

CRITICAL REVIEWS



Cutaneous Manifestations of COVID-19: A Systematic Review

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Objective: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is currently a pandemic. Although pulmonary health has been the primary focus of studies during the early days of COVID-19, development of a comprehensive understanding of this emergent disease requires knowledge of all possible disease manifestations in affected patients. This Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-compliant review focuses on cutaneous manifestations reported in COVID-19 patients.

Approach: 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.

Results: 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.

Innovation and Conclusion: As this virus continues to spread silently, mainly through asymptomatic carriers, an accurate and rapid identification of these cutaneous manifestations may be vital to early diagnosis and lead to possible better prognosis in COVID-19 patients. This systematic review and photo atlas provide a detailed analysis of the skin pathologies related to COVID-19. Study of these cutaneous manifestations and their pathogenesis, as well their significance in human health will help define COVID-19 in its entirety, which is a prerequisite to its effective management.

Keywords: wound, skin lesions, COVID-19, maculopapular, chilblain-like, MIS-C



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SCOPE AND SIGNIFICANCE

CUTANEOUS MANIFESTATIONS HAVE been increasingly reported in association with the coronavirus disease 2019 (COVID-19) pandemic. Despite an increase in relevance, much remains unknown concerning the characterization, incidence, and pathogenesis of these dermatological symptoms. This Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-compliant systematic review provides a detailed analysis on the changes in skin morphology related to COVID-19 and discusses plausible underlying molecular mechanisms. Furthermore, this review discusses cutaneous complications associated with personal protective equipment (PPE) and their potentially serious consequences. Study of these cutaneous manifestations and their pathogenesis, as well as their significance in human health will help define COVID-19 in its entirety, which is a prerequisite to its effective management.

TRANSLATIONAL RELEVANCE

This work is directly translationally relevant because it reviews critical evidence primarily originating from COVID-19 patients. Given that the report is presented at the time when the pandemic is ongoing, it is expected that the content will provide both health care providers as well as researchers with critical insight helpful to improve disease management. In addition, this article will help construct novel experimental hypotheses for future research.

CLINICAL RELEVANCE

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

INTRODUCTION

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a re-

spiratory tract infection that has rapidly spread worldwide since its first identification in Wuhan, China, during December of 2019.^{1,2} The asymptomatic transmission, high infection rate, and high mortality rate among the elderly and immunocompromised associated with this disease led the World Health Organization to declare it as a pandemic in March 2020. As of early August 2020, in excess of 20 million cases of COVID-19 have been confirmed globally with more than 750,000 deaths reported in over 200 countries and territories.

SARS-CoV-2 is a novel enveloped, positive-sense, single-stranded RNA virus that is part of the genus Betacoronavirus.¹ Angiotensin-converting enzyme 2 (ACE2) is a protein that functions as the sole receptor for SARS-CoV-2 to invade cells and cause infection in humans.³ Although this virus primarily attacks the respiratory tract, *ACE2* gene expression has been discovered in several human tissues, including gastrointestinal and skin tissue.³ In a recent analysis of 31 Genotype-Tissue Expression human tissue, Li *et al.*³ have found that among human organs, small intestine, testis, kidneys, heart, thyroid, and adipose tissue have the highest *ACE2* expression levels, while blood, spleen, bone marrow, brain, blood vessels, and muscle have the lowest *ACE2* expression levels.

Other organs like lungs, colon, liver, bladder, and adrenal glands have medium expression of *ACE2* in the human body.³ To investigate whether skin was a potential target for SARS-CoV-2 infection, Xue *et al.*⁴ analyzed datasets available in public domain (GEPIA2 and ARCHS4) to explore *ACE2* mRNA expression and *ACE2*-positive cell composition in skin tissues. The expression of *ACE2* was significantly higher in keratinocytes than other cellular compartments in skin tissues, such as fibroblasts and melanocytes.⁴ This was further validated through independent single-cell RNA-seq data in which Xue *et al.*⁴ have found that out of all *ACE2*-positive cells in skin, keratinocytes account for 97.37% followed by sweat gland cells that account for 2.63%. The widespread expression of *ACE2* suggests that this virus might be responsible for infecting other human tissues alongside the lungs, and could potentially result in additional clinical manifestations.^{3,4}

COVID-19 has a high infectivity rate, primarily due to its spread through respiratory droplets. After an incubation period of 1–14 days, common clinical symptoms such as “fever, cough, fatigue, sputum production, shortness of breath, sore throat, and headache” begin to appear.¹ In addition to these common symptoms, novel symptoms such

as a variety of cutaneous manifestations have been reported worldwide.⁵ Early data from China reported skin symptoms were present in only 0.2% of 1,099 confirmed COVID-19 cases.⁶ However, data from Italy later revealed a higher percentage with skin manifestations present in 20.4% of 88 positive COVID-19 patients.⁵ Despite differences in prevalence, reports of cutaneous lesions have become increasingly common in many age groups, including children who were once thought to be asymptomatic to the infection. Although not much is known concerning the pathophysiologic mechanisms of these cutaneous manifestations, their identification may be vital to early diagnosis and lead to possible better prognosis in COVID-19 patients. This systematic review provides a detailed analysis on the changes in skin morphology related to COVID-19 and the possible molecular mechanisms and health significance underlying these cutaneous manifestations.

METHODS

Literature review was conducted using the PubMed database to examine various cutaneous manifestations related to the SARS-CoV-2 infection. Published articles related to search criteria from the onset of the COVID-19 pandemic to June 30, 2020, were included. Search strategy included “COVID-19,” “coronavirus,” or “SARS-CoV-2” in combination with relevant terminology such as “skin,” “cutaneous,” “chilblain-like,” “maculopapular,” “urticarial,” “livedo,” “vesicular,” “petechiae,” and “multisystem inflammatory syndrome.” Cases series including five or more patients were selected for this review. Individual case reports were excluded from the table data; however, may have been used during analysis of various skin rashes. In total, 56 articles complied with search criteria and were used for data collection (Fig. 1).

Two authors (H.S. and H.K.) worked independently, searched, and scanned all abstracts and titles in duplicate to identify articles relevant to this study. When discrepancies occurred, a third reviewer (K.S.) made the final judgment. Singh and Kaur assessed eligibility from full-text articles, with a similar process for potential disagreements as described above. Data extraction from included studies (*i.e.*, published abstracts and articles) was duplicated with a standardized extraction form. The characteristics of the research (study design, antiviral regimen, therapy duration, etc.), the outcomes of interest mentioned above, and biased risk assessment were extracted. The source of the data presented in this review article was from published

papers available in public domain hence IRB approval was not needed.

RESULTS

Cutaneous manifestations associated with COVID-19 infection are numerous and can vary greatly when compared to one another. The six central dermatological patterns of COVID-19 are described as maculopapular/morbilliform, urticarial, vesicular, chilblain like, petechiae/purpura, and livedoid. These clinical findings can be further classified as either inflammatory (maculopapular/morbilliform, urticarial, and vesicular) or vascular lesions (chilblain-like, petechiae/purpura, and livedoid).⁷ Due to scientific need for appropriate classification of these cutaneous manifestations, an algorithm has been published to provide for easier classification of the main COVID-19 skin findings mentioned earlier.⁸ Finally, multisystem inflammatory syndrome in children (MIS-C), a novel illness thought to be related to COVID-19, can also present with dermatological symptoms, although clarification of their cutaneous classifications is needed.

Maculopapular/morbilliform lesions

Maculopapular lesions are amongst the most prevalent cutaneous manifestations seen throughout the COVID-19 pandemic (Table 1) are maculopapular lesions. These lesions are frequently the result of adverse drug reactions or viral infections.⁹ Maculopapular lesions occurring in children are typically the result of viral infections, whereas drug eruptions are usually the trigger for these lesions in adults¹⁰ (Fig. 2).

A case series of 375 patients with skin lesions associated with COVID-19 identified a 47% prevalence of maculopapular lesions.¹¹ Prevalence of these lesions has varied among studies with a smaller number of cases, ranging from 5% to 70%. Many of the maculopapular rashes reported were observed in middle-aged or elderly patients^{11–14}; however, cases have appeared in younger adults.¹⁵ Anatomically, the majority of these lesions were located on the trunk of the body.^{12,13,15–18} Despite a large case series from Spain reporting simultaneous onset of many maculopapular lesions with COVID-19's systemic symptoms,¹¹ other studies had noticed a later onset in their smaller patient populations.^{12–14,19} Studies with a later onset of cutaneous manifestations reported average latency times of 27.6 days and 27.85 days.^{12,13} Mean duration of the exanthems ranged from 8.6 to 11.6 days.^{11–13} According to one case series, pruritus was present in 56% of patients with maculo-

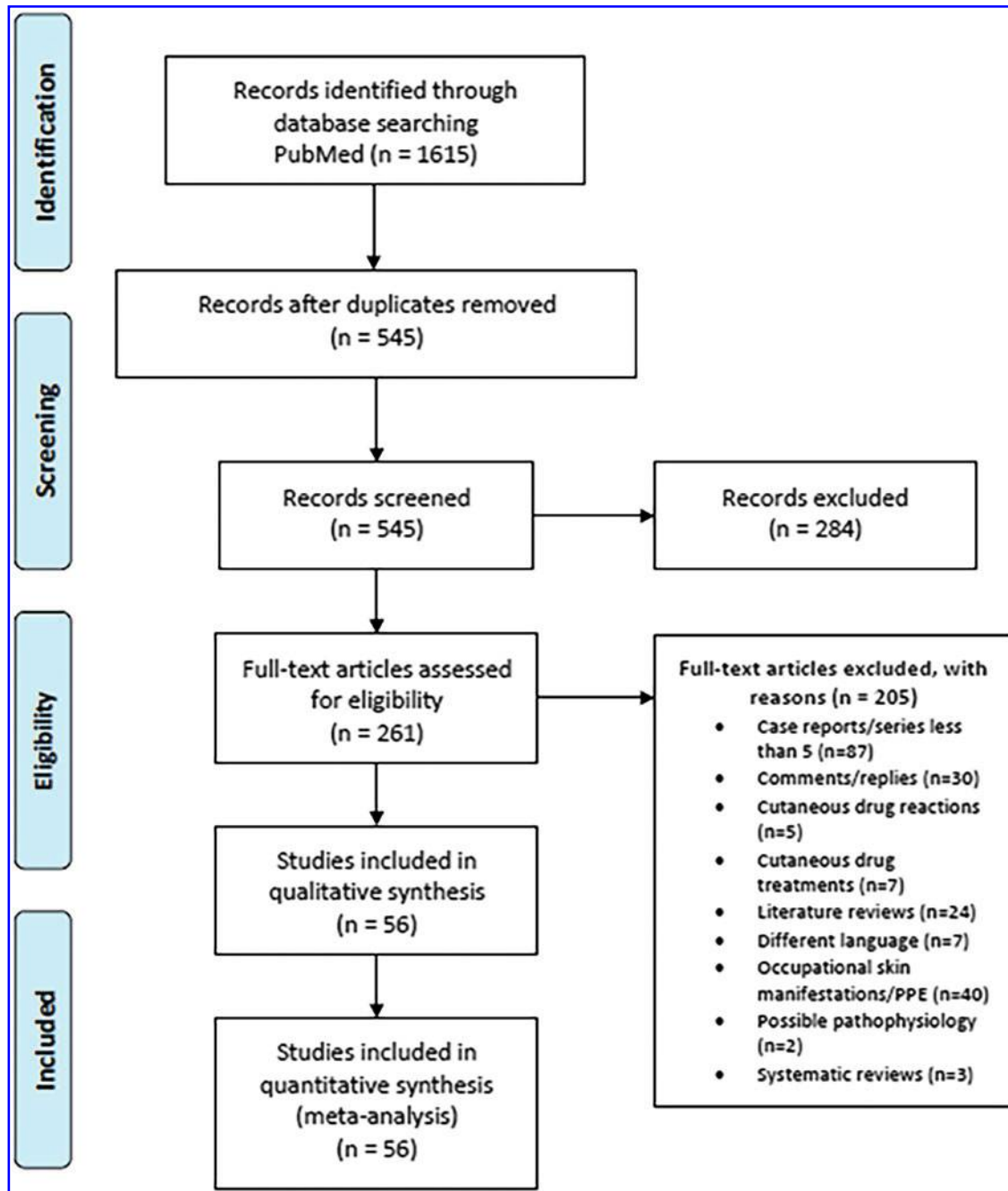


Figure 1. The PRISMA statement of this review. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Source: Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. The PRISMA Group. *PLoS Med* 6:e1000097.

popular lesions. Interestingly, the same study suggested that maculopapular rashes are associated with greater severity of COVID-19 infections; this was supported by a 2% mortality rate reported in patients with these lesions.¹¹ Histopathological findings for these lesions are dependent on the time of onset.¹⁴ Early-onset rashes are presented with moderate epidermal spongiosis and perivascular lymphocytic infiltrate with eosinophils in the dermal region.¹⁴ Contrastingly, histology of late-onset

lesions exhibited perivascular lymphocytic infiltrate and histiocytes among collagen fibers. These late-onset lesions are devoid of mucin deposits.¹⁴ Additional examination by Reymundo *et al.* reported presence of mild superficial perivascular lymphocytic infiltrate in skin biopsies.¹³

There have been a few theories discussed concerning the molecular mechanisms of maculopapular lesions. Galván Casas *et al.* described these lesions as unhelpful toward diagnosis due to

Table 1. Demographic and clinical details of maculopapular rashes observed in COVID-19 patients

