findings all resembled cases of idiopathic chilblains, proving that the correlation with COVID-19 was inappropriate because of several biases [63]. Nonetheless, Colmenero *et al.* revealed opposite results, and they noted the presence of SARS-CoV-2 in seven skin biopsies harvested from patients with chilblain lesions [64]. The pathogenesis of these lesions includes direct endothelial damage, coagulation disorders with thrombosis, and increased IFN-I release with consequent cytokine storms [65]. The proposed therapy is topical corticosteroids alone or combined with antibiotics, with positive results [66], though Recalcati *et al.* noted that the eruptions healed spontaneously after 2–4 weeks [67]. On the other hand, acral ischemia with necrosis worsens the prognosis in patients suffering from COVID-19 disease, as it is the clinical expression of coagulation disorders, such as vascular occlusion or disseminated intravascular coagulation. This feature is associated with high mortality rates (71%) [24]. Anticoagulant therapy in these patients is mandatory [43]. The results are summarized in Table 5. A graphical comparison of acral lesion prevalence between studies is shown in Figure 6.

Table 5 – ***Acral lesions***

Author(s)	Year	Number of patients that developed non-specific skin lesions/total number of patients included in the study	Prevalence of acral lesions	Severity of COVID-19
Galván Casas *et al.* [19]	2020	375/375 (100%) patients	19% of reported cases in a nationwide case study	Mild in lesions resembling chilblains Severe in acral ischemia
Jindal & Chauhan [23]	2020	458/458 (100%) patients	15% in a registry-based study	Not specified
Freeman *et al.* [34]	2020	716/716 (100%) patients	62% of cases in a large registry-based study	Not specified
Bouaziz et at. [39]	2020	14/14 (100%) patients	14% of reported cases in a cohort study	Not specified
Colmenero *et al.* [64]	2020	Not specified	Narrative review	Not specified

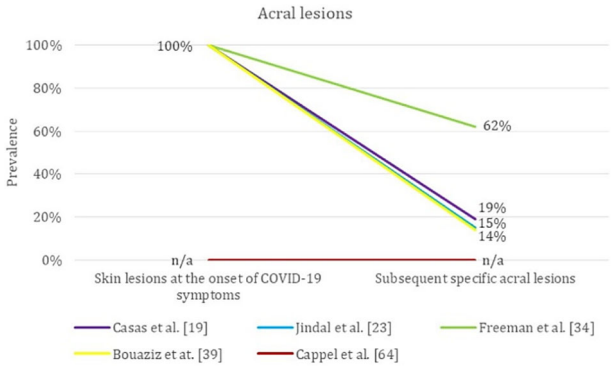

Figure 6 – ***Graphical comparison of the incidence of acral lesions in various studies. n/a: Not available.***

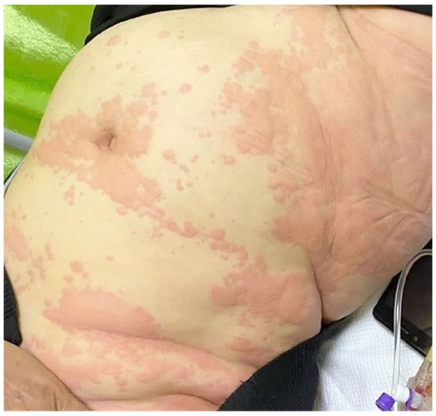

Figure 7 – ***Representative image of urticarial rash presenting as a prodromal sign of COVID-19 infection.***

Urticarial rash

The first description of patients with COVID-19-related urticarial rashes was reported by Recalcati *et al.*, accounting for 16.7% of total skin manifestations [14]. In other studies, the prevalence varies between 9% [42], 19% [19], and 7% to 40% [17], occurring more frequently in middle-aged patients [68, 69] with medium or severe SARS-CoV-2 infections. Clinically, urticarial eruptions consist of erythematous–edematous itchy patches distributed over the feet and hands. Freeman *et al.* noted that the rash spares the acral regions, mainly involving the trunk [34]. This dermatological complication appeared at the same time with systemic manifestations, as per the Galván Casas *et al.* reports [19] or was a prodromal sign and the first sign of a COVID-19 infection (Figure 7) [70–72].

