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REVIEW

Epidemiology and clinical evolution of non-multisystem inflammatory syndrome (MIS-C) dermatological lesions in pediatric patients affected by SARS-CoV-2 infection: A systematic review of the literature

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Abstract

COVID-19 can present with a range of skin manifestations, some of which specific of the pediatric age. The aim of this systematic literature review was to determine the type, prevalence, time of onset, and evolution of cutaneous manifestations associated with COVID-19 in newborns, children, and adolescents, after excluding multisystem inflammatory syndrome in children (MIS-C). PubMed, Tripdatabase, ClinicalTrials, and Cochrane Library databases were searched using an ad hoc string for case reports/series and observational studies, published between December 2019 and February 2022. Study quality was assessed using the STROBE and CARE tools. Seventy-three (49 case reports/series and 24 studies) out of 26,545 identified articles were included in the analysis. Dermatological lesions were highly heterogeneous for clinical presentation, time of onset, and association with other COVID-19 manifestations. Overall, they mainly affected the acral portions, and typically presented a favorable outcome. Pseudo-chilblains were the most common.

Conclusions: Mucocutaneous manifestations could be the only/predominant and early manifestation of COVID-19 that could precede other more severe manifestations by days or weeks. Therefore, physicians of all disciplines should be familiar with them.

What is Known:
- *A variety of cutaneous manifestations have been reported in association with COVID-19.*
- *Urticaria, maculopapular, or vesicular rashes can occur at any age, while chilblains and erythema multiforme are more common in children and young patients.*

What is New:
- *Skin lesions related to SARS-CoV-2 infection often show a peculiar acral distribution.*
- *Mucocutaneous lesions of various type may be the only/predominant manifestation of COVID-19; they could present in paucisymptomatic and severely ill patients and occur at different stages of the disease.*

Keywords COVID-19 · Pseudo-chilblains · Cutaneous acral lesions · Erythema multiforme · Pediatric dermatology

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Abbreviations

COVID-19	Coronavirus disease 2019
EM	Erythema multiforme
IFN-1	Type-I interferon
MIS-C	Multisystem inflammatory syndrome in children
PRISMA	Preferred Reporting Items for Systematic Reviews
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
CARE	CAse REport guidelines
WHO	World Health Organization

Introduction

The first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), was recognized in China in December 2019 [1]. SARS-CoV-2 infection rapidly spread worldwide, and in March 2020, it was declared a global pandemic by the World Health Organization (WHO). Clinical manifestations of COVID-19 are extremely heterogeneous, ranging from mild symptoms affecting the upper airways and the gastrointestinal tract, to severe respiratory failure and septic shock. Young patients are typically asymptomatic or present with mild symptoms, but a few of them can present with severe COVID-19. More rarely, they develop a peculiar hyperinflammatory disorder, multisystem inflammatory syndrome in children (MIS-C), that typically occurs some weeks after the infection and is characterized by persistent fever, gastrointestinal symptoms, mucocutaneous lesions, and, in severe cases, myocarditis, cardiac dysfunction, and acute kidney injury, leading to hypotension and shock [2]. Finally, the long-COVID-19 syndrome may arise [3].

A variety of cutaneous manifestations has been reported in association with COVID-19. Some, like urticaria, maculopapular, or vesicular rashes, can occur at any age, while some others, like chilblains or erythema multiforme (EM), are more common in the pediatric population [4]. Moreover, different skin manifestations have been described at different stages of the COVID-19 disease, sometimes representing the only, or more prominent, and early manifestation.

This systematic review aimed at providing epidemiological and clinical features typical of dermatological manifestations associated with COVID-19 in newborns, children, and adolescents, excluding those associated with MIS-C.

Methods/literature search

We conducted a systematic literature review following the Preferred Reporting Items for Systematic Reviews (PRISMA) approach [5]. Literature search was performed using PubMed (pubmed.ncbi.nlm.nih.gov), Tripdatabase (tripdatabase.com), ClinicalTrials (clinicaltrials.gov), and Cochrane (cochranelibrary.com) databases, using the string: "(((SARS-CoV-2) OR (COVID19) OR (COVID-19) OR (ncov*) OR (coronavirus)) AND ((Child) OR (children) OR (pediatric) OR (paediatric) OR (infant) OR (adolescent)) AND (("2019/12/31"[Date—Entry]: "2022/2/28"[Date—Entry]))".

Articles referring to observational prospective or retrospective studies, case series, and case reports, written in English or in Italian, focusing on skin lesions associated with COVID-19 in people aged < 18 years were initially included. Literature reviews and letters to the Editor; studies of all types in which COVID-19 disease was only clinically suspected but not confirmed biochemically (i.e., molecular or antigenic swab, serology, or RT-PCR on biopsy specimen); and studies not clearly describing clinical presentation and evolution of the dermatological lesions were excluded. Studies involving both pediatric and adult patients were included only if characteristics of people aged < 18 years old were clearly discernible or if they represented a meaningful part of a group/cohort and the mean/median age was < 18 years. The study protocol has been previously published and is available online [6].

Data extraction

Data were extracted by six independent reviewers (AD, DG, FG, GS, LP, MM). Each article retrieved by literature search was then examined by two authors independently, and its eligibility was determined on the basis of the title and the abstract. The inclusion of selected studies in the review was defined according to the information retrieved after examining the full text. A manual search of the bibliography of pertaining articles was finally performed to identify additional studies of interest.