Article and Year	Number of Patients, Age, Gender	Suspected or Confirmed COVID-19	COVID-19 Cutaneous Manifestations	Anatomical Location of Cutaneous Manifestations
Askin <i>et al.</i> (2020) ¹⁶	Total population: 210 patients Male age, mean: 57.44 ± 17.259 years Female age, mean: 58.80 ± 15.918 years 123 male (58.6%), 87 female (41.4%) Skin lesions: 52/210 (24%): 33 male (26.8%), 19 female (21.8%) Maculopapular: 12/52 (23%)	SARS-CoV-2 PCR in total population, PCR performed in 158 patients: Positive: 88/158 (55.7%) Negative: 70/158 (44.3%) SARS-CoV-2 PCR in 52 patients with cutaneous findings: Positive: 34/52 (65.4%) Negative: 18/52 (34.6%)	Classification of 52 patients with skin lesions: Erythematous scaly rash (<i>n</i> = 17, 32.7%) Maculopapular rash (<i>n</i> = 12, 23%) Urticarial lesions (<i>n</i> = 7, 3.5%) Petechial purpuric rash (<i>n</i> = 4, 7.7%) Necrosis (<i>n</i> = 4, 7.7%) Enanthema, aphthous stomatitis (<i>n</i> = 3, 5.8%) Vesicular rash (<i>n</i> = 3, 5.8%) Pernio (<i>n</i> = 1, 1.9%)	Most maculopapular lesions were located on trunk; in one case, lesion was present on the extremities.
Dalal <i>et al.</i> (2020) ²⁷	Total population: 102 patients Age, mean (SD): 39.30 years (SD 17.9) 95 male (93.1%), 7 female (6.9%) Skin lesions: 13/102 (12.7%) Maculopapular: 3/13 (23.1%)	SARS-CoV-2 PCR: Positive: 102/102 (100%)	Classification of 13 patients with skin lesions: Maculopapular rash (<i>n</i> = 3, 23.1%) Urticarial lesions (<i>n</i> = 2, 15.4%) Pruritis without specific cutaneous signs (<i>n</i> = 8, 69.2%)	Location of maculopapular lesions: Trunk (<i>n</i> = 3) Extremities (<i>n</i> = 1) Maculopapular rash presented in centripetal distribution
de Masson <i>et al.</i> (2020) ¹⁵	Total population: 277 patients Age, mean (range): 27 years (2–98) "Half of patients were male" Skin lesions: 277/277 (100%) Morbilliform: 25/277 (9%) Age, median (range): 29 years (2–70) 10 male (48%), 11 female (52%)	SARS-CoV-2 PCR in 34 patients (12%): Positive: 25/34 (73.5%) Negative: 9/34 (26.5%)	Classification: Morbilliform lesions (<i>n</i> = 25, 9%) Acral lesions (<i>n</i> = 142, 51%) Vesicular lesions (<i>n</i> = 41, 15%) Livedo reticularis (<i>n</i> = 4, 1%) Urticarial lesions (<i>n</i> = 26, 9%) Petechial lesions (<i>n</i> = 7, 3%) Other types of lesions (<i>n</i> = 41, 15%)	Location of morbilliform lesions: Trunk and limbs (<i>n</i> = 25, 100%) Face (<i>n</i> = 2, 8%)
Docampo-Simon <i>et al.</i> (2020) ³⁵	Total population: 58 patients Age, median (range): 14 years (3 months–85 years) 29 male (50%), 29 female (50%) Skin lesions: 58/58 (100%) Maculopapular: 3/58 (5.17%)	SARS-CoV-2 PCR in 39 patients (67%): Positive: 1/39 (2.56%) Negative: 38/39 (97.4%)	Classification: Chilblain-like lesions (<i>n</i> = 42) Purpuric (<i>n</i> = 3) Maculopapular (<i>n</i> = 3) Vesiculobullous (<i>n</i> = 3) Eczematous (<i>n</i> = 3) Paronychia (<i>n</i> = 2) Ulcer (<i>n</i> = 1) Desquamation (<i>n</i> = 1)	Location of ALL lesions: Hands (<i>n</i> = 9, 15.5%) Feet (<i>n</i> = 36, 62.1%) Hands and Feet (<i>n</i> = 13, 22.4%)
Galvan <i>et al.</i> (2020) ¹¹	Total population: 375 patients 153 males (40.8%), 222 females (59.2%) Skin lesions: 375/375 (100%) Maculopapular: 176/375 (47%): Age, mean (SD): 55.3 years (20.2) 78 male (44.3%), 98 female (55.7%)	Laboratory confirmation of SARS-CoV-2 Patients with skin lesions: Confirmed: 234/375 (62.4%) Suspected: 141/375 (37.6%) Maculopapular patients: Confirmed: 54/176 (30.6%) Suspected: 122/176 (69.3%)	Classification: Pseudo-chilblain (19%) Vesicular eruptions (9%) Urticarial lesions (19%) Maculopapular eruptions (47%) Livedo or necrosis (6%)	Perifollicular distribution Extremities: dorsum of hands
Herrero-Moyano <i>et al.</i> (2020) ¹²	Total population: 1,177 patients Skin lesions: 8/1,177 (0.7%) Maculopapular: 8/8 (100%) Age, mean (range): 72.2 years (51–88) 4 male (50%), 4 female (50%)	SARS-CoV-2 PCR in 8 patients with cutaneous findings: Positive: 7/8 (87.5%) Negative: 1/8 (12.5%)	Classification: Ill-defined erythematous patches to coalescent maculopapules, some with violaceous center; one patient developed pustules and desquamation	Location of morbilliform lesions: Trunk (<i>n</i> = 7) Flexures (<i>n</i> = 4) Proximal extremities (<i>n</i> = 2) Face (<i>n</i> = 2) Generalized (<i>n</i> = 1)
Reymundo <i>et al.</i> (2020) ¹³	Total population: 18 patients Skin lesions: 7/18 (38.9%) Maculopapular: 7/7 (100%) Age, mean (range): 66.57 years (57–82) 2 male (28.6%), 5 female (71.4%)	SARS-CoV-2 PCR: Positive: 18/18 (100%)	Classification: Maculopapular eruptions	Location of morbilliform lesions: Involvement of the trunk (<i>n</i> = 7) Proximal upper limb involvement (<i>n</i> = 6) Lower limb involvement (<i>n</i> = 1)
Rubio-Muniz <i>et al.</i> (2020) ¹⁴	Total population: 34 patients Age, median (range): 54.5 years (31–66) 14 male (41%), 20 female (59%) Skin lesions: 34/34 (100%) Maculopapular: 10/34 (29.4%) Age, median (range): 53 years (31–61) 4 male (40%), 6 female (60%)	COVID-19 diagnosis (total population): Positive PCR: 17/34 (50%) Positive radiology: 8/24 (23.5%) Negative PCR: 9/34 (26.5%) COVID-19 diagnosis (maculopapular): Positive PCR: 6/10 (60%) Positive radiology: 3/10 (30%) Negative PCR: 1/10 (10%)	Classification: Maculopapular (<i>n</i> = 10) Pseudo-chilblain (<i>n</i> = 9) Targetoid lesions (<i>n</i> = 5) Palpable purpura (<i>n</i> = 4, of which 2 cases are with vesicular lesions) Acute urticaria (<i>n</i> = 3) Vesicular (<i>n</i> = 2, these also have palpable purpura) Remaining 3 cases include livedo reticularis, urticarial exanthem, and prurigo lesions.	N/A

COVID-19, Coronavirus Disease 2019; N/A, not available; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.



Figure 2. Examples of maculopapular rash seen in COVID-19-positive patients. **(A)** Maculopapular lesions, a few of which present with a perfollicular distribution, located on the thigh of patient. **(B, C)** Eleven-year-old child with COVID-19 presenting with pruritis and maculopapular lesions located on her face and shoulder. Duration of lesions was 5 days. **(D, E)** Seventeen-year-old adolescent with COVID-19 presenting with a maculopapular rash and mild pruritis only after receiving HCO treatment, suggesting a drug-induced exanthema. **(F)** Nonspecific maculopapular rash located on the trunk of recovering COVID-19 patient. **(G)** Maculopapular rash appearing on posterior trunk of a confirmed COVID-19 patient. **(H)** Maculopapular lesions described as small plaques after fusion of lesions. COVID-19, Coronavirus Disease 2019. Reproduced with permission from John Wiley and sons **(A–G)**; Wolters Kluwer Health, Inc. **(H)**. The following original reports are credited: Galván Casas *et al.*¹¹; Duramaz *et al.*¹⁹; Rubio-Muniz *et al.*¹⁴; Gianotti *et al.*¹⁸

the potential cause of adverse drug reactions. This is plausible as patients with these rashes had more severe infections and therefore received greater drug therapy.¹¹ Potential drugs given against COVID-19 such as Ribavirin, Colchicine, intravenous immunoglobulin (IVIG) treatments, Lopinavir, Ritonavir, and other antiretroviral drugs are known to result in cutaneous side effects similar to maculopapular and morbilliform rashes.²⁰ However, maculopapular eruptions have been observed in case series with no new medications taken, suggesting that these lesions may not solely be drug related.¹³ Finally, Herrero-Moyano *et al.* proposed a hypothesis that a cytokine storm produced by a hyperactive immune system could be the instigator behind these rashes after observing late-onset maculopapular eruptions.¹² Other significant hypotheses about the potential

causes of maculopapular lesions have been provided in Table 9.

Urticarial lesions

In addition to maculopapular rash, urticarial lesions have also been noted in several COVID-19 case series. These lesions typically present as hives or angioedema and can be characterized as an erythematous slightly raised papular rash followed by intense pruritic sensations.²¹ Although considered one of COVID-19's most frequent cutaneous manifestations, urticarial lesions have been a relatively common dermatological condition even before the pandemic. Acute urticaria, defined as a self-limiting lesion lasting less than 6 weeks, has been reported to affect 20% of the general population.²² Meanwhile, chronic urticaria, described as a recurring lesion present for greater than 6 weeks,

appears to affect 5% of the general population.²² Common triggers include viral/bacterial/parasitic infections, environmental exposures, and immunoglobulin E-mediated allergic reactions in response to medications, food, or biting/stinging insects.²² Urticarial lesions typically resolve after removal

of the offending agent; however, in severe cases, the use of antihistamines and steroids has been implemented for symptomatic relief (Fig. 3).

Acute urticarial lesions have been discussed in several COVID-19 studies^{11,14,16,20,23–26} (Table 2). Prevalence of these lesions among other skin



Figure 3. Examples of urticarial rash seen during the COVID-19 pandemic. (A) Urticarial lesions dispersed along buttocks and proximal lower extremity (thigh). (B) Urticarial rash, similar to hives, appearing on patient's neck and chest. (C, D) Thirty-nine-year-old nurse presenting with generalized pruritic urticarial rash 2 days before the onset of pyrexia, chills, myalgia, and headache. Lesions were located on her thigh (C) and back (D). (E) Generalized pruritic urticaria present on elderly man with COVID-19 infection. (F) Thirty-two-year-old female presenting with a dispersed urticarial rash on her face, trunk, and lower limbs. Lesion onset was 6 days after first COVID-19 clinical symptoms and lesion duration was 5 days. (G) Staff nurse presenting with widespread urticarial eruption involving her face, arms, torso, legs, and loins. Lesion onset was before presentation of COVID-19 clinical symptoms. (H) "Urticarial pattern with mild edema, perivascular inflammation, and dilated vessels in the upper dermis. Inset: vessels filled with neutrophils and mixed perivascular inflammation." Reproduced with permission from John Wiley and sons (A–F, H); BMJ Publishing Group Ltd. (G). The following original reports are credited Galván Casas *et al.*¹¹; Marzano *et al.*⁵⁰; van Damme *et al.*²³; Najafzadeh *et al.*²⁴; Cabrera-Hernández *et al.*²⁵; Hassan.²⁶

Table 2. Demographic and clinical details of urticarial rashes observed in COVID-19 patients

Article and Year	Number of Patients, Age, Gender	Suspected or Confirmed COVID-19	COVID-19 Cutaneous Manifestations	Anatomical Location of Cutaneous Manifestations
Askin <i>et al.</i> (2020) ¹⁶	Total population: 210 patients Male age, mean: 57.44 ± 17.259 years Female age, mean: 58.80 ± 15.918 years 123 male (58.6%), 87 female (41.4%) Skin lesions: 52/210 (24%): 33 male (26.8%), 19 female (21.8%) Urticaria: 7/52 (13.5%)	SARS-CoV-2 PCR in total population, PCR performed in 158 patients: Positive: 88/158 (55.7%) Negative: 70/158 (44.3%) SARS-CoV-2 PCR in 52 patients with cutaneous findings: Positive: 34/52 (65.4%) Negative: 18/52 (34.6%)	Classification of skin lesions: Erythematous scaly rash (<i>n</i> = 17, 32.7%) Maculopapular rash (<i>n</i> = 12, 23%) Urticarial lesions (<i>n</i> = 7, 3.5%) Petechial purpuric rash (<i>n</i> = 4, 7.7%) Necrosis (<i>n</i> = 4, 7.7%) Enanthema, aphthous stomatitis (<i>n</i> = 3, 5.8%) Vesicular rash (<i>n</i> = 3, 5.8%) Pernio (<i>n</i> = 1, 1.9%)	Urticarial lesions were distributed across the entire body
Bouaziz <i>et al.</i> (2020) ⁴⁴	Total population: 14 patients Age/gender NR Skin lesions: 14/14 (100%) Urticaria: 1/14 (7.1%)	SARS-CoV-2 PCR in 14 patients: Positive: 14/14 (100%)	Inflammatory lesions: 7/14 Exanthema (<i>n</i> = 4) Chicken pox-like virus (<i>n</i> = 2) Cold urticaria (<i>n</i> = 1) Vascular lesions: 7/14 Violaceous macules with “porcelain-like” appearance (<i>n</i> = 1) Livedo (<i>n</i> = 1) Non-necrotic purpura (<i>n</i> = 1) Necrotic purpura (<i>n</i> = 1) Chilblain appearance with Raynaud’s phenomenon (<i>n</i> = 1) Chilblain (<i>n</i> = 1) Eruptive cherry angioma (<i>n</i> = 1)	N/A
Dalal <i>et al.</i> (2020) ²⁷	Total population: 102 patients Age, mean (SD): 39.30 years (SD 17.9) 95 male (93.1%), 7 female (6.9%) Skin lesions: 13/102 (12.7%) Urticaria: 2/13 (15.4%)	SARS-CoV-2 PCR in 102 patients: Positive: 102/102 (100%)	Classification of skin lesions: Maculopapular rash (<i>n</i> = 3, 23.1%) Urticarial lesions (<i>n</i> = 2, 15.4%) Pruritis without specific cutaneous signs (<i>n</i> = 8, 69.2%)	Location of urticarial lesions: Trunk (<i>n</i> = 2)
De Giorgi <i>et al.</i> (2020) ¹⁷	Total population: 678 patients Skin lesions: 53/678 (7.8%) Age, mean (range): 55.9 years (28–69) 32 male (60%), 21 female (40%) Urticaria: 14/53 (26%)	SARS-CoV-2 PCR in 678 patients: Positive: 678/678 (100%)	Inflammatory manifestations: Erythematous rash (<i>n</i> = 37, 70%) Diffuse urticaria (<i>n</i> = 14, 26%) Varicelliform rash—vesiculation (<i>n</i> = 2, 4%) Vascular manifestations: Diffuse petechiae, purpura, and acro-ischemia (25%)	Location of ALL lesions: Trunk Upper limbs
de Masson <i>et al.</i> (2020) ¹⁵	Total population: 277 patients Age, mean (range): 27 years (2–98) “Half of patients were male” Skin lesions: 277/277 (100%) Urticaria: 26/277 (9%) Age, median (range): 3 years (2–23) 13 male (56.5%), 10 female (43.5%)	SARS-CoV-2 PCR in 34 patients (12%): Positive: 25/34 (73.5%) Negative: 9/34 (26.5%)	Classification of skin lesions: Morbilliform lesions (<i>n</i> = 25, 9%) Acral lesions (<i>n</i> = 142, 51%) Vesicular lesions (<i>n</i> = 41, 15%) Livedo reticularis (<i>n</i> = 4, 1%) Urticarial lesions (<i>n</i> = 26, 9%) Petechial lesions (<i>n</i> = 7, 3%) Other types of lesions (<i>n</i> = 41, 15%)	Location of urticarial lesions: Trunk and limbs (<i>n</i> = 24, 92%) Face (<i>n</i> = 2, 8%)
Galvan <i>et al.</i> (2020) ¹¹	Total population: 375 patients 153 males (40.8%), 222 females (59.2%) Skin lesions: 375/375 (100%) Urticaria: 73/375 (19%): Age, mean (SD) = 48.7 years (19.9) 26 male (35.6%), 47 female (64.3%)	Laboratory confirmation of SARS-CoV-2 Patients with skin lesions: Confirmed: 234/375 (62.4%) Suspected: 141/375 (37.6%) Urticarial patients: Confirmed: 49/73 (67%) Suspected: 24/73 (33%)	Classification: Pseudo-chilblain (19%) Vesicular eruptions (9%) Urticarial lesions (19%) Maculopapular eruptions (47%) Livedo or necrosis (6%)	Most urticarial lesions were dispersed or located on the trunk. A few cases were located on the palms.
Recalcati <i>et al.</i> (2020) ⁵	Total population: 88 patients Age/gender—N/A Skin lesions: 18/88 (20.5%) Urticaria: 3/18 (16.7%)	SARS-CoV-2 PCR: Positive: 18/18	Classification: Erythematous rash (<i>n</i> = 14) Widespread urticaria (<i>n</i> = 3) Chicken pox-like vesicles (<i>n</i> = 1)	Trunk was the primary location for all lesions.
Rubio-Muniz <i>et al.</i> (2020) ¹⁴	Total population: 34 patients Age, median (range): 54.5 years (31–66) 14 male (41%), 20 female (59%) Skin lesions: 34/34 (100%) Urticaria: 4/34 (11.8%) Age, median (range): 54.5 years (37–65) 1 male (25%), 3 female (75%)	COVID-19 diagnosis (total population): Positive PCR: 17/34 (50%) Positive radiology: 8/24 (23.5%) Negative PCR: 9/34 (26.5%) COVID-19 diagnosis (Urticarial): Positive PCR: 2/4 (50%) Positive radiology: 1/4 (25%) Negative PCR: 1/4 (25%)	Classification: Maculopapular (<i>n</i> = 10) Pseudo-chilblain (<i>n</i> = 9) Targetoid lesions (<i>n</i> = 5) Palpable purpura (<i>n</i> = 4, of which 2 cases are with vesicular lesions) Acute urticaria (<i>n</i> = 3) Vesicular (<i>n</i> = 2, these also have palpable purpura) Remaining 3 cases include livedo reticularis, urticarial exanthem, and prurigo lesions.	N/A
Gaspari <i>et al.</i> (2020) ⁴²	Total population: 20 patients Age, median: 51 years 17 male (85%), 3 female (15%) Skin lesions: 18/20 (90%) Urticaria: 2/18 (11.1%)	Confirmed: 18/18 (41%)	Classification: Exanthematic rashes (<i>n</i> = 9) Acral vasculitis eruptions (<i>n</i> = 6) Polymorpho-like urticaria (<i>n</i> = 2) Varicelliform eruption (<i>n</i> = 1)	Figure 1: Polymorpho-like urticaria located on the left hand