Cepeda-Valdes *et al.* [73] described a familial cluster of urticarial eruptions in a Mexican family (two out of five were affected), with both affected members complaining of anosmia, ageusia, and dizziness. In all documented cases, this eruption usually takes about one week to resolve. A case report by Najafzadeh *et al.* [74] pointed out that angioedema can occur as an associated complication during urticarial eruptions, and vasculitis may evolve as a vasculopathy-related symptom [75]. Urticarial lesions are considered a non-specific COVID-19-related skin manifestation because it is unclear whether the eruption is a consequence of the virus [76] or an adverse reaction to the many drugs used to treat SARS-CoV-2 infections [77]. Like other allergic dermatoses, this condition requires low-dose systemic corticosteroids, in addition to nonsedating antihistamines. The administration of corticosteroids can also help manage cytokine storms in COVID-19 disease, decreasing the morbidity and mortality of this infection [78]. The results are summarized in Table 6. A graphical comparison of urticarial rash prevalence between studies is shown in Figure 8.

Overall, the patterns of skin damage described in these studies coincide without significant differences. Therefore, after more than three years of the pandemic and numerous scientific articles on skin manifestations related to COVID-19 infections, we can conclude that the lesions described in subsections 1–6 are the most representative of the acute phase of the infection. A graphical comparison of the incidence of these clinical patterns between various articles is shown in Figure 9.

Table 6 – ***Urticarial rash***

Author(s)	Year	Number of patients that developed non-specific skin lesions/total number of patients included in the study	Prevalence of urticarial rashes	Severity of COVID-19
Recalcati [14]	2020	18/88 (20.45%) patients	16.7% of cases	Not specified
Singh *et al.* [17]	2021	835/1688 (49.47%) patients	7–40% of cases in a multicenter study	Not specified
Galván Casas *et al.* [19]	2020	375/375 (100%) patients	19% of reported cases in a nationwide case study	Not specified
Carrascosa *et al.* [42]	2020	Not specified	9% of cases	Moderate

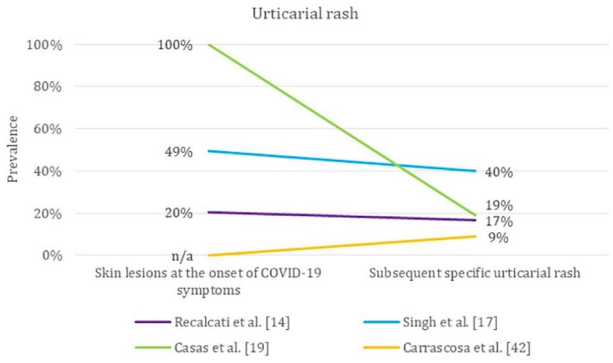

Figure 8 – ***Graphical comparison of the incidence of urticarial rashes in various studies. n/a: Not available.***

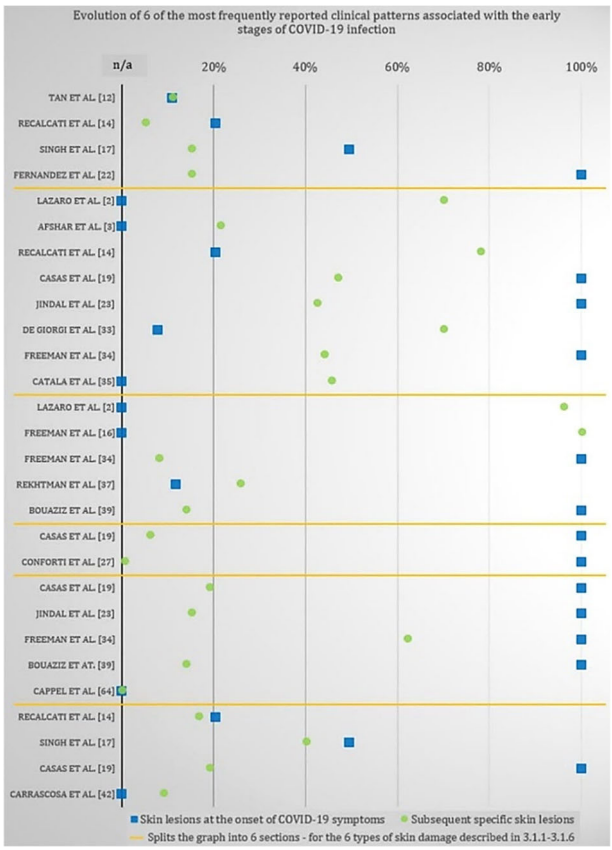

Figure 9 – ***Overall comparative results of the incidence of specific skin lesions. n/a: Not available.***

Other COVID-19-related cutaneo-mucosal dermatoses

Even if various rash patterns have been definitively associated with COVID-19, numerous polymorphic eruptions that could not be classified were identified during SARS-CoV-2 infections. Grover-like syndrome, as a transient papulovesicular eruption, was noted in a 59-year-old male in the setting of COVID-19 disease [79]. In a large registry-based study, similar clinical patterns occurred in <5% of reported cases [34].