The selected articles were hence tabulated according to study design and setting; sample size; patient gender, age; method used for COVID-19 diagnosis; type and time of onset of skin lesions with respect to COVID-19 diagnosis on skin lesion; associated non-dermatological manifestations, comorbidities/risk factors; treatment for COVID-19; treatment for skin lesion(s); other concurrent treatments; follow-up duration; and patient outcome.

Quality assessment

Three authors (AD, DG, MM) independently and blindly assessed the quality of the included studies using STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) [7], a 22-item tool specifically designed to evaluate observational studies quality, made of 17 standard items and 5 items varying according to the study design (i.e., cohort study, case report, or cross-sectional study). We arbitrarily defined score range for the definition of the study quality: (1) poor, 0–14 points; (2) intermediate, 15–25 points; and (3) good, 26–33 points [8]. Quality of case reports/case series was assessed using CARE (CAse REports) guidelines [9], a 13-item tool specifically designed to evaluate case reports quality. We arbitrarily defined score ranges for the definition of case reports/case series quality: (1) poor, 0–5 points; (2) intermediate, 6–9 points; and (3) good, 10–13 points.

Any disagreement between reviewers was resolved through discussion; whenever not sufficient, a third blind reviewer (IN) was appealed as tie breaker.

Results

Seventy-three [10–82] out of the 28,485 papers identified by the initial search were evaluated for the features of interest and analyzed (Fig. 1). Twenty-four were observational studies, and 49 were case reports/series.

Pseudo-chilblains

Chilblains are painful inflammatory skin lesions of the acral sites presenting as erythematous and edematous macules, nodules, or plaques [4]. Since the beginning of the pandemic, infants and children were referred to pediatric

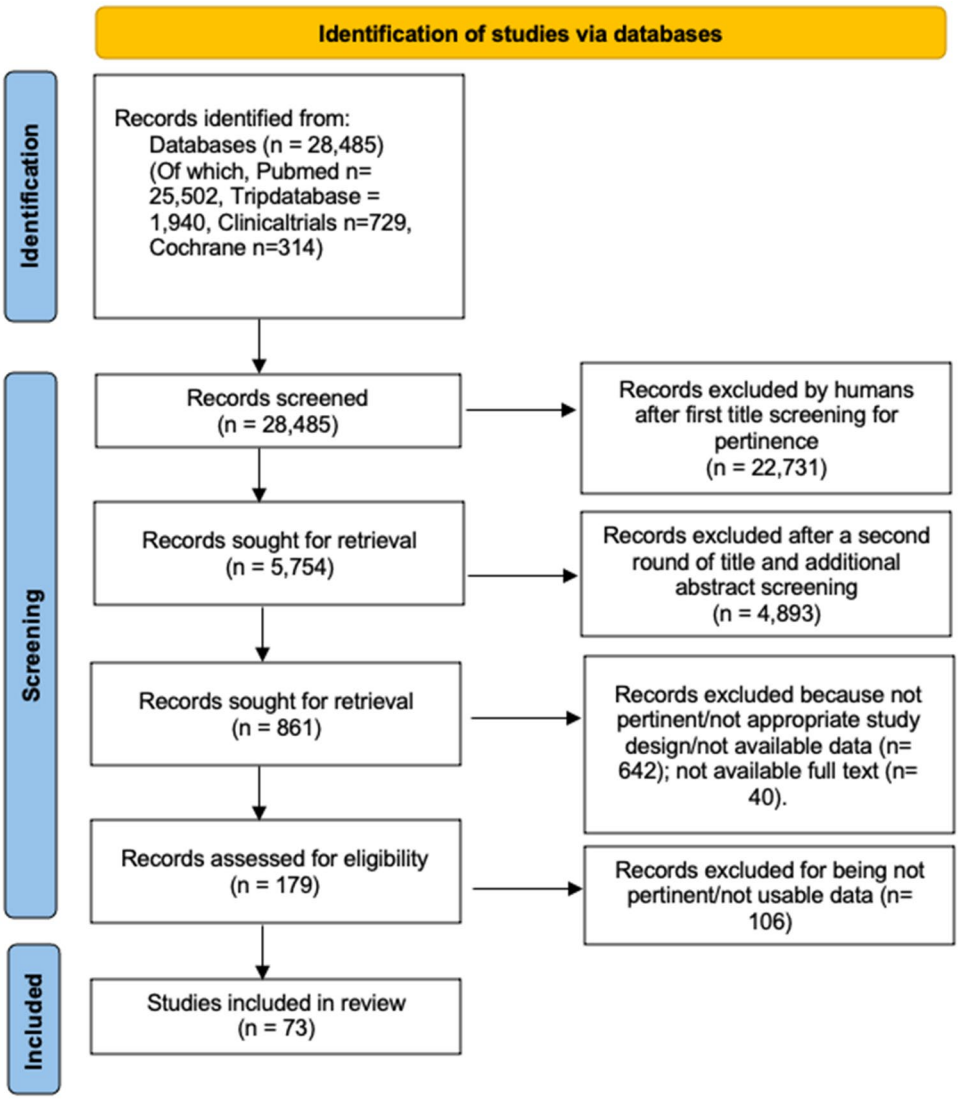

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram showing the process for articles selection [5]

dermatology clinics for chilblain-like lesions or pseudo-chilblains more frequently than usual, and efforts have been made to understand their link with COVID-19 [4].

Literature search retrieved 23 articles demonstrating the occurrence of pseudo-chilblains in young patients with SARS-CoV-2 infection (Table 1). Of these, 6 were case series, 8 case reports, and 9 observational prospective studies. The majority referred to the first COVID-19 wave of spring 2020. Overall, data of 480 patients were available, demonstrating an almost equal gender distribution (males 50.2%). Patient aged ranged from 6 to 17 years; mean age (calculated on the 8 studies in which it was available, $N = 307$) was 14.7 years.