NR, not reported.

manifestations has varied from 7% to 40% in smaller case series. These lesions were common among middle-aged patients^{11,14}; however, a retrospective study conducted in France reported a median age of 3 years of age among 26 patients with urticarial lesions.¹⁵ Many of these lesions were distributed on the trunk or limbs.^{11,15,27} In some cases, the rash was generalized across the entire body or localized to the face.^{15,16} According to the largest case series of urticarial lesions, onset is thought to occur at the same time as other systemic symptoms of COVID-19 with an average duration of 6.8 days.¹¹ However, it should be noted that in a few instances, the onset of urticaria has manifested before COVID-19's systemic symptoms.^{11,28}

Galván Casas *et al.* reported pruritus in 92% of patients with urticarial lesions and associated these lesions with a more severe COVID-19 infection.¹¹ Histopathological examination for urticarial lesions has been sparse; however, the results in one case of urticariform rash present in a 32-year-old woman displayed the presence of perivascular infiltrate of lymphocytes, with few eosinophils and upper dermal edema.²⁹

Due to many cases of urticaria having an association with therapy, possible etiology of urticarial lesions could involve drug-induced exanthema.¹¹ Urticaria has been described as a cutaneous side effect in many potential anti-COVID-19 drugs such as chloroquine, hydroxychloroquine, lopinavir/ritonavir, nitazoxanide, corticosteroids, baricitinib, IVIG treatments, and checkpoint inhibitors.²⁰ In addition to adverse drug effects, another possible pathophysiological mechanism leading to urticaria could be overactivity of the immune system, resulting in a potential "cytokine storm" involving the skin.³⁰ Interestingly, cases of delayed pressure urticaria have also been reported, although they are thought to be a result of vertical pressure caused by PPE.³¹

Finally, a direct cutaneous effect by the SARS-CoV-2 virus is always a possibility, considering viral infections have sometimes been implicated as the primary agent in urticarial cases in the past. On account of the extreme variability in etiology of urticarial skin lesions, these lesions are thought to be a potentially inaccurate marker for diagnosis or verification of COVID.¹¹ Other significant hypotheses about the potential causes of urticarial lesions have been provided in Table 9.

Chilblain-like lesions (COVID toes)

Chilblain lesions, also referred to as pernio, are characterized as a localized inflammatory skin disorder, thought to be induced by exposure to cold temperatures or damp humid environments

resulting in swelling and discoloration of the extremities (Fig. 4). The increased incidence of pernio/acral-like or chilblain-like lesions, coupled with the temporal association with viral symptoms, has led to the colloquialization "COVID toes." The term comes from the cutaneous description in which the skin involving their toes presents as erythematous or violaceous lesions. Although some cases are idiopathic, previous literature supports chilblain association with autoimmune diseases such as lupus.³² In some cases, the rash is seen with the Raynaud's phenomenon in which a trigger (cold exposure or emotional stress) leads to skin discolorations of extremities through vasoconstriction.³³

A retrospective review conducted by Cappel *et al.* reported additional potential associations with hematologic disease as well as hyperviscosity syndrome. The rash is typically located on distal acral extremities such as fingers and/or toes.³² Per UpToDate, the rash typically presents as "erythematous-violaceous papules, macules, or nodules (UpToDate)." The pathogenesis behind chilblains is not entirely understood. One suspected mechanism revolves around cold-induced vasoconstriction and vasospasm leading to hypoxemia and inflammation. Other theories suggest hyperviscosity or autoantibody-induced endothelial damage (UpToDate). Treatment modalities include heating, nonsteroidal anti-inflammatory drugs (NSAIDs), topical steroids, and vasodilators.³²

Lesions similar to chilblains, labeled as chilblain like or pernio like, have rapidly become the most familiar of COVID-19's cutaneous manifestations, in part, due to the numerous studies published concerning them (Table 3). The prevalence of these lesions varied considerably between studies. An international case series consisting of 505 patients with dermatological conditions reported pernio-like lesions present in 63%.³⁴ Among other studies, the prevalence of chilblain-like lesions fluctuated from 14.3% to 72%.^{11,15,34-36} These vascular lesions were commonly identified among adolescents and young adults.^{11,15,34,35,37-43} Anatomical locations of chilblain-like lesions were consistent between studies with feet and hands being affected the most often. On the hands and feet, the acral lesions would typically localize on the fingers and toes, respectively.

The onset of chilblain-like lesions was almost always after the onset of COVID-19's systemic symptoms and they normally lasted for about a week or two on average. In one case series, chilblain-like lesions were the only symptom in 55% of cases.³⁴ Dermatological symptoms commonly associated with chilblain-like lesions were pain and pruritus.^{11,34,35,37,38} Many of the patients



Figure 4. Examples of chilblain-like rash seen during the COVID-19 pandemic. (A) Acral chilblain-like lesions located on toes of patient. (B) Acral chilblain-like lesions located on fingers of patient. (C) Pseudo-chilblain lesions present on the fingers of pediatric patient with no prior history of chilblains. (D) Acral chilblain-like lesions located on toes of patient. (E) Chilblain-like lesions acrally located on toes of pediatric patient. (F, G) Lesions clinically similar to chilblains, acrally located on toes of child during COVID-19 pandemic. (H) Chilblain-like lesions located on the heel of an adolescent. (I) Chilblain-like acral lesion present on toes of patient from Italy. Examples of chilblain-like rash seen during the COVID-19 pandemic. (J) Acral pseudo-chilblains are seen on the toes of a patient. (K) Acral pernio-like lesions affecting the toes of patient. (L) Perno-like lesions affecting the distal extremity of patient. (M) Acral chilblain-like lesions located on toes of an adolescent patient. (N) Pseudo-chilblain lesions described as erythematopurpuric macules appeared on patient's heel. (O) "Dense, superficial, and deep angiocentric and eccrinotropic lymphocytic infiltrate (H&E stain, 10 \times)."
(P) "Papillary dermal edema, vacuolar degeneration of the basal layer and lymphocytic exocytosis. Endothelia of small vessels appear swollen (H&E stain, 20 \times)."
(Q) "Intense lymphocytic vascular reaction in dermal vessels (H&E stain, 40 \times)."
(R) "Red cell extravasation and focal thrombosis (arrow) in papillary dermis capillaries (H&E stain, 100 \times)."
H&E, hematoxylin and eosin. Reproduced with permission from John Wiley and sons (A–R). The following original reports are credited: Galván Casas *et al.*¹¹; García-Lara *et al.*⁴¹; Andina *et al.*³⁷; Wollina *et al.*⁴³; Marzano *et al.*⁵⁰; Gaspari *et al.*⁴²; Rubio-Muniz *et al.*¹⁴

presenting with pernio-like lesions were young and healthy. These rashes were typically associated with relatively mild COVID-19 infections.³⁴ Histopathological examination performed by Rubio-Muniz *et al.* showed different patterns. In many of the pseudo-chilblain cases, the histology displayed focal vacuolar degeneration of the basal layer. Regenerative changes were also observed in the epidermis along with perivascular lymphocytic cuffs in the dermal regions. Histology conducted in

another sample discovered presence of perivascular neutrophilic cuffs with clear inflamed endothelium and regions of epidermal necrosis.¹⁴

The exact mechanism of chilblain-like lesions is not fully known as its presentation is unrelated to cold exposure. Bouaziz *et al.* hypothesized pathophysiology behind chilblain could involve "immune dysregulation, vasculitis, vessel thrombosis, or neoangiogenesis."⁴⁴ It also noted previous cases with acro-ischemia and disseminated intravascu-

Table 3. Demographic and clinical details of pseudo-chilblain rashes observed in COVID-19 patients

Article and Year	Number of Patients, Age, Gender	Suspected or Confirmed COVID-19	COVID-19 Cutaneous Manifestations	Anatomical Location of Cutaneous Manifestations
Andina <i>et al.</i> (2020) ³⁷	Total population: 22 patients Age, median (range): 12 years (6–17) 13 male (59%), 9 female (41%) Skin lesions: 22/22 (100%) Chilblain like: 22/22	SARS-CoV-2 PCR in 19 patients (86%): Positive: 1/19 (5.3%) Negative: 18/19 (94.7%)	Acral chilblain-like lesions: Concomitant erythema multiforme; erythematous-violaceous or purpuric macules; swollen toes with dusky violaceous discoloration and less frequently, dark ischemic areas with superficial blisters	Feet affected in all cases, toes most common. (n=22) Lesions on fingers (n=3)
Bouaziz <i>et al.</i> (2020) ⁴⁴	Total population: 14 patients Age/gender NR Skin lesions: 14/14 (100%) Chilblain like: 2/14 (14.3%)	SARS-CoV-2 PCR: Positive: 14/14 (100%)	Inflammatory lesions = 7/14: Exanthema (n=4) Chicken pox-like virus (n=2) Cold urticaria (n=1) Vascular lesions = 7/14: Violaceous macules with “porcelain-like” appearance (n=1) Livedo (n=1) Non-necrotic purpura (n=1) Necrotic purpura (n=1) Chilblain appearance with Raynaud’s phenomenon (n=1) Chilblain (n=1) Eruptive cherry angioma (n=1)	N/A
Colonna <i>et al.</i> (2020) ³⁸	Total population: 30 patients Age, median (range) = 11 years (2–17) 17 male (56.7%), 13 female (43.3%) Skin lesions: 30/30 (100%) Chilblain like: 30/30	SARS-CoV-2 PCR in 6 patients (20%): Negative: 6/6	Chilblain-like acral lesions: Lesions were erythematous-violaceous patches or slightly infiltrated plaques.	Location of lesions: Feet (n=26) Ankles (n=2) Hands (n=4) Of 4 patients with hand lesions, 2 of them also had foot lesions.
de Masson <i>et al.</i> (2020) ¹⁵	Total population: 277 patients Age, mean (range): 27 years (2–98) “Half of patients were male” Skin lesions: 277/277 (100%) Chilblain like: 106/277 (38%) Age, median (range): 27 years (6–73)	SARS-CoV-2 PCR in 34 patients (12%): Positive: 25/34 (73.5%) Negative: 9/34 (26.5%)	Classification: Morbilliform lesions (n=25, 9%) Acral lesions (n=142, 51%) Vesicular lesions (n=41, 15%) Livedo reticularis (n=4, 1%) Urticarial lesions (n=26, 9%) Petechial lesions (n=7, 3%) Other types of lesions (n=41, 15%) Chilblain like: 106/142 acral lesions	Location of 34 acral lesions: Hands (n=23, 68%) Face (n=18, 53%)
Docampo-Simon <i>et al.</i> (2020) ³⁵	Total population: 58 patients Age, median (range): 14 years (3 months–85 years) 29 male (50%), 29 female (50%) Skin lesions: 58/58 (100%) Chilblain like: 42/58 (72.4%)	SARS-CoV-2 PCR in 39 patients (67%): Positive: 1/39 (2.56%) Negative: 38/39 (97.4%)	Classification: Chilblain-like lesions (n=42) Purpuric (n=3) Maculopapular (n=3) Vesiculobullous (n=3) Eczematous (n=3) Paronychia (n=2) Ulcer (n=1) Desquamation (n=1)	Location of ALL lesions: Hands (n=9, 15.5%) Feet (n=36, 62.1%) Hands and Feet (n=13, 22.4%)
Duong <i>et al.</i> (2020) ³⁶	Total population: 295 patients Age/gender NR Skin lesions: 295/295 (100%) Chilblain like: 146/295 (49.5%)	N/A	Classification: Chilblain-like lesions (n=146), Other manifestations such as urticaria, rash, chicken pox like, or pityriasis rosea (n=149)	N/A
El Hachem <i>et al.</i> (2020) ³⁹	Total population: 19 patients Age, mean (range): 14 years (11–17) Skin lesions: 19/19 (100%) Chilblain like: 19/19	SARS-CoV-2 PCR: Negative: 19/19	Acral chilblain-like lesions: Swelling, erythema, purpuric macules and papules, pustules, and crusts.	Lesions almost exclusively located on feet, predominately distributed to distal toes. In addition to toes, 9 patients also had lesions on soles and heel. Minority of patients had only hand lesions.