The same authors reported that erythroderma appeared in a few cases, less than 1% of patients included in their registry [34].

Recently, an increased predisposition for developing Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) was documented in patients suffering from COVID-19, occurring either during the illness or during the recovery phase. As per their case reports, Aulakh *et al.* propose that SARS-CoV-2 infections are a possible trigger of SJS–TEN onset [80].

In their review of case reports and case series, Mashayekhi *et al.* summarized a wide spectrum of potential life-threatening dermatoses, such as angioedema, vascular lesions, toxic shock syndrome, erythroderma, hemorrhagic bulla, *erythema multiforme*, SJS and TEN, and generalized pustular figurate erythema that were virus- or drug-associated [81].

Cutaneous manifestations associated with SARS-CoV-2 variants

Coronaviruses are prone to genetic evolution while adapting to their new human hosts, developing mutations over time, and generating new variants with different characteristics. Since the beginning of the pandemic, the *World Health Organization* (WHO) has documented five SARS-CoV-2 variants of concern (VOCs): Alpha, Beta, Gamma, Delta, and Omicron [82].

Data on the impact of the new variants on the integumentary system are limited; few reports describe a higher incidence of vascular involvement caused by the Delta variant [2].

The fifth VOC, Omicron, represented the dominant SARS-CoV-2 variant in many countries and causes a less severe disease compared with the original variants, Alpha and Delta. In the United Kingdom (UK), the ZOE app – an app that offers a new way to track diseases, with users inputting symptoms and experts analyzing the data – revealed a lower frequency of skin lesions in both the Delta and Omicron variants compared with the original after analyzing the queries of 348 691 UK users [83]. Furthermore, in a UK study cohort available online, the frequency of skin eruptions related to Omicron variant infections was lower than that observed in patients infected with Delta (11.4% *versus* 17.6%) [84]. A recent publication revealed six cutaneous warning symptoms related to the Omicron variant: discolored skin because of decreased oxygen levels; hives starting with intense itchy palms or soles; heat rash or *miliaria rubra*; inflamed COVID toes; sores; chapped lips and dry skin, such as eczema-like eruptions on the neck and chest [85]. Unfortunately, reports regarding the cutaneous findings associated with the Omicron variant are lacking because of a reduction in the number of case reports.

COVID-19 disease and nails

Nails can also reflect the impact of this virus on the patient's state of health [86]. Non-specific manifestations, such as Beau lines, small grooves, and horizontal spots on the surface of the nails can occur a few weeks after the acute phase of the disease [87–89]. On the other hand, specific abnormalities, such as the COVID-19 red half-moon sign (which consists of red bands bordering the lunula) suggest microvascular involvement [90, 91], and the appearance of orange horizontal and transverse lines have been noted in patients in the acute phase of SARS-CoV-2 infection [92, 93].

Cutaneous long COVID

Multiple studies have outlined the major impact of the virus on the integumentary system during the acute phase and beyond. The attention is now turning to the persistence of skin symptoms associated with COVID-19 months after the disease, which defines the cutaneous "long COVID" phenomenon (Figure 10, A and B) [94].

Figure 10 – ***(A and B) Representative image of a female patient who developed a severe, generalized, scaly purpuric rash within four days after she was tested positive for SARS-CoV-2 infection. The above clinical aspect was 45 days after the eruption onset at the time she was admitted to a dermatology clinic.***

According to the *UK National Institute for Health and Care Excellence* (NICE) guidelines, post-COVID-19 syndrome involves the persistence of symptoms such as fatigue, difficulty in concentration, anosmia, ageusia, cutaneous manifestations, and hair loss for more than 12 weeks [94].