An observational multicenter study by Hubiche et al. [18] reported pseudo-chilblains in almost 80% of the 103 children referred to French dermatology clinics from February to June 2020 for acute acral eruptions with suspected SARS-CoV-2 etiology, of whom 2/103 had a positive serology, and 64% had a positive household contact. SARS-CoV-2 infection was confirmed only in 72 of the 443 (16.3%) tested patients (24/219, 11%, by nasopharyngeal RT-PCR, and 48/224, 21.4%, by serologic tests, IgM, and/or IgG) (Table 1). The rate of test positivity could be underestimated since this information was not reported by Hubiche et al. [18] and Feito Rodrìguez et al. [16] Moreover, SARS-CoV-2 particles were identified in skin biopsy of 8 patients with negative nasopharyngeal swab/serology [13, 14].

Histological examination of the skin lesions was performed in 53 patients from 11 studies (11%) (Table 2) [13–16, 18–22, 24, 31, 32]. Main findings were papillary dermis edema, perivascular and perieccrine lymphocytic infiltrate, lymphocytic vasculitis, and fibrin thrombi.

Pseudo-chilblains typically affected feet (291/363; 80.2%) and, more rarely, hands (33/299, 11%). Most of the cases were asymptomatic. When present, the most frequent symptoms were itching and pain. According to the 9 studies reporting this information, pseudo-chilblains presented 3 days to 2 months before the detection of SARS-CoV-2 infection (Table 1). Most of the cases resolved spontaneously; only a few required topic or oral corticosteroids. Feito-Rodrıguez et al. [16] and Papa et al. [26] observed lesion worsening in some patients at follow-up, while Neri et al. [24] recorded relapse at 3 and 6 weeks after SARS-CoV-2 infection.

Erythema multiforme and other acral lesions

Erythema multiforme (EM) and other acral lesions different from pseudo-chilblains were often reported in infants and children with COVID-19 (Table 3).

EM is an immune-mediated reaction triggered by infections or drugs that involves the skin, typically of the distal extremities, and, less frequently, the mucosa, and consists of a polymorphous eruption of macules, papules, and characteristic "target" lesions. EM-like eruptions have been observed more frequent than usual during the SARS-CoV-2 pandemic, in both children and adults [83].

In a cohort of 103 French children with acute acral eruptions likely related to SARS-CoV-2 infection, Hubiche et al. [18] identified EM in 2.9%, and other acral lesions, i.e., palmar/plantar erythema, acral vesicles, acral edema, and acrocyanosis, in 40.8%, 18.4%, 13.6%, and 12.6% of the patients, respectively.

Other 4 cases of EM were reported [41]. Histopathology was performed only in 2 of them and did not demonstrate specific nor typical features of classical EM.

Moreover, acral peeling was reported in 7 patients by 2 studies [34, 40]. Acral edema, erythematous papules and purpura, and nail Beau lines were rarely detected (Table 3).

Lesions manifested from 3 days up to 4 weeks after SARS-CoV-2 diagnosis, although this information was reported only in a minority of patients. Prognosis was good in all cases.

Rash, urticaria, and other mucocutaneous manifestations

Various types or rash, urticaria, and other mucocutaneous lesions were reported in children of any age with SARS-CoV-2 infection (Supplementary Table 1). Literature search identified 25 case reports/case series, 12 retrospective observational studies, and 6 prospective studies.

Overall, 0.5 to 15% of the patients presented with rash, typically maculopapular, and 0.4 to 0.9% with urticaria. A study by Feldstein et al. [52] performed in 577 children and adolescents affected by severe acute COVID-19 reported a 10.2% incidence of mucocutaneous lesions. Of note, the study by Gale et al. [54] analyzed a cohort of 62 newborns (mean age 9.5 days) with SARS-CoV-2 and reported the presence of a rash in 1 of them (2%).

Purpuric lesions (i.e., thrombocytopenic purpura, Henoch-Schonlein purpura (HSP); $n = 8$), reactive infectious mucocutaneous eruptions ($n = 2$), eczema ($n = 1$), Gianotti-Crosti dermatitis ($n = 1$), oral mucosa lesions ($n = 15$), erythema nodosum ($n = 2$), and severe cutaneous adverse reactions (SCARs; $n = 5$) were also reported. More details can be found at Supplementary Table 1.

Timing of lesion appearance in relation with SARS-CoV-2 infection was reported by 21 studies and ranged from 3 weeks before to 5 weeks after the occurrence of other COVID-19 symptoms, being concomitant in most of the cases. Lesions typically resolved spontaneously; few others were treated with topical or oral corticosteroids and/or oral antihistamines. Prognosis was good, although outcome

Table 1 Studies evaluating the occurrence of pseudo-chilblains in pediatric patients affected by COVID-19 (excluding multisystem inflammatory syndrome in children, *MIS-C*)