(continued)

Table 3. (Continued)

Article and Year	Number of Patients, Age, Gender	Suspected or Confirmed COVID-19	COVID-19 Cutaneous Manifestations	Anatomical Location of Cutaneous Manifestations
Fernandez-Nieto <i>et al.</i> (2020) ²⁹	Total population: 346 patients Skin lesions: 132/346 (38%) Age, mean (range): 19.9 years (1–56) 71 male (53.8%), 61 female (46.2%) Chilblain like: 95/132 (72%) Age, mean (range): 23.4 years (2–56) 49 male (51.6%), 46 female (48.4%)	SARS-CoV-2 PCR in 11 patients (8.33%): Positive: 2/11 (18.2%) Negative: 9/11 (81.8%)	Acral lesions: Chilblain like ($n=95$, 72%) Erythema multiforme like ($n=37$, 28%)	Location of lesions: Hands ($n=33$, 34.7%) Feet ($n=73$, 76.8%) Distribution: Digital ($n=87$, 91.6%) Dorsal ($n=23$, 24.2%) Ventral ($n=3$, 3.2%) Heels/wrists ($n=12$, 12.6%)
Freeman <i>et al.</i> (2020) ³⁴	Total population: 505 patients Skin lesions: 505/505 (100%) Chilblain like: 318/505 (63%) Age, mean (IQR): 25 years (17–38) 163 male (51%), 155 female (49%)	Confirmed: 23/318 (7.23%) Suspected: 295/318 (92.8%)	Acral chilblain-like lesions: Acrocyanosis in 9.2% Acral desquamation in 4.4%	Location of lesions: Only on feet (84%) Only on hands (5.1%) Combination of hands and feet (10%)
Galvan <i>et al.</i> (2020) ¹¹	Total population: 375 patients 153 males (40.8%), 222 females (59.2%) Skin lesions: 375/375 (100%) Chilblain like: 71/375 (19%) Age, mean (SD): 32.5 years (21.5) 23 male (32%), 48 female (68%)	Laboratory confirmation of SARS-CoV-2 Patients with skin lesions: Confirmed: 234/375 (62.4%) Suspected: 141/375 (37.6%) Chilblain-like patients: Confirmed: 29/71 (41%) Suspected: 42/71 (59%)	Classification: Pseudo-chilblain (19%) Vesicular eruptions (9%) Urticarial lesions (19%) Maculopapular eruptions (47%) Livedo or necrosis (6%)	Hands or Feet Usually asymmetrically
Garcia-Lara <i>et al.</i> (2020) ⁴¹	Total population: 27 patients Age, mean: 14.4 years 18 male (66%), 9 female (34%) Skin lesions: 27/27 (100%) Chilblain like: 25/27 (92.6%)	SARS-CoV-2 tests: PCR negative ($n=2$) IgM negative ($n=9$) IgA negative ($n=9$) IgG negative ($n=9$)	Classification: Chilblain-like lesions ($n=25$, 92.6%) Erythema multiforme-like rash ($n=2$, 7.4%)	Location of lesions: Only on feet (74%) Only on hands (22%) Combination of hands and feet (4%)
Gaspari <i>et al.</i> (2020) ⁴²	Total population: 20 patients Age, median: 51 years 17 male (85%), 3 female (15%) Skin lesions: 18/20 (90%) Chilblain like: 6/18 (33.3%)	Confirmed: 18/18	Classification: Exanthematic rashes ($n=9$, 50%) Acral vasculitis eruptions ($n=6$, 33.3%) Polymorpho-like urticaria ($n=2$, 11.1%) Varicelliform eruption ($n=1$, 5.55%)	Located on extremities of patients
Recalcati <i>et al.</i> (2020) ⁵	Total population: 14 patients Age, mean (range): 14.4 years (13–18), $n=11$ Age, mean (range): 29 years (23–39), $n=3$ 6 male (42.9%), 8 female (57.1%) Skin lesions = 14/14 (100%)	SARS-CoV-2 PCR in 5 patients (35.7%): Negative: 5/5	Classification: Pernio-like lesions ($n=14$) Erythematopapular targetoid lesions ($n=2$) Description: Acral eruption of erythematoviolaceous papules and macules	Location of lesions: Feet ($n=8$) Hands ($n=4$) Both hands and feet ($n=2$)
Rubio-Muniz <i>et al.</i> (2020) ¹⁴	Total population: 34 patients Age, median (range): 54.5 years (31–66) 14 male (41%), 20 female (59%) Skin lesions: 34/34 (100%) Chilblain like: 9/34 (26.5%)	COVID-19 diagnosis (total population): Positive PCR: 17/34 (50%) Positive radiology: 8/24 (23.5%) Negative PCR: 9/34 (26.5%) COVID-19 diagnosis (pseudo-chilblain): 9 cases with livedo: 1 case: Positive PCR: 2/10 (20%) Positive radiology: 2/10 (20%) Negative PCR: 6/10 (60%)	Classification: Maculopapular ($n=10$) Pseudo-chilblain ($n=9$) Targetoid lesions ($n=5$) Palpable purpura ($n=4$, of which 2 cases are with vesicular lesions) Acute urticaria ($n=3$) Vesicular ($n=2$, these also have palpable purpura) Remaining 3 cases include livedo reticularis, urticarial exanthem, and prurigo lesions.	N/A

IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; IQR, interquartile range.

lar coagulation (DIC) from initial reports from Wuhan, China. The three main hypotheses of the article were confounding factors, postviral immune response, or immune antiviral response.⁴⁴ In regard to a hypercoagulable state, one of the studies

reported the presence of microthrombi.³⁹ Recent studies have not been able to associate chilblain-like lesions with positive COVID-19 infections; therefore; these lesions should not be considered an accurate indicator for diagnosis of COVID-19.^{45,46}

Other significant hypotheses about the potential causes of chilblain-like lesions have been provided in Table 9.

Vesicular lesions

Vesicular is a descriptive term used to characterize lesions that are clear fluid-filled sacs under the epidermal layer. These lesions are commonly referred to as blisters and tend to be less than 1 cm in diameter, with many often appearing in clusters. Most common causes are heat, contact dermatitis, medications, autoimmune, or infectious (bacterial or viral). Examples of viral infections that display vesicular lesions include varicella-zoster, herpes simplex, coxsackievirus, and echovirus infections.⁴⁷

The prevalence of vesicular lesions among COVID-19 patients with cutaneous manifestations is not very common when compared to the lesions mentioned earlier (Fig. 5). Various studies have reported percentages ranging from 3.77% to 15%. Vesicular lesions typically appear in middle-aged patients^{11,15,48–50} (Table 4). The trunk of the body was the most common location for this type of rash; however, a fair number of these lesions were also identified on the extremities.^{11,15,16,48–50} A prospective study conducted by Fernandez-Nieto *et al.* was able to further characterize vesicular rash. Among 22 patients with vesicular lesions, 75% of them presented with a diffuse pattern of polymorphic lesions and 25% displayed a localized pattern of monomorphic lesions on the trunk.⁴⁸ Other cases have also identified monomorphic vesicles located on the trunk.^{11,16} The time of onset of cutaneous manifestations relative to other COVID-19 symptoms varied between the few studies reported.

A study from Spain found the majority of vesicular lesions to occur at the same time as other systemic symptoms,¹¹ while two studies from Italy reported most of their lesions appearing after COVID-19 symptoms.^{48–50} The studies with later onset of cutaneous manifestations had median latency times of 3 days and 14 days.^{48–50} Despite differences in rash onset, the studies did report a few cases of vesicular lesions appearing before COVID-19 symptoms. Duration of rash in the Spanish study was 8.4 days on average.¹¹ The two Italian studies reported median duration of rash being 8 and 10 days.^{48,49} Prevalence of additional pruritic symptoms among patients with vesicular lesions fluctuated between 40.9% and 83.3% depending on which study.^{11,48–50} Vesicular lesions are thought to be associated with intermediate severity of COVID-19.^{11,48} Histopathological examination was performed in two studies and both described their

findings as being consistent with known viral infections.^{48,49} In the first study, the skin biopsies of two cases revealed presence of intraepidermal vesicles associated with mild acantolysis and ballooned keratinocytes.⁴⁸ Second study conducted skin biopsies in seven patients with histological examination showing “basket-wave hyperkeratosis; slightly atrophic epidermis; and vacuolar degeneration of the basal layer with multinucleate, hyperchromatic keratinocytes and dyskeratotic cells.”⁴⁹

There are a few theories regarding the pathophysiologic mechanisms involved with vesicular lesions. Criado *et al.* mentioned that vesicular eruption could be a result of immune system overactivity causing a potential “cytokine storm” involving the skin.³⁰ The same study hypothesized a direct cytopathic effect of SARS-CoV-2 on endothelium dermal vessels could produce vesicular lesions.³⁰ Unlike maculopapular and urticarial lesions, vesicular lesions associated with COVID-19 are thought to be etiologically unrelated to antiviral drugs or other COVID-19 treatments.⁴⁸ Finally, vesicular lesions have been described as “specific cutaneous manifestations” of COVID-19; therefore, their identification could potentially be useful for diagnosis. Other significant hypotheses about the potential causes of vesicular lesions have been provided in Table 9.

Petechiae/purpura lesions

Petechiae are typically described as being small nonblanching spots that are less than 2 mm in diameter.^{51,52} These miniature lesions are characterized as nonblanching due to them not vanishing after brief pressure is applied to the skin manifestation area. If the nonblanching lesions are greater than 2 mm in diameter, they are labeled as purpura. These subdermal hemorrhages have many pathophysiological causes, including “thrombocytopenia, platelet dysfunction, disorders of coagulation, and loss of vascular integrity.”⁵¹ Petechial rashes are associated with some viral infections, including enterovirus, parvovirus B19, and dengue virus.⁵¹

Petechiae/purpura rashes are among the less commonly described cutaneous manifestations in association with COVID-19 (Fig. 6). A retrospective study from France consisting of 277 patients with skin lesions reported petechial patterns present in only 3% of patients (Table 5). The lesions were located diffusely, acral, or on limbs.¹⁵ Another study involving petechial purpuric rash noticed that the majority of cases were petechiae located on distal extremities.¹⁶ Two case series with a small number of petechiae/purpuric lesions reported their onset



Figure 5. Examples of vesicular rash seen during the COVID-19 pandemic. (A) Vesicular lesions, characterized as monomorphic, dispersed along patient's back. (B) Polymorphic vesicular lesions diffusely affecting patient's entire trunk and upper/lower extremities. (C) Vesicular lesions scattered or clustered along patient's trunk. (D) Maculopapular lesions disseminated along patient's trunk with additional vesicular lesions located on distal upper extremities (hands). (E) Vesicular rash localized to patient's anterior trunk with lesions appearing as monomorphic. (F) Patient's palmar surfaces exhibiting vesicles. (G) Dispersed vesicular rash appearing on the anterior trunk of a patient. (H) Patient presented with atypical papulovesicular eruptions, in addition to the purpuric lesions. (I) Vesicular rash, similar in appearance to chicken pox, located along patient's anterior trunk. (J) "Histological examination showing an intraepidermal vesicle containing scattered multinucleated and ballooned keratinocytes, with mild acantolysis." (K) "A deeper section of the vesicle reveals more extensive damage, with epidermal detachment and confluent keratinocytic necrosis. The vesicle contains fibrinoid material with acute inflammation." Reproduced with permission from John Wiley and sons (A–H, J–K); Wolters Kluwer Health, Inc. (I). The following original reports are credited: Galván Casas *et al.*¹¹; Fernández-Nieto *et al.*⁴⁸; Marzano *et al.*⁵⁰; Rubio-Muniz *et al.*¹⁴; Gianotti *et al.*¹⁸

to be after COVID-19 symptoms.^{14,53} De Giorgi *et al.* stated that diffuse petechiae and generalized palpable purpura usually appeared in cases with a greater severity of infection.¹⁷ This statement was supported through a case series conducted in Spain claiming that palpable purpuric lesions, present in 4 of 34 cases (11.8%), were more frequent in middle-

aged patients recovering from severe COVID-19 infections. Interestingly, of the four patients presenting with palpable purpuric lesions, two of them additionally exhibited atypical polymorphic papulovesicular eruptions, while a third patient also displayed an urticarial exanthem.¹⁴ A rare case of necrotic purpura was reported among 2 purpura

Table 4. Demographic and clinical details of vesicular lesions observed in COVID-19 patients