In their registry analysis, McMahon *et al.* synthesized the duration of dermatological manifestations in 234 patients confirmed to have SARS-CoV-2 infections, defining "long-haulers" as those patients with cutaneous manifestations that persisted for more than 60 days. As per their report, seven of 103 patients with pernio were long-haulers; this papulosquamous eruption lasted 70 days, while morbilliform and urticarial lesions had a relatively fast resolution, with a maximum duration of 28 days. Notably, one patient included in the report experienced pernio and *livedo reticularis* lesions for over five months [95]. In their cross-sectional study conducted in three German districts, Förster *et al.* reported long-term skin sequelae with a duration of more than 12 weeks in 15 out of 127 hospitalized patients and in 26 out of 588 non-hospitalized patients [96]. During their follow-up visits, Mehta *et al.* observed a subgroup of long COVID patients with persistent chilblain lesions and called for further research to better understand the complex pathogenic mechanisms of the disease. As per previous studies, most acral cutaneous reactions occur in previously healthy patients with mild infection symptoms. Interestingly, this fact reveals the hypothesis of persistent inflammation even in those who experienced less severe or even asymptomatic disease [97]. In their clinic, Tammaro *et al.* observed various rashes and ungual lesions related to SARS-CoV-2 infections that lasted for more than six months after the acute peak of the disease [98]. In their cohort study, Desai *et al.* revealed that only 3% of patients developed a persistent rash after acute infection [99]. The results are summarized in Table 7.

Table 7 – ***Long-hauler patients in various studies***

Author(s)	Year	Total number of patients that developed skin lesions in the initial stages of COVID-19 infection	Specific types of skin lesions	Long-hauler patients	Maximum duration
McMahon *et al.* [95]	2021	234	Pernio	7	60 days
			Morbilliform and urticarial lesions	Not specified	28 days
			Pernio and *livedo reticularis*	1	150 days
			Papulosquamous eruptions	1	70 days
Förster *et al.* [96]	2022	715	Not specified	41	84 days
Desai *et al.* [99]	2022	1665	Not specified	47	180 days
		120	Hair loss	24	110 days

To sum up, COVID-19 is still a challenge that is raising questions. Therefore, there is a growing need to understand the mechanisms of this prolonged inflammatory reaction in long COVID patients to apply focused interventions. An overall incidence comparison of long-hauler patients in various articles is shown in Figure 11. Regarding long-term persistence, the principal endpoint of our paper shows that no clear pattern in the acute phase that could predict the persistence of long-term lesions or the progression to a chronic skin disease was identified in our study. We have not identified a particular type of skin lesion that is more prone to long-term persistence, although numerous analyzed articles describe pernio lesions as the most plausible for long-term evolution. This is because the results of various studies are sometimes contradictory, and the skin injuries documented in some articles do not coincide with those in other studies.

New-onset and exacerbated dermatoses after SARS-CoV-2 infections

In a recently published review, Chularojanamontri *et al.* documented new-onset dermatoses and flare-ups after COVID-19 disease. From a total of 345 cases, new-onset skin diseases were noticed in 325 patients. The most frequent were hair disorders with telogen effluvium (TE), seen in

260 patients, with a female predominance (77.7%) and a mean period for the appearance of symptoms of 57.1 days, although other conditions seem to be propagated by COVID-19 infections, such as *alopecia areata* [100] (Figure 12, A and B).

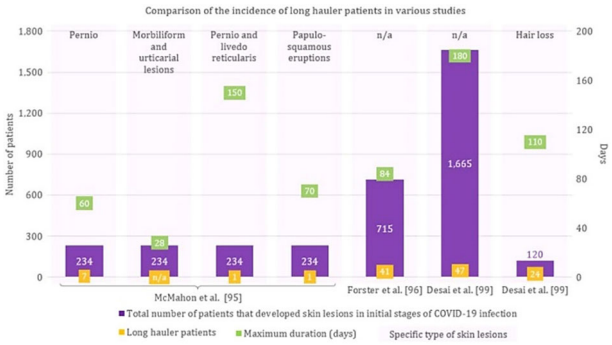

Figure 11 – ***Long-hauler patients in various studies. n/a: Not available.***

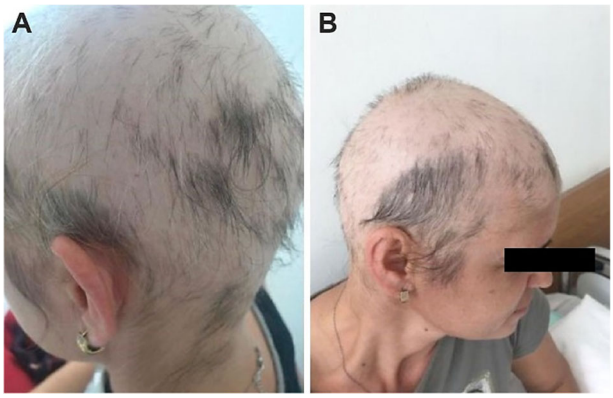

Figure 12 – ***(A and B) Representative image of severe hair loss – alopecia areata due to COVID-19 infection.***

New-onset varicella-zoster infections were seen in 11 patients, vasculitis was documented in eight patients; pityriasis rosea was documented in five patients; and dermatomyositis, Gianotti–Crosti syndrome, morphea, panniculitis, and pityriasis rubra pilar were all noticed in two patients [100].