Author, year	*n* (M)	Age (mean; range) (yr)	RT-PCR on oro-/nasopharyngeal swab or endotracheal aspirate (total, positive)	Serology (Y/N, *n*)	RT-PCR on biopsy (Y/N, *n*)	Contact with COVID-19 patients (*n*)	SARS-CoV2 detection (Y/N; *n*)
Andina et al. 2020 [10]	22 (13)	12 (6–17)*	19; 1	N/A	N/A	contact with household of a confirmed COVID-19 case (1); contact with a probable case (12)	Y (1)
Carazo-Gallego et al. 2021 [11]	62 (37)	10 (N/A)	36; 0	Immunochromatographic assay IgM/IgG (43); CLIA; 61; IgM-/IgG; 7 IgM + /IgG + : 1; IgM + /IgG-: 1	N/A	N/A	Y (N/A)
Chua et al. 2021 [12]	1 (NA)	N/A	1; 1	N/A	N/A	N/A	Y
Colmenero et al. 2020 [13]	7 (4)	N/A (11–17)	6; 0	N/A	N/A (SARS-CoV-2 spike protein in immunohistochemistry)	Contact with probable COVID-19 case (4)	Y (7)
Colonna et al. 2020 [14]	8 (NA)	N/A	8; 0	IgG test spike protein S1/S2 subunit (8) IgG + : 1	N/A	N/A	Y (1)
El Hachem et al. 2020 [15]	19 (14)	14 (11–17)	19; 0	IgG test (19) Ig + : 0 IgG and IgA spike protein S1 subunit test (19) IgG + : 1 IgG borderline: 3 IgA + : 6 IgA borderline: 3	Y (3) 0 positive	Contacts with family member with COVID-19 symptoms 1–2 m before (7)	Y (10)

Table 1 (continued)

Author, year	*n* (M)	Age (mean; range) (yr)	RT-PCR on oro-/ nasopharyngeal swab or endotracheal aspirate (total, positive)	Serology (Y/N, *n*)	RT-PCR on biopsy (Y/N, *n*)	Contact with COVID-19 patients (*n*)	SARS-CoV2 detection (Y/N; *n*)
Feito-Rodrıguez et al. 2021 [16]	37 (17)	22.1 (N/A); 14*	37; 3	IgG and IgM test (31) IgM + : 3 IgG + : 2 IgM intermediate: 1 IgG e IgM test (13) IgM + : 1 IgG + : 2 2 weeks later IgG e IgM test (12) IgG + : 1 IgG e IgM (25) IgM-/intermediate: 3 IgG + : 1 IgG test (24) IgG + : 1	Y (3) Positive 0	N/A	Y (N/A)
Fertitta et al. 2021 [17]	17 (10)	11.2 (1.8–17.3)	3; 0	IgG test (17) IgG + : 1	N/A	Contact with a confirmed COVID-19 case (2); contact with a probable case (13)	Y (1)
Hubiche et al. 2021 [18]	103 (55)	11 (8–15)	18; 0	IgG and IgM test (14) IgG + : 2 IgM + : 0	N/A	Contact with a probable COVID-19 case (66)	Y (N/A)
Kerber et al. 2020 [19]	1 (1)	7	1; 0	IgG + , IgM-	N/A	N/A	Y
Ladha et al. 2020 [20]	1 (0)	16	1; 0	IgA + IgG +	N/A	N/A	Y
Locatelli et al. 2020 [21]	1 (1)	16	1;1	N/A	N/A	Concomitant mother COVID-19 positive	Y
Magro et al. 2021 [22]	1 (1)	16	1; 0	N/A	Y (rare SARS-CoV-2 RNA + cellS)	Contact with sibling with fever and cough (not tested for SARS-CoV-2) several weeks earlier	Y
Maniaci et al. 2020 [23]	1 (1)	15	1; 1	N/A	N/A	Contact with a confirmed COVID-19 case and contact with a probable case	Y
Neri et al. 2021 [24]	1 (0)	6	1; 1	IgG test IgG +	Y (negative)	N/A	Y

Table 1 (continued)

Author, year	*n* (M)	Age (mean; range) (yr)	RT-PCR on oro-/nasopharyngeal swab or endotracheal aspirate (total, positive)	Serology (Y/N, *n*)	RT-PCR on biopsy (Y/N, *n*)	Contact with COVID-19 patients (*n*)	SARS-CoV2 detection (Y/N; *n*)
Oliva Rodriguez-Pastor et al. 2021 [25]	34 (20)	11.4 (8.6–13.1)	17; 0	IgM and IgG test (34) IgG + : 3 IgM + : 1	N/A	Contact with a confirmed COVID-19 case (1); contact with a probable case (3)	Y (4)
Papa et al. 2021 [26]	11 (7)	11 (8–15)	11; 11	IgG test (11) IgG + : 11	N/A	N/A	Y (11)
Pavone et al. 2021 [27]	2 (0)	7–11	2; 2	N/A	N/A	Contact with a confirmed COVID-19 (1)	Y (2)
Piccolo et al. 2020 [28]	63 (30)	14 (12–16)*	11; 2	Type of test: N/A (6) Positive: 2	N/A	Contact with a confirmed COVID-19 case (2); contact with a probable case (6)	Y (2)
Quintana-Castanedo et al. 2020 [29]	1 (1)	11	1; 0	IgG + IgM-	N/A	No contact	Y
Rizzoli et al. 2020 [30]	12 (4)	12.3 (9–19)	12; 0	IgM and IgG test IgM—IgG + : 1	N/A	Contact with a confirmed COVID-19 cases (2)	Y (1)
Rodrıguez-Villa Lario et al. 2020 [31]	1 (1)	17	1; 0	IgG +	N/A	Contact with a confirmed COVID-19 case	Y
Saenz Aguirre et al. 2021 [32]	74 (42)	19.6 (3–100); 14.5*	11; 1	N/A	N/A	25/103 contact with a confirmed or suspected COVID-19 case	Y (1)