Article and Year	Number of Patients, Age, Gender	Suspected or Confirmed COVID-19	COVID-19 Cutaneous Manifestations	Anatomical Location of Cutaneous Manifestations
Askin <i>et al.</i> (2020) ¹⁶	Total population: 210 patients Male age, mean: 57.44 ± 17.259 years Female age, mean: 58.80 ± 15.918 years 123 male (58.6%), 87 female (41.4%) Skin lesions: 52/210 (24%): 33 male (26.8%), 19 female (21.8%) Vesicular: 3/52 (5.8%)	SARS-CoV-2 PCR in total population, PCR performed in 158 patients: Positive: 88/158 (55.7%) Negative: 70/158 (44.3%) SARS-CoV-2 PCR in 52 patients with cutaneous findings: Positive: 34/52 (65.4%) Negative: 18/52 (34.6%)	Classification of 52 patients with skin lesions: Erythematous scaly rash (<i>n</i> =17, 32.7%) Maculopapular rash (<i>n</i> =12, 23%) Urticarial lesions (<i>n</i> =7, 3.5%) Petechial purpuric rash (<i>n</i> =4, 7.7%) Necrosis (<i>n</i> =4, 7.7%) Enanthema, aphthous stomatitis (<i>n</i> =3, 5.8%) Vesicular rash (<i>n</i> =3, 5.8%) Pernio (<i>n</i> =1, 1.9%)	Location of vesicular lesions: A couple of them were “unilateral and monomorphic on the upper part of the trunk”
Bouaziz <i>et al.</i> (2020) ⁴⁴	Total population: 14 patients Age/gender NR Skin lesions: 14/14 (100%) Vesicular: 2/14 (14.3%)	SARS-CoV-2 PCR in 14 patients: Positive: 14/14 (100%)	Inflammatory lesions: 7/14 Exanthema (<i>n</i> =4) Chicken pox-like virus (<i>n</i> =2) Cold urticaria (<i>n</i> =1) Vascular lesions: 7/14 Violaceous macules with “porcelain-like” appearance (<i>n</i> =1) Livedo (<i>n</i> =1) Non-necrotic purpura (<i>n</i> =1) Necrotic purpura (<i>n</i> =1) Chilblain appearance with Raynaud’s phenomenon (<i>n</i> =1) Chilblain (<i>n</i> =1) Eruptive cherry angioma (<i>n</i> =1)	N/A
De Giorgi <i>et al.</i> (2020) ¹⁷	Total population: 678 patients Skin lesions: 53/678 (7.8%) Age, mean (range): 55.9 years (28–69) 32 male (60%), 21 female (40%) Vesicular: 2/53 (4%)	SARS-CoV-2 PCR in 678 patients: Positive: 678/678 (100%)	Inflammatory manifestations: Erythematous rash (<i>n</i> =37, 70%) Diffuse urticaria (<i>n</i> =14, 26%) Varicelliform rash—vesiculation (<i>n</i> =2, 4%) Vascular manifestations: Diffuse petechiae, purpura, and acro-ischemia (25%)	Location of ALL lesions: Trunk Upper limbs
de Masson <i>et al.</i> (2020) ¹⁵	Total population: 277 patients Age, mean (range): 27 years (2–98) “Half of patients were male” Skin lesions: 277/277 (100%) Vesicular: 41/277 (15%) Age, median (range): 43 years (8–74) 22 male (57.9%), 16 female (42.1%)	SARS-CoV-2 PCR in 34 patients (12%): Positive: 25/34 (73.5%) Negative: 9/34 (26.5%)	Classification of skin lesions: Morbilliform lesions (<i>n</i> =25, 9%) Acral lesions (<i>n</i> =142, 51%) Vesicular lesions (<i>n</i> =41, 15%) Livedo reticularis (<i>n</i> =4, 1%) Urticarial lesions (<i>n</i> =26, 9%) Petechial lesions (<i>n</i> =7, 3%) Other types of lesions (<i>n</i> =41, 15%) Description of vesicular: Vesicles/varicella-like lesions = 21/41 (51%) Acral dyshidrosis-like lesions = 20/41 (49%)	Vesicles/varicella-like lesion locations: Trunk and limbs Dyshidrosis-like lesion location: Acral
Fernandez-Nieto <i>et al.</i> (2020) ⁴⁸	Total population: 24 patients: Skin lesions: 24/22 Vesicular: 24/24 Age, mean (range): 45 years (19–65) 6 male (25%), 18 female (75%)	SARS-CoV-2 PCR: Positive: 24/24 (100%) (Positive nasopharyngeal swab)	Classification: Disseminated pattern in 18 pts (75%)— Diffuse described as small papules, vesicles, pustules with varying sizes (7–8 mm in diameter), also lesions appeared in different stages. Localized pattern in 6 patients (25%)— Localized pattern was monomorphic, 3–4 mm diameter, same stage of evolution	Location of vesicular lesions: Head (<i>n</i> =4, 22.2%) Anterior trunk (<i>n</i> =17, 94.4%) Posterior trunk (<i>n</i> =12, 66.7%) Arms (<i>n</i> =8, 44.4%) Legs (<i>n</i> =10, 55.6%) Palms/soles (<i>n</i> =2, 11.1%)
Galvan <i>et al.</i> (2020) ¹¹	Total population: 375 patients 153 males (40.8%), 222 females (59.2%) Skin lesions: 375/375 (100%) Vesicular: 34/375 (9%) Age, mean (SD)=45.6 years (20) 15 male (44%), 19 female (56%)	Laboratory confirmation of SARS-CoV-2 Patients with skin lesions: Confirmed: 234/375 (62.4%) Suspected: 141/375 (37.6%) Vesicular patients: Confirmed: 17/34 (50%) Suspected: 17/34 (50%)	Classification: Pseudo-chilblain (19%) Vesicular eruptions (9%) Urticarial lesions (19%) Maculopapular eruptions (47%) Livedo or necrosis (6%)	Location of vesicular lesions: Trunk and limbs.
Marzano <i>et al.</i> (2020) ⁴⁹	Total population: 22 patients Age, median: 60 years 16 male (72.7%) and 6 female (27.3%) Skin lesions = 22/22 (100%)	SARS-CoV-2 PCR: Positive: 12/22 Negative: 7/22 Not tested: 3/22	Classification: Varicella-like exanthem, papulovesicular pattern with predominance of papules or vesicles in individual patients	Vesicular lesions: Scattered (<i>n</i> =16) Diffuse (<i>n</i> =6) Truncal involvement (<i>n</i> =22) Limbs (<i>n</i> =4)
Recalcati <i>et al.</i> (2020) ⁵	Total population: 88 patients Age/gender—N/A Skin lesions: 18/88 (20.5%) Vesicular: 1/18 (5.56%)	SARS-CoV-2 PCR: Positive: 18/18	Classification: Erythematous rash (<i>n</i> =14) Widespread urticaria (<i>n</i> =3) Chicken pox-like vesicles (<i>n</i> =1)	Trunk was the primary location for all lesions.



Figure 6. Examples of petechial/purpuric rash seen during the COVID-19 pandemic. **(A)** Purpuric rash thought to be associated with mild COVID-19 infections according to Wollina *et al.* **(B)** Rash on patient's chest is described as erythematous. Additional petechial lesions are exhibited on patient's abdomen and arms. **(C)** Purpuric lesions present on knees of patient. **(D)** Palpable purpuric lesions, resulting from subdermal hemorrhages, were distally located on lower extremity of COVID-19 hospitalized patient. **(E)** Maculopapular purpuric exanthema presenting symmetrically on the trunk of a 59-year-old man with severe respiratory failure due to COVID-19. **(F)** Purpuric eruption on the distal upper extremities of a 59-year-old man with severe COVID-19 infection. **(G, H)** "Skin biopsy revealed a dermal perivascular neutrophilic infiltrate (H&E, 10 \times) with sparse leukocytoclasia, red blood cell extravasation, and fibrinoid necrosis (H&E, 40 \times)." Reproduced with permission from John Wiley and sons **(A, H)**. The following original reports are credited: Wollina *et al.*⁴³, Marzano *et al.*⁵⁰, Rubio-Muniz *et al.*¹⁴, Caputo *et al.*⁵²

cases seen in 14 positive COVID-19 patients with cutaneous manifestations.⁴⁴ Finally, a case series of five patients suffering from respiratory failure due to severe COVID-19 infections had three of the patients exhibiting purpuric skin rashes.⁵³ Histopathological examination involving one of these patients with retiform purpura showed significant interstitial and perivascular neutrophilia along with prominent leukocytoclasia.⁵³

Proposed pathogenesis for petechiae/purpura skin lesions involves a "pauci-inflammatory thrombogenic vasculopathy." Immunohistochemistry performed by Magro *et al.* displayed extensive deposition of complement components C5b-9 and C4d within the cutaneous microvasculature of both lesional and nonlesional (normal appearing) skin. These complement components could sometimes be seen colocalized with COVID-19 spike glycoproteins.⁵³ Due to the severity of COVID-19 cases seen with petechiae/purpura an alternate etiology of the lesions could involve adverse dermatological effects associated with potential COVID-19 drugs. Cutaneous side effects of high-dose IVIG treatments include petechiae among many others. Purpura is an adverse skin effect of the possible anti-COVID-19 agent camostat mesylate.²⁰ Finally, a direct cutaneous manifestation from SARS-CoV-2 could be a possibility considering petechiae are the result of other viral infec-

tions. Other significant hypotheses about the potential causes of petechiae/purpura lesions have been provided in Table 9.

Livedoid eruption lesions

Livedo reticularis (LR) is a transient or persistent cutaneous manifestation that classically presents with a reticular (net-like, lace-like) pattern of reddish-blue to purple mottled discolorations (Fig. 7). This dermatosis is a consequence of disturbed cutaneous vasculature yielding diminished blood flow and deoxygenated hemoglobin to the skin. Benign manifestations of livedoid eruptions that primarily occur due to physiological conditions (*cutis marmorata*) or idiopathically are referred to as being LR. Livedoid eruptions that occur secondary to pathological conditions are termed livedo racemosa (LRC).⁵⁴ LRC presents as a permanent manifestation while exhibiting a more widespread appearance on the body and a broken/irregular shape compared to LR.⁵⁴

Livedoid eruptions appear to be one of the least common cutaneous manifestations reported during the COVID-19 pandemic (Table 6). In a study of 375 confirmed COVID-19 patients with cutaneous manifestations, only 6% of them presented with varying degrees of livedoid lesions and necrosis.¹¹ Anatomical locations for these lesions include the

Table 5. Demographic and clinical details of petechiae/purpura lesions observed in COVID-19 patients

Article and Year	Number of Patients, Age, Gender	Suspected or Confirmed COVID-19	COVID-19 Cutaneous Manifestations	Anatomical Location of Cutaneous Manifestations
Askin <i>et al.</i> (2020) ¹⁶	Total population: 210 patients Male age, mean: 57.44 years (17.259) Female age, mean: 58.80 years (15.918) 123 male (58.6%), 87 female (41.4%) Skin lesions: 52/210 (24%) 33 male (26.8%), 19 female (21.8%) Petechiae/Purpura: 4/52 (7.7%)	SARS-CoV-2 PCR in total population, PCR performed in 158 patients: Positive: 88/158 (55.7%) Negative: 70/158 (44.3%) SARS-CoV-2 PCR in 52 patients with cutaneous findings: Positive: 34/52 (65.4%) Negative: 18/52 (34.6%)	Classification from 52 patients with skin lesions: Erythematous scaly rash (<i>n</i> = 17, 32.7%) Maculopapular rash (<i>n</i> = 12, 23%) Urticarial lesions (<i>n</i> = 7, 3.5%) Petechial purpuric rash (<i>n</i> = 4, 7.7%) Necrosis (<i>n</i> = 4, 7.7%) Enanthema, aphthous stomatitis (<i>n</i> = 3, 5.8%) Vesicular rash (<i>n</i> = 3, 5.8%) Pernio (<i>n</i> = 1, 1.9%)	Location of petechial lesions: Petechiae located on distal extremities (<i>n</i> = 3) Generalized petechial purpuric eruption (<i>n</i> = 1)
Bouaziz <i>et al.</i> (2020) ⁴⁴	Total population: 14 patients Age/gender N/A Skin lesions: 14/14 (100%) Purpura: 2/14 (14.3%) Non-necrotic purpura: 1/14 Necrotic purpura: 1/14	SARS-CoV-2 PCR in 14 patients: Positive: 14/14 (100%)	Inflammatory lesions = 7/14: Exanthema (<i>n</i> = 4) Chicken pox-like virus (<i>n</i> = 2) Cold urticaria (<i>n</i> = 1) Vascular lesions = 7/14: Violaceous macules with "porcelain-like" appearance (<i>n</i> = 1) Livedo (<i>n</i> = 1) Non-necrotic purpura (<i>n</i> = 1) Necrotic purpura (<i>n</i> = 1) Chilblain appearance with Raynaud's phenomenon (<i>n</i> = 1) Chilblain (<i>n</i> = 1) Eruptive cherry angioma (<i>n</i> = 1)	NA
de Masson <i>et al.</i> (2020) ¹⁵	Total population: 277 patients Age, mean (range): 27 years (2–98) "Half of patients were male" Skin lesions: 277/277 (100%) Petechial: 7/277 (3%) Age, mean (range): 21 years (5–70) 5 male (71.4%), 2 female (28.6%)	SARS-CoV-2 PCR completed in 34 (12%) patients: Positive: 25/34 (73.5%) Negative: 9/34 negative (26.5%)	Classification: Morbilliform lesions (<i>n</i> = 25, 9%) Acral lesions (<i>n</i> = 142, 51%) Vesicular lesions (<i>n</i> = 41, 15%) Livedo reticularis (<i>n</i> = 4, 1%) Urticarial lesions (<i>n</i> = 26, 9%) Petechial lesions (<i>n</i> = 7, 3%) Other types of lesions (<i>n</i> = 41, 15%)	Location of petechial lesions: Diffuse (<i>n</i> = 3, 43%) Acral (<i>n</i> = 2, 29%) Limbs (<i>n</i> = 2, 29%)
Docampo-Simon <i>et al.</i> (2020) ³⁵	Total population: 58 patients Age, median (range): 14 years (3 months–85 yrs) 29 male (50%), 29 female (50%) Skin lesions: 58/58 (100%) Purpuric: 3/58 (5.17%)	SARS-CoV-2 PCR performed in 39 (67%) patients: Positive: 1/39 (2.56%) Negative: 38/39 (97.4%)	Classification: Chilblain-like lesions (<i>n</i> = 42) Purpuric (<i>n</i> = 3) Maculopapular (<i>n</i> = 3) Vesiculobullous (<i>n</i> = 3) Eczematous (<i>n</i> = 3) Paronychia (<i>n</i> = 2) Ulcer (<i>n</i> = 1) Desquamation (<i>n</i> = 1)	Location of ALL lesions: Hands (<i>n</i> = 9, 15.5%) Feet (<i>n</i> = 36, 62.1%) Hands and Feet (<i>n</i> = 13, 22.4%)
Magro <i>et al.</i> (2020) ⁵³	Total population: 5 patients Skin lesions: 3/5 (60%) 1 male, age 32 years old 2 females, ages 40 and 66 years Purpuric skin rash: 3/3 (100%)	SARS-CoV-2 PCR: Positive: 5/5 (100%)	Classification: Purpuric lesions (<i>n</i> = 3) Description: Retiform purpura (33.3%) Dusky purpuric patches (33.3%) Mildly purpuric reticulated eruptions (33.3%)	Location of purpuric lesions: Buttocks (retiform purpura) Palms and soles (dusky purpuric patches) Chest, legs, and arms (mildly purpuric reticulated eruptions)
Rubio-Muniz <i>et al.</i> (2020) ¹⁴	Total population: 34 patients Age, mean (range): 54.5 years (31–66) 14 male (41%), 20 female (59%) Skin lesions: 34/34 (100%) Palpable purpura: 4/34 (11.8%) Age, mean (range): 62 years (57–69) 1 male (25%), 3 female (75%)	SARS-CoV-2 PCR: Positive PCR: 17/34 (50%) Negative PCR: 9/34 (26%) Radiological diagnosis: Confirmed: 8/34 (23.5%), 4 with negative PCR Total confirmed: 25/34 (73.5%) Patients with palpable purpura: Positive RT-PCR: 2/4 (50%) Radiological diagnosis: 1/4 (25%) Suspected: 1/4 (25%)	Classification: Maculopapular (<i>n</i> = 10) Pseudo-chilblain (<i>n</i> = 9) Targetoid lesions (<i>n</i> = 5) Palpable purpura (<i>n</i> = 4 of which 2 cases are with vesicular lesions) Acute urticaria (<i>n</i> = 3) Vesicular (<i>n</i> = 2, these also have palpable purpura) Remaining 3 cases include livedo reticularis, urticarial exanthem, and prurigo lesions.	A figure displayed palpable purpura lesions on the lower extremities of a patient suffering from COVID-19 pneumonia.

RT-PCR, reverse transcription polymerase chain reaction.