Regarding flare-ups, the authors found psoriasis to be the most common exacerbated dermatosis resulting from COVID disease, which occurred up to 120 days after the acute phase, as per Aram *et al.*'s findings, which documented psoriasis flare-ups in nine out of 14 patients [101].

Thus, it would seem that persistent inflammatory reactions in SARS-CoV-2 infections could trigger disruptions in the immune system with bullous dermatosis in patients with a history of chronic dermatological conditions (Figure 13, A–C).

Apart from these COVID-19-related skin disorders, this pandemic has been a challenge for dermatologists, with a wide range of cutaneous side effects related to SARS-CoV-2 treatments being reported. However, one should not disregard all dermatological manifestations because of excessive hand sanitizer use or skin injuries from using personal protective equipment (contact dermatitis, abrasion, ulceration, the exacerbation of pre-existing dermatoses, etc.) [102–104]. To reduce the incidence of occupational skin damage among healthcare workers, specialists have released some basic skincare practices, such as shorter rotation shifts with masks and goggles to avoid pressure and abrasion, thus reducing the appearance of ulceration. Applying hand moisturizers to intact skin after hand washing is highly recommended for preventing or treating maceration and hand dermatitis [103, 104]. We are aware of other polymorphic clinical presentations, with novel data being reported periodically, but the pathophysiological mechanisms and evolution are largely unknown.

Figure 13 – ***(A–C) Representative image of a bullous eruption in a patient with dermatological history: pemphigus vulgaris and psoriasis in a male patient who tested positive for COVID-19 six months before the bullous eruption.***

COVID-19 disease and hair

Hair loss following the course of SARS-CoV-2 infection is a frequent manifestation, secondary only to emotional and physical stress induced by COVID-19 or related to newly restrictive life habits [105]. COVID-19-related alopecia may consist of anagen effluvium [105, 106] with excessive and sudden hair loss caused by a severe inflammatory response or, more often, TE, a reversible form of widespread hair loss that occurs, on average, 7–8 weeks after SARS-CoV-2 real-time reverse transcription polymerase chain reaction (RT-PCR) positivity because of a stressor [107]. Other hair abnormalities observed in SARS-CoV-2 infections are *alopecia areata* [108] and androgenetic alopecia [109], both related to physiological and psychosocial stress.

Limitations of the study

Because of the overwhelming number of papers published daily on the COVID-19 topic, we have tried to limit our citations and summarize only articles that we found most relevant to our research. Hence, one of this study's weaknesses is the possibility that we may have missed relevant original patient series because of these criteria.

Conclusions

No clear pattern in the acute phase that could predict the persistence of long-term lesions or progression to a chronic skin disease was identified in our study. We have not identified a particular type of skin lesion that is more prone to long-term persistence, although numerous articles describe pernio lesions as the most plausible for long-term evolution.

Given the wide variety of skin manifestations described in various articles and considering the subjective component regarding the interpretation of rash severity, the possibility of misdiagnosis, and three years being a short time to determine long-term effects, we believe that no conclusion can be drawn to establish a clear pattern of evolution for skin damage that could be universally applied to all cases.

Further studies should be performed to establish a precise relationship between the patterns of skin lesions described and SARS-CoV-2 infections, as the virus may not be the cause. They could also be due to the side effects of the drugs used, or other viruses may be involved. In addition, more complex serological and histological examinations should be undertaken to rule out misdiagnoses.

Once dermatologists are familiar with the multiple cutaneous findings in this pandemic disease, they could play a critical role in the management of acute-phase COVID-19 and long COVID. They could engage in early diagnosis by recognizing lesions and, later, noticing indicators of clinical condition deterioration. Additionally, dermatologists must be involved in registry reporting, thus improving the presently available data.

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Conflict of interests

The authors declare no conflict of interests.

Authors' contribution

Oana Maria Ică and Cornelia Andreea Tănasie equally contributed to this article.

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