Author, year	Histology (Y/N; *n*)	Electron microscopy (Y/N; n)	Lesion localization (*n*)	Latency between symptoms (SARS-CoV-2 infection) and the appearance of pseudo-chilblains	Other symptoms (type, n)	Dermatological lesion treatment (type, *n*)	Follow-up and outcome of skin lesions
Andina et al. 2020 [10]	Y (6)	N/A	Feet (22); hands (3)	14 (1–28) d before	Cough/rhinitis (9); diarrhea/abdominal pain (2)	Topical corticosteroids (1)	1–10 d (regression after 3–5 w)
Carazo-Gallego et al. 2021 [11]	N/A	N/A	Feet, hands, chest, abdomen (N/A)	N/A	N/A	N/A	N/A
Chua et al. 2021 [12]	N/A	N/A	Feet	N/A	N/A	none	N/A (regression after 1 w)
Colmenero et al. 2020 [13]	Y (7)	Y (7)	Feet (6), hands and feet (1)	N/A	Respiratory symptoms (5), GI symptoms (1)	N/A	8 weeks (complete regression)
Colonna et al. 2020 [14]	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 1 (continued)

Author, year	Histology **(Y/N; *n*)**	Electron microscopy **(Y/N; n)**	Lesion localization (*n*)	Latency between symptoms (SARS-CoV-2 infection) and the appearance of pseudo-chilblains	Other symptoms (type, n)	Dermatological lesion treatment (type, *n*)	Follow-up and outcome of skin lesions
El Hachem et al. 2020 [15]	Y (18)	Y (4)	Toes (9), heel (10), sole (9)	2 months before (4); 1,5 months before (4); 1 month before (1); 1 week after (1)	Fever (5); headache (1); pharyngodynia (2); diarrhea (2); cough (1)	No	14 d
Feito-Rodrıguez et al. 2021 [16]	Y (11)	Y (3)	Toes (15); fingers (10); toes + foot side (7); toes + heel (2); toes + fingers (2); toes + fingers + foot side	21.8 ± 23 days	N/A	Topical corticosteroids (8); oral corticosteroids (1); pentoxifylline (4)	2 w (complete regression: 16; partial regression: 14; persistence: 4; worsening:3)
Fertitta et al. 2021 [17]	N/A	N/A	Feet (14); hands (2); hands + feet (1)	22(5–46) d before (6); 19 d after (2); at the same time (2)	Fever (3); flu symptoms (7); respiratory symptoms (7); GI symptoms (3); anosmia (7)	N/A	41 (11–72) d; resolution in 27 (10–50) d; relapse at 15 d (1) e 45 d (1)
Hubiche et al. 2021 [18]	Y (5)	N/A	Hands + feet (71); hands (15); feet (16)	N/A	N/A	N/A	4 w (complete regression: 36; partial regression: 25; stability: 8; worsening: 2)
Kerber et al. 2020 [19]	N/A	N/A	Toes	2 m before	N/A	N/A	N/A
Ladha et al. 2020 [20]	Y	N/A	Toes	N/A	No	Topical corticosteroids	Regression after 3 w
Locatelli et al. 2020 [21]	Y	N/A	Fingers + second right toe	3 days before	Diarrhea, dysgeusia	No	N/A
Magro et al. 2021 [22]	N/A	N/A	Toes	N/A	N/A	N/A	N/A
Maniaci et al. 2020 [23]	N/A	N/A	Lower limbs	3 d before	Fever, asthenia, pharyngodynia, rhinitis	No	21 d (complete regression)
Neri et al. 2021 [24]	Y	N/A	Feet + fingers	3 w and 2 m before	No	No	N/A (complete regression)
Oliva Rodriguez-Pastor et al. 2021 [25]	N/A	N/A	Mostly feet	N/A	Fever (4); cough (2); pharyngodynia (3); abdominal pain (4); diarrhoea (7); vomit (2); myalgia (1); headache (1)	N/A	1 m (complete regression)
Papa et al. 2021 [26]	N/A	N/A	Feet > hands	N/A	N/A	N/A	2–12 (complete regression)

Table 1 (continued)

Author, year	Histology (Y/N; *n*)	Electron microscopy (Y/N; n)	Lesion localization (*n*)	Latency between symptoms (SARS-CoV-2 infection) and the appearance of pseudo-chilblains	Other symptoms (type, n)	Dermatological lesion treatment (type, *n*)	Follow-up and outcome of skin lesions
Pavone et al. 2021 [27]	N/A	N/A	Toes	6 days before—4 days before	Cough (2); fever (1)	Topical corticosteroids (1)	3 d to 2 w (complete regression)
Piccolo et al. 2020 [28]	N/A	N/A	Feet (54); hands + feet (5); hands (4)	N/A	GI symptoms (7); respiratory symptoms (4); fever (3)	N/A	N/A (stability 50; relapse 9; quick regression 4)
Quintana-Castanedo et al. 2020 [29]	N/A	N/A	Toes	N/A	Retinal vasculitis	N/A	N/A
Rizzoli et al. 2020 [30]	N/A	N/A	Hands (2); hands + feet (1); feet (9)	N/A	No	N/A	N/A
Rodriguez-Villa Lario et al. 2020 [31]	Y	Y	Toes	N/A	N/A	N/A	N/A
Saenz Aguirre et al. 2021 [32]	Y (1)	N/A	Feet (71); hands (6); hands + feet (3)	N/A	N/A	N/A	N/A

Legend to table: *CLIA*, chemiluminescence; *CS*, corticosteroids; *d*, days; *GI*, gastrointestinal; *m*, months; *M*, males; *N*, number of patients enrolled in the study; *N/A*, not available; *NC*, nucleocapsid; *y*, years; *S*, spike; *w*, weeks; *median.

was reported in a minority of the studies. Kari et al. [63], in a study performed in 88 children, identified an association between rash and higher risk of death; however, about 1/3 of the patients presented with one or more severe comorbidities (Supplementary Table 1).