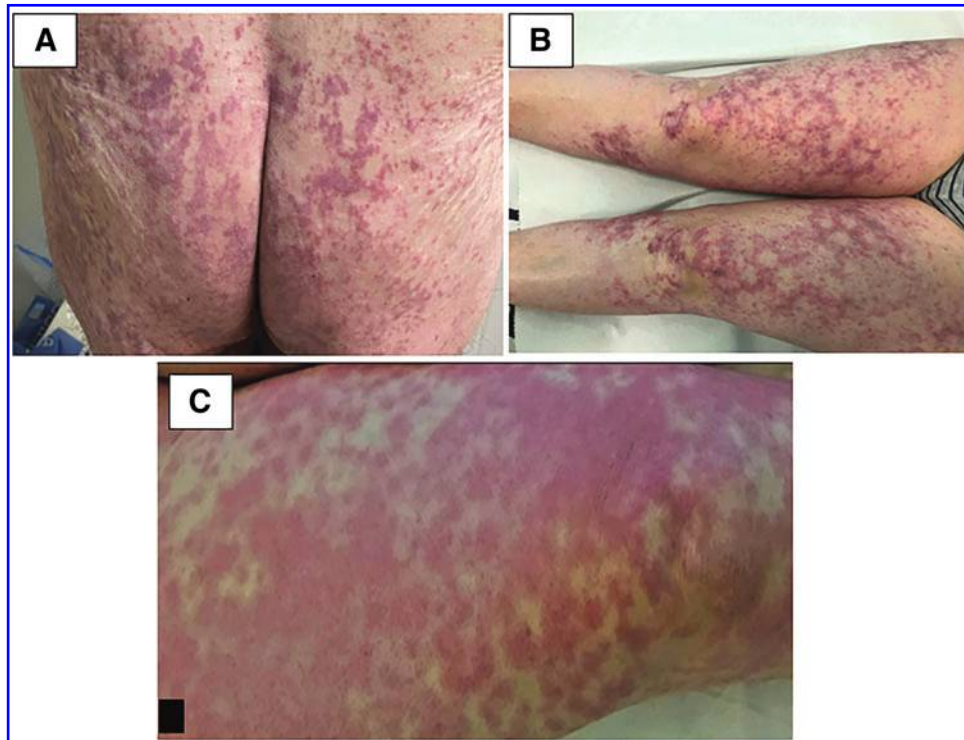


Figure 7. Examples of livedoid rash seen during the COVID-19 pandemic. **(A)** Livedoid lesions, often a product of vasculopathy, present on patient's buttocks. **(B)** Lesions affecting the patient's lower extremities (thighs) are characterized as livedo racemose like. **(C)** Livedoid eruption present in an intubated patient with severe systemic and pulmonary symptoms associated with COVID-19. Reproduced with permission from John Wiley and sons **(A, B)**; Wolters Kluwer Health, Inc. **(C)**. The following original reports are credited: Galván Casas *et al.*⁵²; Marzano *et al.*⁵⁰; Gianotti *et al.*¹⁸

trunk, flexor surface of forearms, dorsal hand, and dorsal foot.^{11,44,55} These lesions occurred at the same time as other Covid-19 symptoms and primarily appeared in elderly patients with more severe infections. Duration of this lesion was 9.4 days on average. According to a Spanish case series, the mortality rate among patients with livedoid lesions was the highest of all cutaneous manifestations at 10%.¹¹

While the molecular mechanisms of livedoid eruptions are not yet known, a few theories have been discussed. One of these theories is the relationship of hypercoagulability to Covid-19 infections. A retrospective study of 183 patients with Covid-19 showed that nonsurvivors of the study had higher D-dimer and fibrin degradation product levels, in addition to a longer prothrombin time, suggesting that patients with severe COVID-19, similar to those presenting with livedoid lesions, are at a greater risk for coagulation abnormalities.⁵⁶ Manalo *et al.* hypothesize that DIC and macrothromboses may be associated to the production of LR in more severe cases of infection. In less severe cases of COVID-19, microthrombi formation created by inflammatory cytokines or ACE2 entry into cells may be impli-

cated in the production of LR.⁵⁷ Other significant hypotheses about the potential causes of livedoid lesions have been provided in Table 9.

Multisystem inflammatory syndrome in children

Throughout the pandemic, children have remained relatively unscathed from severe COVID-19-related complications. This remained true until late April 2020, when multiple reports of critically ill children exhibiting severe inflammatory syndrome with Kawasaki disease-like features were first made public in the United Kingdom.⁵⁸ Verdoni *et al.* later reported that within a short time span, they had witnessed a 30-fold increased incidence of Kawasaki-like disease primarily in children who tested positive for antibodies against SARS-CoV-2.⁵⁹ Since then, cases of this new and serious health condition labeled as MIS-C have grown incrementally throughout the world (Fig. 8). MIS-C is said to exhibit overlapping features of Kawasaki disease and toxic shock syndrome in a minute number of children exposed to COVID-19.⁵⁸ However, it is important to note that MIS-C also has a few noticeable differences when compared to Kawasaki disease such as an older onset (older children and adoles-

Table 6. Demographic and clinical details of livedoid lesions observed in COVID-19 patients

Article and Year	Number of Patients, Age, Gender	Suspected or Confirmed COVID-19	COVID-19 Cutaneous Manifestations	Anatomical Location of Cutaneous Manifestations
Bouaziz <i>et al.</i> (2020) ⁴⁴	Total population: 14 patients Age/gender NR Skin lesions: 14/14 (100%) Livedo: 1/14 (7.1%)	SARS-CoV-2 PCR in 14 patients: Positive: 14/14 (100%)	Inflammatory lesions = 7/14: Exanthema (<i>n</i> =4) Chicken pox-like virus (<i>n</i> =2) Cold urticaria (<i>n</i> =1) Vascular lesions = 7/14: Violaceous macules with "porcelain-like" appearance (<i>n</i> =1) Livedo (<i>n</i> =1) Non-necrotic purpura (<i>n</i> =1) Necrotic purpura (<i>n</i> =1) Chilblain appearance with Raynaud's phenomenon (<i>n</i> =1) Chilblain (<i>n</i> =1) Eruptive cherry angioma (<i>n</i> =1)	Trunk Digital involvement in the feet
Cordoro <i>et al.</i> (2020) ⁵⁵	Total population: 6 patients: Pediatric population, range 12–17 5 male (83.3%), 1 female (16.6%) Skin lesions: 6/6 (100%) Livedo/necrosis: 3/6 (50%)	SARS-CoV-2 PCR: All negative Serology: IgM and IgG negative	Classification: Acral perniosis-like lesions Livedo reticularis Description: Red to violaceous macules and dusky purpuric plaques scattered mid- and distal parts of the toes; severely affected digits with edematous, superficial bullae and focal hemorrhagic crust; petechial and purpuric macules on heels, soles, and dorsolateral foot; few cases with erythematous macule around the distal nail folds; half the cases with livedo reticularis of flexor surface of forearms, dorsal hand, and dorsal feet	Flexor surface of forearm, dorsal hand, and dorsal foot
de Masson <i>et al.</i> (2020) ¹⁵	Total population: 277 patients Age, mean (range): 27 years (2–98) "Half of patients were male" Skin lesions: 277/277 (100%) Livedo reticularis: 4/277 (1.4%)	SARS-CoV-2 PCR completed in 34 (12%) patients: Positive: 25/34 (73.5%) Negative: 9/34 (26.5%)	Classification: Morbilliform lesions (<i>n</i> =25, 9%) Acral lesions (<i>n</i> =142, 51%) Vesicular lesions (<i>n</i> =41, 15%) Livedo reticularis (<i>n</i> =4, 1%) Urticarial lesions (<i>n</i> =26, 9%) Petechial lesions (<i>n</i> =7, 3%) Other types of lesions (<i>n</i> =41, 15%)	Morbilliform—trunk, limbs, and face Acral—hands and feet Vesicular—trunk and limbs Livedo—N/A Urticarial—trunk, limbs, and face Petechial—diffuse, acral, and limbs Other—trunk, limbs, and face Truncal or acral ischemia
Galvan <i>et al.</i> (2020) ¹¹	Total population: 429 patients 54 patients excluded, 375 patients in study, 153 males (40.8%), 222 females (59.2%) Skin lesions: 375/375 (100%) Livedo/necrosis: 21/375 (6%) Age, mean (SD): 63.1 years (17.3) 11 male (52.4%), 10 female (47.6%)	Laboratory confirmation of SARS-CoV-2 Patients with skin lesions: Confirmed: 234/375 (62.4%) Suspected: 141/375 (37.6%) Livedo/necrosis patients: Confirmed: 17/21: (81%) Suspected: 4/21 (19%)	Classification: Vesicles/pustules (pseudo-chilblain) (19%) Vesicular eruptions (9%) Urticarial lesions (19%) Maculopapular eruptions (47%) Livedo or necrosis (6%)	
Rubio-Muniz <i>et al.</i> (2020) ¹⁴	Total population: 34 patients Age, mean (range): 54.5 years (31–66) 14 male (41%), 20 female (59%) Skin lesions: 34/34 (100%) Livedo: 1/34 (2.94%)	SARS-CoV-2 PCR: Positive PCR: 17/34 (50%) Negative PCR: 9/34 (26%) Radiological diagnosis: Confirmed: 8/34 (23.5%), 4 with negative PCR Total confirmed: 25/34 (73.5%)	Classification: Maculopapular (<i>n</i> =10) Pseudo-chilblain (<i>n</i> =9) Targetoid lesions (<i>n</i> =5) Palpable purpura (<i>n</i> =4, of which 2 cases are with vesicular lesions) Acute urticaria (<i>n</i> =3) Vesicular (<i>n</i> =2, these also have palpable purpura) Remaining 3 cases include livedo reticularis, urticarial exanthem, and prurigo lesions.	N/A

cents), abdominal symptoms, and a greater number of cases with heart conditions.⁶⁰

Diagnostic criteria for Kawasaki disease involve a diffuse polymorphic rash, including maculopapular, erythema multiforme like, or diffuse erythroderma.⁶¹ Similar erythematous polymorphic rashes are predominantly seen in patients reported to have MIS-C.⁵⁹ Whittaker *et al.* reported a case series in which 30 of the 58 patients diagnosed with MIS-C had erythematous rashes, with one patient having additional purpuric manifestations.⁶² A retrospective chart review conducted by Miller *et al.* likewise discovered rashes present in 31 out of 44 patients; this was the third most common symptom in patients with MIS-C after fever and gastrointestinal symptoms.⁶³ One study comprised 35 patients positive for MIS-C and described the location of rash seen in 13 patients (37%) as being variably distributed, including limbs, face, and generalized.⁶⁴ Many other studies found rash to be common in MIS-C patients; however, detailed analysis on the type of rash, onset, and duration was not mentioned^{59,65–73} (Table 7). Additional research is needed to study and clarify the skin manifestations of MIS-C and its association with COVID-19.

Etiology of Kawasaki disease is largely unknown, although a genetic predisposition has been established. Similarly, the molecular mechanisms

behind MIS-C's cutaneous manifestations and their relationship to COVID-19 are also unidentified.⁷⁴

DISCUSSION

The COVID-19 pandemic, a consequence of the recent emergence of SARS-CoV-2 in humans, continues to spread rapidly resulting in an ongoing global health crisis. Despite the daily emergence of new data, much remains relatively unknown in regards to COVID-19's clinical characteristics, including its cutaneous manifestations. As a novel strain of the Coronavirus family, which is most commonly known for its respiratory tract infections, SARS-CoV-2 has been associated with many viral exanthems. Although a few respiratory viruses have been associated with cutaneous manifestations in the past,⁴⁷ these rashes are uncharacteristic of the Coronavirus family.⁷⁵ COVID-19's cutaneous manifestations can be divided into two categories, either inflammatory exanthems or vascular lesions.⁷ Knowledge of the changes in skin morphology related to COVID-19 may be instrumental in helping physicians diagnosis and treat future COVID-19 patients.

Patterns of COVID-19 exanthems include maculopapular, urticarial, vesicular, and MIS-C rash. Among these exanthems, maculopapular rashes

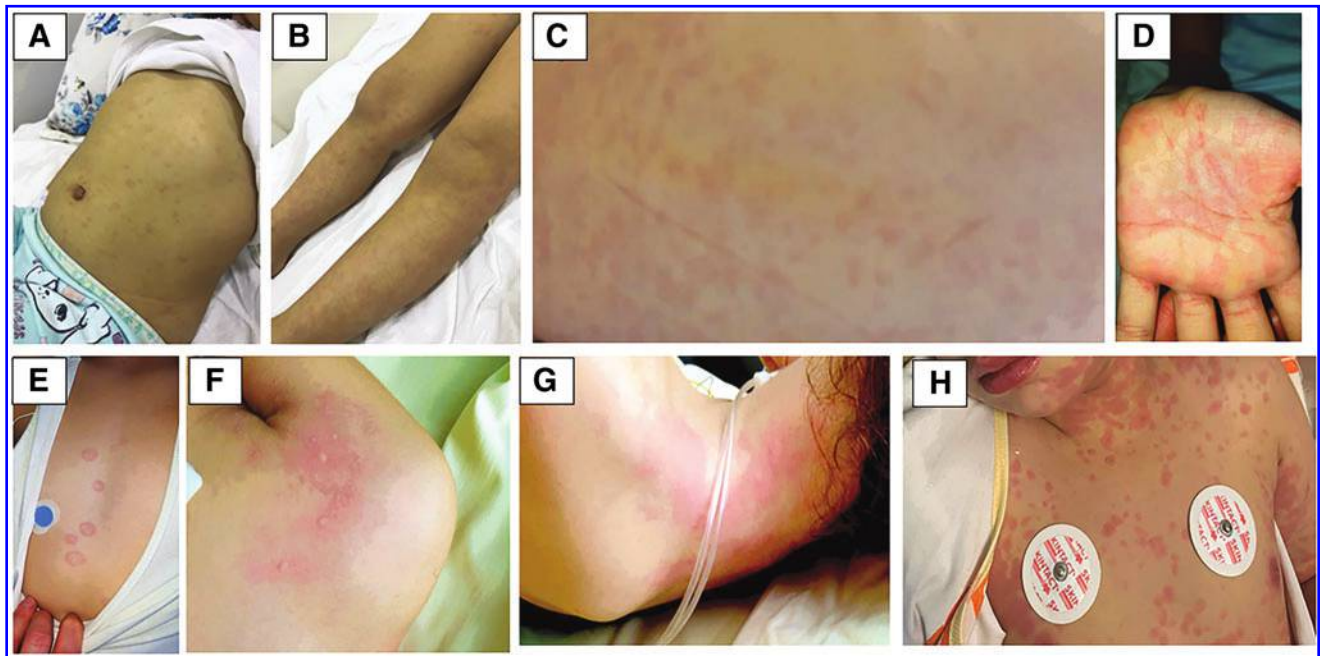


Figure 8. Examples of maculopapular rash seen in MIS-C patients during the COVID-19 pandemic. (A, B) Maculopapular/morbilliform rash, described as polymorphous, present on 3-year old's trunk and lower extremities. (C) Maculopapular rash present in a 12-year-old patient with Kawa-COVID-19. (D–G) Maculopapular lesions present in a 12-year-old girl with MIS-C. (H) Skin rash present on 5-year-old patient with MIS-C. MIS-C, multisystem inflammatory syndrome in children. Reproduced with permission from John Wiley and sons (A, B, H), BMJ Publishing Group Ltd. (C) and Wolters Kluwer Health, Inc. (D–G). The following original reports are credited: Yozgat *et al.*⁷²; Pouletty *et al.*⁶⁷; Belhadjer *et al.*⁶⁵; Bahrami *et al.*⁷³

Table 7. Demographic and clinical details of multisystem inflammatory syndrome in children (Kawasaki like) lesions observed in COVID-19 patients