Quality assessment

Based on the STROBE evaluation performed in the 24 observational studies retrieved, 12 were classified as low, 5 as intermediate, and 7 as high quality (Supplementary Table 2). Based on the CARE evaluation performed in the 49 case reports/series retrieved, 19 were classified as low, 20 as intermediate, and 12 as high quality (Supplementary Table 3).

Discussion

We present the results of a systematic literature review showing an overall high prevalence and wide heterogeneity of mucocutaneous lesions associated with SARS-CoV-2 infection in newborns, children, and adolescents.

Overall, skin lesions presented a peculiar acral distribution, a characteristic common to other viruses, in particular Parvovirus B19, presenting with purpuric exanthems of the limbs and arms, i.e., "gloves and socks syndrome" and "acropetechial syndrome" [84, 85]. Although the exact underlying pathogenic mechanism(s) remain to be determined, direct endothelial injury induced by the virus has been suggested [85]. This could be particularly true for SARS-CoV-2 for its ability to induce vascular damage by infecting endothelial cells through the ACE2 receptors [86]. Other risk factors could be represented by the characteristics of the microcirculation in these sites, as well as the immune response to the virus.

Pseudo-chilblains may be considered one of the most peculiar skin manifestation associated with pediatric SARS-CoV-2 infection, and their etiology has been thoroughly debated. However, our review highlighted that SARS-CoV-2 infection was ascertained only in a minority of the cases. This could depend on methodological study limitations (i.e., data collected by telemedicine; limited availability of diagnostic tests, mainly during the first pandemic wave), diagnostic test precision, but also on the high number of children that remained untested because pauci-/asymptomatic for typical COVID-19, as well as the extremely variable time of onset of pseudo-chilblains with regard to SARS-CoV-2 infection, and, finally, on the absence of a humoral response (due to the activation of the type-I interferon, IFN-1, pathway) [87, 88].

Table 2 Histology of SARS-CoV-2-related pseudo-chilblains reported in the selected studies

Author, year	N patients	Papillary dermis edema	Extravasal erythrocytes	Perivascular and perieccrine lymphocyte infiltrate	Perivascular and perieccrine lymphocyte and neutrophil infiltrate	Lymphocytic vasculitis	Thrombi of fibrin	Spongiosis	Vacuolation of the basal dermis
Andina et al. 2020 [10]	6	Yes (6/6)	Yes (N/A)	Yes (6/6)	N/A	Yes (6/6)	Yes (N/A)	N/A	Yes (6/6)
Colmenero et al. 2020 [13]	7	Yes (7/7)	N/A	Yes (7/7)	N/A	N/A	Yes (4/7)	Yes 7/7	Yes 7/7
El Hachem et al. 2020 [15]	18	Yes (12/18)	Yes (15/18)	Yes (18/18)	N/A	Yes (3/18)	Yes (2/18)	Yes (13/18)	Yes (14/18)
Feito-Rodrıguez et al. 2021 [16]	11	Yes (4/11)	Yes (6/11)	Yes (9/11)	Yes (2/11)	Yes (11/11)	No (11/11)	N/A	No (11/11)
Hubiche et al. 2021 [18]	5	N/A	N/A	Yes (5/5)	N/A	Yes (2/5)	N/A	Yes (4/5)	Yes (1/5)
Ladha et al. 2020 [20]	1	Yes	N/A	Yes	N/A	N/A	N/A	N/A	N/A
Locatelli et al. 2020 [21]	1	Yes	N/A	Yes	No	N/A	N/A	N/A	N/A
Magro et al. 2020 [22]	1	Yes	Yes	Yes	No	N/A	Yes	N/A	NA
Neri et al. 2021 [24]	1	Yes	N/A	Yes	No	N/A	No	N/A	N/A
Rodrıguez-Villa Lario et al. 2020 [31]	1	Yes	N/A	Yes	N/A	N/A	No	N/A	N/A
Saenz Aguirre et al. 2020 [32]	1	N/A	N/A	Yes	N/A	N/A	N/A	N/A	N/A

Author, year	Exocytosis	Keratinocyte necrosis	Mucin	Acrosirnigia	Lymphocytic eccrine hidradenitis	Vascular ectasia	Hemorrhagic parakeratosis of the stratum corneum	Presence of eosinophils
Andina et al. 2020 [10]	N/A	N/A	Yes (N/A)	Yes (6/6)	Yes (N/A)	Yes (N/A)	N/A	N/A
Colmenero et al. 2020 [13]	Yes (3/7)	Yes (4/7)	N/A	N/A	N/A	Yes (3/7)	Yes (4/7)	N/A
El Hachem et al. 2020 [15]	Yes (6/18)	N/A	Yes (17/18)	N/A	N/A	N/A	N/A	N/A
Feito-Rodrıguez et al. 2021 [16]	N/A	N/A	Yes (5/11)	N/A	N/A	N/A	N/A	N/A
Hubiche et al. 2021 [18]	N/A	Yes (1/5)	Yes (2/3)	N/A	N/A	N/A	N/A	Yes (2/5)

Table 2 (continued)

Author, year	Exocytosis	Keratinocyte necrosis	Mucin	Acrosirnigia	Lymphocytic eccrine hidradenitis	Vascular ectasia	Hemorrhagic parakeratosis of the stratum corneum	Presence of eosinophils
Ladha et al. 2020 [20]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Locatelli et al. 2020 [21]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Magro et al. 2020 [22]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Neri et al. 2021 [24]	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A
Rodrıguez-Villa Lario et al. 2020 [31]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Saenz Aguirre et al. 2020 [32]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Legend to table: *N/A*, not available.

On the other hand, albeit rare, the retrieval of SARS-CoV-2 RNA and other components in cells from pseudo-chilblain biopsies supports its pathogenic role [13, 22, 89]. Other elements supporting pseudo-chilblains as a COVID-19 manifestation are their rapid increase concomitant to the SARS-CoV-2 pandemic; the co-occurrence of mild respiratory or gastrointestinal symptoms in a non-negligible portion of children; a frequent history of contact with suspected/confirmed COVID-19 cases; and the onset of similar skin lesions in siblings, together with the occasional virus detection by RT-PCR, serological test, or electron microscopy within endothelial cells of vessels [90]. In this respect, Andina et al. hypothesized some possible pathogenetic mechanisms [4]: (1) an early, strong interferon type I response against the viral infection that might attenuate viral replication, but induce microangiopathic changes producing a chilblain-like eruption (virus-induced type I interferonopathy hypothesis); (2) chilblains as a manifestation of thrombosis/coagulopathy, as increased risk of thromboembolism with high levels of D-dimer and acral ischemia have been clearly demonstrated in patients with COVID-19, and microthrombi have been observed in chilblains; (3) chilblains as a specific microvascular pathology induced by SARS-CoV-2 (vasculitis hypothesis), in which pericytes endothelial cells play a major role, due to their expression of high levels of ACE2 receptor [91]; (4) change in patient habits secondary to SARS-CoV-2 lockdown, i.e., reduced physical activity and physical and mental stress. Moreover, even if this topic is out of the scope of the present review, pseudo-chilblains have also been reported following the administration of COVID-19 vaccines [92–94], further supporting the link between SARS-CoV-2 and these skin manifestations.

Among the various mucocutaneous lesions reported in association with pediatric SARS-CoV-2 infection, five authors describe the occurrence of HSP [43, 47, 59, 62, 73] (Supplementary Table 1). SARS-CoV-2 has been suggested as trigger for HSP in children [95], but its pathogenic role beyond incidental co-infection remains to be demonstrated. The case described by Borocco et al. [47] of SARS-CoV-2 associated with Epstein Barr virus (EBV), that is reported to act as a trigger in 4.2% of childhood HSP cases [96], further questions this association.

Mucocutaneous lesions of various type can present at any age (newborn to adolescent) in paucisymptomatic as well as in severely ill patients, or they may be the only manifestation of COVID-19. They can appear at different stages of the disease, i.e., some days/weeks before, in concomitance with or some weeks after the resolution of the other more typical COVID-19 manifestations and/or serological negativization [26]. The late appearance can be one possible explanation for negative RT-PCR test in most of the cases [90, 97].

Before SARS-CoV-2 pandemic, chilblains typically occurred in children affected by type 1 interferonopathies (i.e., systemic lupus erythematosus) [98] as an expression of the associated microangiopathy. The interferon type 1 response developed by pediatric patients, in which the immune response induces skin lesions, but downregulates the release of other cytokines, thus preventing the "cytokine storm," might be the reason why children with chilblains present with mild forms of COVID-19 [26].

Main strengths of the present review are the comprehensive literature assessment, which covers the entire time period of SARS-CoV-2 pandemic, from the first wave up to the most recently reported cases (indeed, another

Table 3 Studies evaluating the appearance of erythema multiforme (EM) and other acral lesions in pediatric patients affected by COVID-19 (excluding multisystem inflammatory syndrome in children, *MIS-C*)

Author, year	Lesion type	*n* (M)	Age	RT-PCR on oro-/nasopharyngeal swab or endotracheal aspirate (total; positive)	Serology (Y/N, *n*)	RT-PCR on biopsy (Y/N, n)	Electronic microscopy, histology	SARS-CoV-2 detection (Y/N; n)	Dermatological lesion description	Latency between symptoms (SARS-CoV-2 infection) and the appearance of skin lesions	Other symptoms (type, *n*)	Dermatological lesion treatment	Follow-up and outcome of skin lesions
Andina et al. 2021 [33]	acral purpura	1 (0)	2 m	1; 0	N	N/A (SARS-CoV-2 spike protein at immunohistochemistry)	Dilated superficial dermal vessels lined by swollen endothelial cells; significant red cell extravasation	Y; 1	Reticulated purpura on both soles	3 w	Nasal congestion	None	Regression after 2 w
Andina-Martinez et al. Pediatr Dermatol 2021 [34]	acral peeling	6 (4)	5–13 y	3; 3	N	N/A	N/A	Y; 5 (2/6 antigenic test; 1/6 symptoms and household contact)	Peeling of fingertips and toe, mild erythema	3–21 d	Headache (2), fever (2), cough (2), GI (1), anosmia (1), dysgeusia (1), myalgia (1)	None	Regression
Hubiche et al. 2021 [18]	Acral lesions (chilblain 79.6%, EM 2.9% and others)	103 (55)	mean 11.1 ± 5.2 y—median 13 (8–15) y	18; 0	14; 2 (IgG+, IgM-)	N/A	5/103; direct immunofluorescence: IgM deposition; histology: dermal perivascular lymphocytic infiltrate, spongiosis, keratinocyte necrosis, eosinophils, mucin deposition, basal layer vacuolization	Y; 2 (66/103 household contact)	Chilblain, vesicles, palmar/plantar erythema, purpura, acrocyanosis, teleangectasia, acral edema, EM, papules	N/A	N/A	N/A	71/103 1-m follow-up: 35/71 total recovery, 25/71 partially regressed, 8/71 stable, 2/71 worsened
Janah et al. 2020 [35]	EM	1 (1)	17 y	N/A	N	N/A	N/A	Y	Erythematous maculopapular atypical targetoid eruption of palms	15 d	Mild COVID-19	N/A	N/A
Klimach et al. 2020 [36]	Acral erythematous eruption	1 (1)	13 y	1; 1	N	N/A	N/A	Y	1-cm erythematous papules on plantar surface and erythematous macules + petechiae in distal lower extremities	Concomitant	Flu-like symptoms	N/A	resolution in 10–14 d
Kumar et al. 2021 [37]	Acral purpura	1 (1)	13 y	1; 1	N	N/A	No IgA deposits (excludes HSP); superficial epidermal necrosis with intraepidermal pustules and small vessel neutrophilic vasculitis	Y	Palpable purpuric-petechial rash on both feet spreading to ankles and lower legs (HSP excluded by histology)	4 w	None	None	Slow improvement—still some lesions after 4 w
Labè et al. 2020 [38]	EM	1 (1)	6 y	1; 1	N	N/A	N/A	Y	Targetoid elements on cheek, hands and feet	N/A	Fever, painful cheilitis, conjunctivitis	N/A	Discharged in 2 w