Article and Year	Number of Patients, Age, Gender	Suspected or Confirmed COVID-19	COVID-19 Cutaneous Manifestations
Belhadjer <i>et al.</i> (2020) ⁶⁵	Total population: 35 patients Age, median (range): 10 years (2–16) 18 male (51%), 17 female (49%) Skin rash: 20/35 (57%)	Positive SARS-CoV-2 PCR: 14/35 (40%) Positive serology: 30/35 (86%) CT chest: typical for infection in 2 patients Total confirmed = 31/35 (88.5%)	Classification: Unspecified MIS-C rash (<i>n</i> = 19) Description: Maculopapular rash seen in one patient, 12-year-old female
Cheung <i>et al.</i> (2020) ⁶⁹	Total population: 17 patients Age, median (range): 8 years (1.8–16) 8 male (47%), 9 female (53%) Skin rash: 12/17 (71%) Skin desquamation: 3/17 (18%)	Positive SARS-CoV-2 PCR: 8 Positive serology: 9 Confirmed: 17/17 (100%)	Classification: Unspecified MIS-C rash (<i>n</i> = 12)
Grimaud <i>et al.</i> (2020) ⁶⁸	Total population: 20 patients Age, median (range): 10 year (2.9–15) 10 male (50%), 10 female (50%) Skin rash: 10/20 (50%)	Positive SARS-CoV-2 PCR: 12/20 (60%) Positive serology: 15/20 (75%) Confirmed: 19/20 (95%) 1 patient with negative PCR and serology however, chest CT chest typical for infection.	Classification: Unspecified MIS-C rash (<i>n</i> = 10)
Hameed <i>et al.</i> (2020) ⁶⁴	Total population: 35 patients Age, median (IQR): 11 years (8) (4/35 patients under the age of 5 years) 27 male (77%), 8 female (23%) Skin rash: 13/35 (37%)	SARS-CoV-2 PCR: 35/35 negative Serology performed in 30 patients: 27/30 positive (90%) 3/30 negative (10%)	Unspecified MIS-C rash (<i>n</i> = 13)
Kaushik <i>et al.</i> (2020) ⁷¹	Total population: 33 patients Age, median (IQR): 10 years (6–13) 20 male (60.6%), 13 female (39.4%) Skin rash: 14/33 (42%)	Positive SARS-CoV-2 PCR: 11/33 (33%) Positive serology: 27/33 (81%) RT-PCR and serology positive: 6 (18%)	Unspecified MIS-C rash (<i>n</i> = 14)
Miller <i>et al.</i> (2020) ⁶³	Total population: 44 patients Age, median (range): 7.3 years (7 months–20 years) (SD 4.98) 20 male (45%), 24 female (55%) Skin rash: 31/44 (70.5%)	SARS-CoV-2 PCR in 44 patients: Positive: 15 (34.1%) Negative: 25 (56.8%) Indeterminate: 4 (9.1%) Serology completed in 32 patients: Positive: 31 (96.9%) Indeterminate: 1 (3.1%)	Unspecified MIS-C rash (<i>n</i> = 44)
Pouletty <i>et al.</i> (2020) ⁶⁷	Total population: 16 patients Age, median (IQR): 10 years (4.7 to 12.5) 8 male (50%), 8 female (50%) Skin rash: 13/16 (81%)	Positive SARS-CoV-2 PCR: 11/16 (69%) Positive serology: 7/8 (87%) Negative using both PCR and serology: 2	Classification: Unspecified MIS-C rash (<i>n</i> = 13) Description: Diffuse skin rash (<i>n</i> = 13) Maculopapular rash (<i>n</i> = 1) Rash/edema of hands and feet (<i>n</i> = 11)
Riollano-Cruz <i>et al.</i> (2020) ⁷⁰	Total population: 15 patients Age, mean (range): 12 years (3–20) 11 male (73%), 4 female (27%) Skin rash: 7/15 (47%)	Positive SARS-CoV-2 PCR: 9/15 (60%) Positive serology: 15/15 (100%) Total confirmed 15/15 (100%)	Classification: Unspecified MIS-C rash (<i>n</i> = 7)
Toubiana <i>et al.</i> (2020) ⁶⁶	Total population: 21 patients Age, median (range): 7.9 years (3.7–16.6) 9 male (43%), 12 female (57%) Skin rash: 16/21 (76%)	Positive RT-PCR: 8/21 (38%) Positive IgG serology: 19/21 (90.5%) Total confirmed 19/21 (90.5%)	Classification: Unspecified MIS-C rash (<i>n</i> = 16) Description: Polymorphous skin rash (<i>n</i> = 16)
Verdoni <i>et al.</i> (2020) ⁵⁹	Total population: 10 patients Age, mean (SD): 7.5 years (3.5) 7 male (70%), 3 female (30%) Skin rash: 8/10 (80%)	Positive SARS-CoV-2 PCR: 2/10 (20%) Positive serology: 8/10 (80%)	Classification: Unspecified MIS-C rash (<i>n</i> = 8) Description: Polymorphous skin rash (<i>n</i> = 8)
Whittaker <i>et al.</i> (2020) ⁶²	Total population: 58 patients Age, median (IQR): 9 years (5.7–14) 25 male (43%), 33 female (57%) Skin rash: 30/58 (52%)	Positive SARS-CoV-2 PCR: 15/58 (26%) for respiratory PCR only Positive IgG antibody: 40/46 (87%) Any SARS-CoV2 PCR or IgG: 45/58 (78%) Patients with erythematous rash: Positive: 21/30 (70%) Negative: 9/30 (30%)	Erythematous rash (<i>n</i> = 30) Purpuric features (<i>n</i> = 1)

MIS-C, multisystem inflammatory syndrome in children.

appear to be the most common followed by urticarial, vesicular, and MIS-C rashes. Maculopapular and urticarial exanthems are more commonly seen in middle-aged to older patients and are typically associated with severe COVID-19 infections. Rash onset of both varies between studies. Both are reported to be unhelpful in diagnosis as the rash can be due to possible drug-induced dermatological adverse reactions. Onset of vesicular eruptions also vary, while the majority are seen after the presentation of systemic symptoms, few cases have noted onset prior to systemic symptoms. The rash was noted frequently among middle-aged patients.

Of note, this type of exanthem is commonly seen in other viral infections, such as varicella zoster and herpes simplex. MIS-C is a novel and severe disease seen in children; therefore, not much is known concerning its clinical characteristics. Despite the lack of information, published data show that skin manifestations appear in a majority of MIS-C patients. There is also a possible correlation with Kawasaki's disease along with an association involving immunoglobulins as a treatment modality.

Vascular lesions associated with COVID-19 are characterized into pseudo-chilblain, petechiae/purpura, or livedoid. Chilblain-like lesions are very similar to pernio lesions that occur after exposure to very cold temperatures; however, unlike pernio, these lesions appear in warmer climates. These lesions are commonly located on the fingers and toes of younger patients and are associated with less severe COVID-19 infections. Onset of pseudo-chilblain lesions is typically after the onset of COVID-19 systemic symptoms. Petechiae/purpura lesions are more common in middle-aged patients. These lesions have been associated with a greater severity of COVID-19 infection. Studies involving these lesions have described their location as being diffuse, acral, or on distal extremities/limbs.^{15,16} Livedoid lesions are among the least common skin manifestations seen during the pandemic. They are primarily seen in elderly patients and have been correlated with particularly severe COVID-19 infections.¹¹

The pathophysiologic mechanisms behind COVID-19's skin manifestations are not well known; however, many theories have been considered. Maculopapular and urticarial rashes are believed to be due to an adverse reaction to pharmaceutical COVID-19 drugs or overproduction of cytokines triggered by hyperinflammation.^{12,20} Possible molecular mechanisms of chilblain-like lesions are numerous, including "immune dysregulation, vasculitis, vessel thrombosis, or neoangiogenesis."⁴⁴ Pathogenesis for petechial/purpuric

skin lesions involves pauci-inflammatory thrombogenic vasculopathy with extensive deposition of complement components C5b-9 and C4d within the cutaneous microvasculature. Alternative etiology of these skin lesions could be adverse dermatological side effects to medications used for COVID-19. Livedoid's molecular mechanisms are hypothesized as being dependent on the severity of the COVID-19 infection. In more severe infections, livedoid eruptions are thought to be due to DIC and macrothromboses. In less severe COVID-19 infections, these vascular lesions are assumed to be a product of microthrombi formation created by inflammatory cytokines or ACE2 entry into cells. Vesicular lesions are thought to result from "cytokine storm" due to hyperactivity of the immune system. Proposed etiology of MIS-C remains unknown. Finally, it should also be noted that the cutaneous manifestations seen during this pandemic might be a direct effect of the SARS-CoV-2 virus.

Although skin rashes as seen in SARS-CoV-2 are unusual in comparison to other coronaviruses, many respiratory viruses have been associated with cutaneous manifestations (Table 8). Similar to SARS-CoV-2, certain adenovirus serotypes can present with maculopapular, vesicular, or petechial exanthems.⁴⁷ Exanthems due to influenza viruses are extremely rare, seen in only 2–8% of cases and present more frequently in children compared to adults.⁴⁷ Skin manifestations seen in influenza A are petechial, macular, papular, maculopapular, reticular, or purpuric patterns, while influenza B exanthems are less common and include localized or generalized morbilliform patterns.⁷⁶

Human bocavirus rashes were primarily seen in children and include maculopapular erythema, macular erythema, and petechial exanthema.^{77,78} Nonpolio enteroviruses, such as echovirus and coxsackie virus, are the leading cause of rashes in children, especially during the summer and fall.⁴⁷ Coxsackievirus causes hand-foot-mouth disease (HFMD) and typically presents with diffuse maculopapular or vesicular exanthems along with a fever.⁴⁷ In addition to HFMD, echoviruses can also cause aseptic meningitis and are known to exhibit macular, maculopapular, petechial, or vesicular rashes.^{47,79} Nonpruritic, maculopapular, and transient rashes were located on the trunk and back of some children with human metapneumovirus infections.⁸⁰ Exanthems described as erythematous, maculopapular, and discrete were found to be associated with rhinoviruses, respiratory syncytial virus, and parainfluenza viruses (types 1–3).^{47,81}

Table 8. Comparative analysis of other respiratory viruses with cutaneous manifestations

	<i>First Circulated</i>	<i>Transmission</i>	<i>Clinical Presentation</i>	<i>Cutaneous Manifestations</i>
Adenoviridae (naked dsDNA)				
Human adenovirus ⁴⁷	1953	Person to person through respiratory droplets, fecal-oral, and close contact. Touching infected objects. (UpToDate)	Respiratory tract infections, including pharyngitis, coryza, otitis media, bronchiolitis, and pneumonia. (UpToDate)	Maculopapular, vesicular, or petechial exanthems. Primarily seen in children, but sometimes in adults.
Coronaviridae (enveloped +ssRNA)				
SARS-CoV ⁷⁵	2003	Person to person through respiratory droplets and close contact. Speculation of fecal-oral or airborne spread. (UpToDate)	3–7 day prodrome with fever, malaise, headache, and myalgias. Respiratory phase begins with nonproductive cough followed by dyspnea. Could lead to respiratory failure. (UpToDate)	None reported
MERS-CoV ⁷⁵	2012	Person to person through respiratory droplets and close contact.	Most common were severe pneumonia, acute respiratory distress syndrome, and acute kidney injury. (UpToDate)	None reported
SARS-CoV-2	2019	Person to person through respiratory droplets and close contact. Touching infected objects.	Fever, cough, myalgia, and pneumonia when severe.	Maculopapular/morbilliform, vesicular, urticarial, livedo/necrosis, MIS-C rash, pseudo-chilblain, petechial.
Orthomyxoviridae (enveloped –ssRNA)				
Influenza A ⁷⁶	1933	Person to person through respiratory droplets and close contact. Touching infected objects.	Fever, headache, myalgia, and malaise. Respiratory tract symptoms include nonproductive cough, sore throat, nasal discharge, and pneumonia. (UpToDate)	Rash characterized as petechial, macular, papular, maculopapular, reticular, or purpuric. Could be localized multifocal, generalized, pruritic, and nonpruritic.
Influenza B ⁷⁶	1940	Person to person through respiratory droplets and close contact. Touching infected objects.	Fever, headache, myalgia, and malaise. Respiratory tract symptoms include nonproductive cough, sore throat, nasal discharge, and pneumonia. (UpToDate)	Localized or generalized morbilliform rash. More common in children than adults.
Parvoviridae (naked ssDNA)				
Human bocavirus 1 ^{77,78}	2005	Not much is known about the routes of transmission. (PMID 18400798)	Cough, fever, rhinorrhea, asthma exacerbation, bronchiolitis, acute wheezing, and pneumonia. Primarily in children.	Maculopapular erythematous rash, macular erythema, and petechial exanthema.
Paramyxoviridae (enveloped –ssRNA)				
Parainfluenza 1–3 ^{47,81}	Late 1950s	Person to person primarily through inhalation of large droplets or fomites. (UpToDate)	Adults: Upper respiratory infections, including fever, rhinorrhea, cough, and/or sore throat. Other symptoms include acute bronchitis and pneumonia. Child: Croup, pneumonia, and bronchiolitis. (UpToDate)	Rash observed in 6.5% of 398 HPIV-infected children. Rash is erythematous, maculopapular, and discrete.
RSV ^{47,81}	1956	Person to person through respiratory droplets and close contact. Touching infected objects.	Infants and young children: lower respiratory tract infections, including bronchiolitis or pneumonia. Older children and adults: upper respiratory tract symptoms, including cough, coryza, rhinorrhea, and conjunctivitis. Also, lower respiratory tract disease. (UpToDate)	Rash more frequent in RSV-B patients compared to RSV-A patients. Rash is erythematous, maculopapular, and discrete.
Picornoviridae (naked +ssRNA)				
Coxsackievirus (enterovirus) ⁴⁷	Late 1940s	Predominantly through direct or indirect oral contact with fecally shed virus. Routes include contaminated water, food, and fomites. (UpToDate)	Begins with low-grade fever and malaise followed by hand-foot-mouth disease.	Diffuse maculopapular or vesicular exanthems.
Echovirus (enterovirus) ^{47,79}	1950s	Predominantly through direct or indirect oral contact with fecally shed virus. Routes include contaminated water, food, and fomites. (UpToDate)	Can cause hand, foot, and mouth disease in children. In adults, it can cause aseptic meningitis, encephalitis, and rarely pleurodynia.	Diffuse erythematous macular/maculopapular/petechial rashes. Disseminated or localized vesicles.
Rhinovirus ^{47,81}	1956	Person to person through respiratory droplets and close contact. Touching infected objects.	Children: Cough, nasal discharge, and obstruction more frequently than adults. May initially have a fever. Adults: Nasal discharge, nasal obstruction, cough, and/or a sore or scratchy throat. No fever. (UpToDate)	Rash is erythematous, maculopapular, and discrete.
Pneumoviridae (enveloped –ssRNA)				
Human metapneumovirus ⁸⁰	2001	Person to person through respiratory droplets and close contact. Touching infected objects. (CDC)	Cough, fever, nasal congestion, and shortness of breath. Can progress to bronchitis and pneumonia. (CDC)	Nonpruritic, maculopapular, and transient rash.