Table 3 (continued)

Author, year	Lesion type	*n* (M)	Age	RT-PCR on oro-/nasopharyngeal swab or endotracheal aspirate (total; positive)	Serology (Y/N, *n*)	RT-PCR on biopsy (Y/N, n)	Electronic microscopy, histology	SARS-CoV-2 detection (Y/N; n)	Dermatological lesion description	Latency between symptoms (SARS-CoV-2 infection) and the appearance of skin lesions	Other symptoms (type, *n*)	Dermatological lesion treatment	Follow-up and outcome of skin lesions
Ozsurekci et al. 2021 [39]	Acral edema	22 (15)	median 12 y (range 0–17)	22; 22	N	N/A	N/A	Y	acral oedema 2/22, rash 1/22, conjunctivitis 1/22	NA	Severe COVID-19 infection	None	N/A
Roulo et al. 2021 [40]	Acral peeling, urticaria	1 (0)	6 y	1; 1	N	N/A	N/A	Y	giant urticaria and acral peeling	1 d before (urticaria) and 2 d after (acral peeling)	fever, sore throat	antihistamines for symptomatic relief	resolution in 4 d
Torrelo et al. 2020 [41]	EM	4 (3)	11–17 y	4; 1	N	N/A 2/4 (SARS-CoV-2 spike protein at immunohistochemistry))	2/4 histology: deep perivascular and pericecrine infiltrate; absence of necrosis of keratinocytes	Y; 3	EM—4/4 associated pseudo-chilblains	N/A	Respiratory or GI symptoms, itch, pain	1/4 oral CS, 1/4 topical CS, 2/4 none	Complete recovery in 1–3 w
Wolf et al. 2021 [42]	Beau lines	2 (NA)	2 and 5 y	2; 2	N	N/A	N/A	Y	Beau lines of all fingernails	3 w	Fever, GI	None	Complete regression after 4 m

Legend to table: *CS* corticosteroids, *d* days, *EM* erythema multiforme, *GI* gastrointestinal, *HSP* Henoch-Schonlein purpura, *m* months, *MIS-C* multisystem inflammatory syndrome in children, *N* no, *N/A*, not available, *w* weeks, *y* years, *Y* yes

systematic review on this topic referred to the first pandemic wave only had been previously published [99]) and the systematic evaluation of the quality of both observational and case studies included in the analysis. On the other hand, results remain inconclusive due to the important methodological limitations of the primary studies: properly designed studies were few and heterogeneous in terms of clinical evaluations, study setting, sample size, and follow-up duration, as well as the methods used for the assessment of Sars-CoV-2 infection. Indeed, in a non-negligible number of studies, the presence of COVID-19 disease was established on the basis of patient symptoms, and/or detection of the virus RNA/particles in mucocutaneous lesion, and/or in patient siblings/contacts, and not on the positivity to serological/molecular tests.

Conclusions

The comprehensive assessment of literature focusing on COVID-19 manifestations all along the pandemic period has demonstrated that dermatological lesions of different types frequently occur in affected newborns, children, and adolescents, independently from the presence and severity of other more typical signs and symptoms. Skin lesions typically present with a peculiar acral distribution and include pseudo-chilblains, EM, or acral purpura, peeling, or edema and, more rarely, HSP and reactive infectious mucocutaneous eruption. Mucocutaneous lesions usually subside spontaneously, and only a minority persist/worsen so to require topic/systemic therapy. However, it is fundamental for physicians of all specialties to be aware and promptly recognize them, not only for a timely and adequate management, but, even more important, since they can precede other more typical COVID-19 manifestations, to adopt all required measures to prevent disease diffusion. On the other hand, underlying pathogenic mechanisms have only been hypothesized, and the actual role of SARS-CoV-2 remains to be ascertained. Finally, our work highlights that most of the evidence available up to now is low-to-medium quality, so that further well-designed studies should be conducted to clarify the association of SARS-CoV-2 with dermatological lesions in children.

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Declarations

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Conflict of interest The authors declare no competing interests.

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