CDC, Centers for Disease Control and Prevention; MERS-CoV, Middle East respiratory syndrome coronavirus; RSV, respiratory syncytial virus.

Table 9. Potential causes of each dermatological findings

Dermatologic Finding	Potential Causes
Maculopapular rash	Viral exanthem, Scarlet fever, measles, rubella, medication reaction, secondary syphilis, heat rash, leukemia, graft-versus-host disease
Urticaria	Allergic reaction, anaphylaxis, angioedema, autoimmune disease (e.g., systemic lupus erythematosus), hypereosinophilia, chronic urticaria, malignancy
Vesicular	Varicella zoster (i.e., chicken pox), herpes zoster (i.e., shingles), herpes simplex, Rhus dermatitis (e.g., poison ivy, poison oak, and poison sumac), pemphigoid
Petechiae/purpura	Thrombocytopenia, systemic lupus erythematosus, leukemia, DIC, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, vasculitis, vitamin C deficiency
Chilblains	Raynaud's phenomenon, systemic lupus erythematosus, systemic sclerosis, Buerger's disease
Livedo racemosa	Antiphospholipid antibody syndrome, Sneddon syndrome, cryoglobulinemia, multiple myeloma, DIC, hemolytic uremic syndrome, deep venous thrombosis, systemic lupus erythematosus, rheumatoid arthritis, polyarteritis nodosa, Sjogren's syndrome, multiple sclerosis, Parkinson's disease, cancer (e.g., renal cell cancer, breast cancer, lymphoma, and leukemia)
Distal ischemia/necrosis	Arterial ischemia, DIC, Buerger's disease

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DIC, disseminated intravascular coagulation.

So far, we have discussed about the virus-induced or drug-induced skin lesions seen in patients infected with SARS-CoV-2. However, this pandemic has silently resulted in additional cutaneous complications, although indirectly through the use of PPE (Fig. 9). These complications include pressure injury, contact dermatitis, urticaria, skin dryness, and aggravation of existing skin diseases.³¹ PPE refers to wearable personal items used to protect against accidental injuries and occupational hazards.⁸² Due to the possible asymptomatic transmission of SARS-CoV-2 among unknowing individuals, the widespread use of PPE has become mandatory for the reduction of infection rates and prevention of viral spread, especially among front-line health care personnel. These individuals must protect both themselves from occupational hazards and their most vulnerable patients by wearing multiple types of PPE equipment, including goggles/disposable face shields, N95 respirator masks, protective gowns, and latex gloves.

Despite the overall benefits of wearing PPE, their frequent and prolonged use among health care personnel during the COVID-19 pandemic have been associated with various adverse skin injuries⁸³ (Fig. 9). PPE-related skin complications are of serious concern since broken cutaneous barriers can create an opening for potential COVID-19 infections and increase contamination by inadvertently spreading the virus.⁸⁴ In the following section, we will discuss the causes and characteristics of skin damage caused by the use of various types of PPE, and introduce the possible measures for skin protection and treatment strategies.

Incidences of PPE-associated skin rashes in COVID-19 pandemic

A cross-sectional study from China reported the overall prevalence of skin injuries instigated by PPE

use in medical personnel to be 42.8% among 4,306 surveyed participants. Analysis of the survey conducted by Jiang *et al.* discovered three main types of skin injuries. These were device-related pressure ulcers (DRPU, now known as pressure injuries), moisture-associated skin damage, and skin tears.⁸³ Multivariate analysis of risk factors related to PPE-induced skin injuries revealed higher prevalence among males, doctors, participants wearing grade 3 PPE opposed as grade 2 PPE, those with daily wearing times greater than 4 hours, age older than 35 years, and finally those who reported heavy sweating.⁸³

Another quantitative study out of China surveyed 61 health care workers regularly using PPE (N95 mask, latex gloves, and protective clothing). Adverse skin reactions were discovered in 95.1% of N95 mask users, the most majority of which being nasal bridge scarring followed by facial itching and skin damage. Around 88.5% of health care workers reported cutaneous complications due to latex gloves. The most common skin reactions by these gloves were dry skin and itching followed by rash and chapped skin. Finally, only 67% of the health care workers reported adverse skin reactions due to protective clothing, the most frequent being dry skin and itching.⁸⁵

Of the cutaneous complications caused by PPE, DRPU/pressure injuries are the most noteworthy. Pressure ulcer/injury is defined by the National Pressure Injury Advisory Panel (NPIAP) as "localized damage to the skin and underlying soft tissue usually over a bony prominence or related to a medical or other device." Before the COVID-19 pandemic, DRPU were primarily seen in patients who were critically ill; however, this pandemic has introduced DRPU as a novel complication resulting in facial injuries among health care personnel wearing PPE.^{86–88} The PPE devices used among medical staff inducing DRPU were



Figure 9. Examples of personal protective equipment-induced pressure ulcers seen during the COVID-19 pandemic. **(A)** Example of N95 respirator mask used by health care professionals. **(B)** Pressure sore, caused by an N95 mask, located on the nasal bridge. **(C)** Possible preventable method includes the application of benzalkonium chloride bridge before wearing mask. **(D)** Device-related pressure injury present on forehead of medical staff member fighting COVID-19 in China. **(E)** Device-related pressure injuries and impressions on face of health care personnel. **(F)** Device-related pressure injury located on the neck. Reproduced with permission from John Wiley and sons **(A–C)**; Mary Ann Liebert, Inc. **(D–F)**. The following original reports are credited: Yin⁹¹; Jiang *et al.*⁸³

N95 respirators, goggles, and protective masks. PPE-induced DRPU in medical staff had an overall prevalence of 30.03%, the highest among PPE-induced skin injuries. For context, a systematic review conducted in 2019 estimated the pooled prevalence of non-PPE-acquired DRPU in adult patients to be only 11%, a number significantly lower compared to DRPU in medical personnel during COVID-19.⁸⁹ The majority of PPE-induced DRPU were located on the nasal bridge and cheeks (59.65%); lesser known locations included the auricle, forehead, zygoma, mandible, and eyebrow arch.⁸⁷ Non-PPE-acquired DRPU locations included head, face, ears, feet, neck, sacrum, and buttocks.⁸⁹ Around 98.84% of DRPU reported in the medical staff belonged to Stage 1 and Stage 2 of pressure ulcer categories. Risk factors for PPE-induced DRPU were similar to those seen in overall PPE-induced skin injuries; however, age was excluded as a significant risk factor.⁸⁷

As mentioned earlier, the PPE primarily responsible for DRPU among the medical staff in China included N95 respirators, goggles, and protective masks.⁸⁷ Etiology of PPE-induced DRPUs is thought to be very similar to etiology of DRPUs from continuous positive airway pressure masks, used for sleep apnea. The proposed mechanism triggering pressure ulcers begins with prolonged use of medical face masks and protective goggles, resulting in facial skin indentation or damage. Movement of facial muscles can inflict frictional damage of the skin caused by tightening of PPE straps and continuous movement of PPE over the skin. This frictional damage can be increased by perspiration of the medical personnel, eventually leading to the shearing of skin and subdermal tissues. In addition, the skin's tolerance to mechanical stress is weakened by increasing humidity at the PPE-skin boundary. As a consequence of these two unfavorable effects to the skin, tissue and cell

deformation can occur, potentially leading to cell death if the deformation is sustained. Cell death can initiate a damaging cycle of DRPU involving inflammation, edema, interstitial pressure, ischemia, and tissue death.⁸⁶ However, this cycle is an unlikely outcome for PPE-induced DRPU due to health care personnel being able to respond when they sense any uncomfortable feeling.⁸⁶

Treatment and management for PPE-induced pressure ulcers

Treatment strategies vary among studies due to the low number of cases reported. Lam *et al.* reported a case series of five health care workers presenting with nasal bridge pressure ulcers associated with N95 respirators.⁸⁸ In all cases, the N95 respirator remained on for an average of 5 h each time the mask was applied. Four of these cases were categorized as grade 1 pressure ulcers and treated with Duoderm Extra Thin dressings (hydrocolloid dressings), while one case was categorized as a grade 3 pressure ulcer and treated with BETAplast.⁸⁸ Thin hydrocolloid dressing was also used as treatment in a case report of a nurse presenting with a grade 2 pressure ulcer on the nasal bridge. This case was also associated with an N95 respirator mask.⁹⁰ One study proposed an improved treatment option for health care personnel involving the addition of a benzalkonium chloride patch to the pressure ulcer before using hydrocolloid dressing and applying the N95 mask. Reasoning behind this method included protection of the existing pressure ulcer, while preventing additional severity of the ulcer when the patch was removed.⁹¹

Other treatment recommendations for PPE-induced ulcers included wet dressing to promote wound convergence, silver ion dressings to prevent infection and secondary damage by frequent dressing replacements, and epidermal growth factor/fibroblast growth factor to stimulate cell proliferation and expedite wound healing.⁸²

Possible complications arising from PPE-induced ulcers could involve an introduction to new infections and a breach of PPE protocol leading to increased contamination. Interestingly, the introduction of viral infections other than COVID-19 or bacterial infections could lead to cutaneous manifestations of their own, mimicking those associated with COVID-19. Due to these complications, prevention of PPE-induced pressure ulcers is paramount. One of the preventative methods discussed include proper PPE training; this could reinforce the proper use of an N95 respirator and discuss problems associated with ex-

Innovation: COVID-19 is an emergent disease, of which there is a clear void in understanding. Current actions are based on scientific information as they emerge. Comprehensive understanding of COVID-19 requires critical examination of all manifestations as evident in patients. A growing body of scientific evidence points toward consistent skin pathologies in COVID-19-affected patients. This article offers a critical review of the current literature on COVID-19 cutaneous manifestations. It also addresses the risk of PPE-associated ulcer in health care providers managing COVID-19.

tremely tight N95 mask securement.⁸⁸ Other preventative measures include the relief of pressure buildup in N95 masks every 2 h and the addition of prophylactic barrier creams at least 30 min before applying the respirator mask.⁸⁸ Finally, wearing a properly fitted mask, correct goggle use, the application of moistures/gels, and management of skin indentations could help protect one from a pressure injury.³¹

There are few limitations of this systematic review. One of them being the large number of suspected, but unverified COVID-19 patients due to lack of testing or faulty tests. Also, studies over the dermatologic side effects of medications are absent. In addition, statistical analysis of the results is lacking due to the vast heterogeneity of cutaneous manifestations, rash onset, duration, and associated symptoms. The primary literature articles included in this study were mainly from France, Spain, Italy, and the United Kingdom. Because a majority of articles originate from Europe, this can present with its own limitations in providing a diverse population/methodology. Finally, some literature reviews concerning the cutaneous manifestations were unable to be translated to English; this may have also interfered with data collection. Careful documentation and examination by physicians experienced with cutaneous manifestations are needed for improved understanding of rashes, treatments, and pathophysiological mechanisms.

MANAGEMENT CONSIDERATIONS OF CUTANEOUS MANIFESTATIONS OF COVID-19

As the number of articles written about COVID-19's cutaneous manifestations increase daily, the same cannot be said for possible treatments options. During primary literature review, most

articles were geared toward the classification, histology, and descriptions of the cutaneous manifestations as well as explanations of possible etiologies. Many reports, including Galvin *et al.*, reported the use of proposed medications for the treatment of COVID-19 itself: hydroxychloroquine, NSAIDs, lopinavir/ritonavir, tocilizumab, azithromycin, and systemic corticosteroids.¹¹ As mentioned, these treatment options were not used for the rash, but many did note skin-associated side effects. For example, Sharma *et al.* reported common adverse reactions of pruritus, urticaria, and erythema multiforme with the use of hydroxychloroquine.⁹² Some of these adverse cutaneous manifestations fall within the abovementioned COVID-19 skin manifestations. However, most of the discussed cutaneous manifestations of COVID-19 have been shown to be self-resolving.⁹³ De Giorgi *et al.* reported spontaneous resolution of inflammatory cutaneous lesions, including vesicular, petechial, and maculopapular lesions.¹⁷ However, Reymundo *et al.* reported use of systemic corticosteroids in six of seven patients in the retrospective study looking into the presence of maculopapular rash.¹³ Cordoro *et al.* reported conservative care for patients with livedo-like lesions.⁵⁵ Few studies also reported spontaneous resolution for chilblain lesions.^{37,39} Mastrolonardo *et al.* proposed the use of topical corticosteroids and antibiotics for chilblains, but only as a means to allow a faster recovery time otherwise the lesions can self-heal.⁹⁴ In the review article by Algaadi, the author noted treatment for urticaria was challenging as there are many triggers that can lead to this type of rash from simple allergic reaction to viral to medication induced. In this review, treatment involved the use of antihistamines with or without steroid use.⁹⁵ Majority of articles covering multisystem inflammatory syndrome (Kawasaki-like rash) reported use of IVIGs.^{65,68,69,96} The exact effects of these treatments on COVID-19 skin manifestations are unclear and need further investigation.

SUMMARY

In conclusion, knowledge of COVID-19 cutaneous manifestations may be vital to early diagnosis and lead to possible better prognosis in COVID-19 patients. This systematic review provides a detailed analysis of the primary skin complications associated with COVID-19 and

TAKE-HOME MESSAGES

- Coronavirus Disease 2019 (COVID-19) is commonly associated with skin pathologies that may lead to lesions
- 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
- Personal protective equipment-related skin wounds are of serious concern since broken cutaneous barriers can create an opening for potential COVID-19 infections
- As the SARS-CoV-2 virus continues to spread silently, mainly through asymptomatic carriers, an accurate and rapid identification of these cutaneous manifestations may be vital to early diagnosis and lead to possible better prognosis in COVID-19 patients.

their plausible underlying molecular mechanisms. Furthermore, the importance and pathogenesis of PPE-induced pressure ulcers are provided, in addition to their possible treatments. Further research concerning COVID-19's cutaneous manifestations is very much needed for a complete analysis of COVID-19.

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Abbreviations and Acronyms

ACE2	=	angiotensin-converting enzyme 2
CDC	=	Centers for Disease Control and Prevention
COVID-19	=	Coronavirus Disease 2019
DIC	=	disseminated intravascular coagulation
DRPU	=	device-related pressure ulcer
H&E stain	=	hematoxylin and eosin stain
HFMD	=	hand-foot-mouth disease
IgA	=	immunoglobulin A
IgG	=	immunoglobulin G
IgM	=	immunoglobulin M
IQR	=	interquartile range
IVIG	=	intravenous immunoglobulin
LR	=	livedo reticularis
LRC	=	livedo racemosa
MERS-CoV	=	Middle East respiratory syndrome coronavirus
MIS-C	=	multisystem inflammatory syndrome in children
N/A	=	not available
NPIAP	=	National Pressure Injury Advisory Panel
NR	=	not reported
NSAIDs	=	nonsteroidal anti-inflammatory drugs
PPE	=	personal protective equipment
PRISMA	=	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RSV	=	respiratory syncytial virus
RT-PCR	=	reverse transcription polymerase chain reaction
SARS-CoV	=	severe acute respiratory syndrome coronavirus
SARS-CoV-2	=	severe acute respiratory syndrome coronavirus 2

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