A systematic review on mucocutaneous manifestations of COVID-19 in children

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Background: About 20% of patients with coronavirus disease 2019 (COVID-19) present with mucocutaneous eruptions. Early skin or dermatological manifestations can help pediatricians prevent the spread of the disease by suspecting COVID-19 in asymptomatic or minimally symptomatic patients.

Methods: PubMed, Scopus, Embase, Google Scholar, and the Nottingham University website were searched on Sep. 1st, 2020, to retrieve studies regarding COVID-19-related mucocutaneous manifestations in patients under the age of 18.

Results: Data were extracted from 76 articles including 38,387 cases. Chilblain/pernio-like lesions were the most common dermatological manifestation, followed by multisystem inflammatory syndrome in children (MIS-C)/Kawasaki-like syndrome. Most dermatological signs were self-limited, presenting before, simultaneously with, or after other COVID-19 manifestations. In 40% of the affected children, these signs were the sole presentation of COVID-19.

Conclusion: During the COVID-19 pandemic, each new mucocutaneous event in children, especially acral lesions with vascular color, should be considered a possible indicator of COVID-19.

Keywords: COVID-19, SARS-CoV-2, mucocutaneous manifestation, dermatologic manifestation, cutaneous manifestation, pediatric, children

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INTRODUCTION

Rationale

In December 2019, an outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in Wuhan, China, led to the rapid worldwide spread of coronavirus disease 2019 (COVID-19) [1]. Children's average viral incubation period is shorter than adults, necessitating further investigations [2]. Human-to-human transmission is prevalent in the latent period by asymptomatic infected persons through respiratory droplets and other modes, particularly in pediatrics [3]. The diagnostic test of COVID-19 is the RT-PCR of specimens from a nasopharyngeal swab, bronchoalveolar lavage (BAL), or tracheal aspirate. Spiral chest computed tomography (CT) illustrates ground-glass opacities, particularly on the lower lung lobes and periphery, in the typical form of COVID-19 [3,4]. Inflammatory markers (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], ferritin, and procalcitonin) surge in the majority of patients [5]. Studies report that approximately 90% of children with COVID-19 experience mild to moderate symptoms and have a better prognosis without hospitalization [1].

In children, COVID-19 is divided into five categories according to disease severity: 1) asymptomatic or silent; 2) acute upper respiratory tract infection; 3) mild pneumonia; 4) severe pneumonia; 5) critical presentation. Between 9–15% of confirmed COVID-19 cases are asymptomatic in children [2]. The most common symptoms among children are fever, sore throat, rhinorrhea, fatigue, conjunctivitis, headache, cough, shortness of breath, anosmia, ageusia, diarrhea, vomiting, and abdominal pain, and 20% of the patients present with skin eruptions [2]. The common skin lesions are urticarial lesions, maculopapular rashes, vesicular eruptions, erythema multiforme-like lesions, pernio (chilblain)-like acral lesions, and transient livedo reticularis [2]. Chilblain-Like Lesions (CLL) associated with COVID-19 (COVID toes) may be an overresponse of the skin to the cold in vulnerable children [6]. In early May 2020, some published studies reported children with COVID-19 were affected with hyper-inflammatory syndromes, presenting with Kawasaki disease or atypical Kawasaki disease and toxic shock syndrome. This presentation was named multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 by the Centers for Disease Control and Prevention (CDC) [7]. Early skin manifestations could be a useful clue to suspect the diagnosis of COVID-19 in asymptomatic or minimally symptomatic pediatric patients to prevent the infection's spread in the community [8].

Studies in children have had almost the same results in adults in that the most common skin phenotypes were erythematous/maculopapular/morbilliform rashes and chilblain-like acral patterns [9].

Objective

Skin lesions can be one of the MIS-C presentations. We can also stop complications caused by skin rash-like scars by identifying different types of skin manifestations in children and managing them promptly. There is an obvious need for the widest-aspect systematic review to improve physicians' clinical knowledge about skin manifestations and how to approach them in children.

PARTICIPANTS AND METHODS

Protocol and registration

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10].

Eligibility criteria

The Population-Intervention-Comparator-Outcomes-Study (PICOS) design framework was used to identify eligible cases in this systematic review. Inclusion criteria were all types of studies reporting COVID-19-related mucocutaneous manifestations in patients aged 0–18 years old. Skin eruptions related to COVID-19, their treatment, or their correlation with protective behaviors were included. Cases were included in case of a clinical diagnosis of COVID-19 (suspected cases), confirmed RT-PCR, or positive serum antibody tests.

The exclusion criteria were all publications that did not meet the above criteria and those published in non-English literature. Unavailable articles, review articles, medical hypothesis articles, non-COVID-19 skin presentations, and skin manifestations due to non-COVID-19 treatment were also excluded (Figure 1, 2).

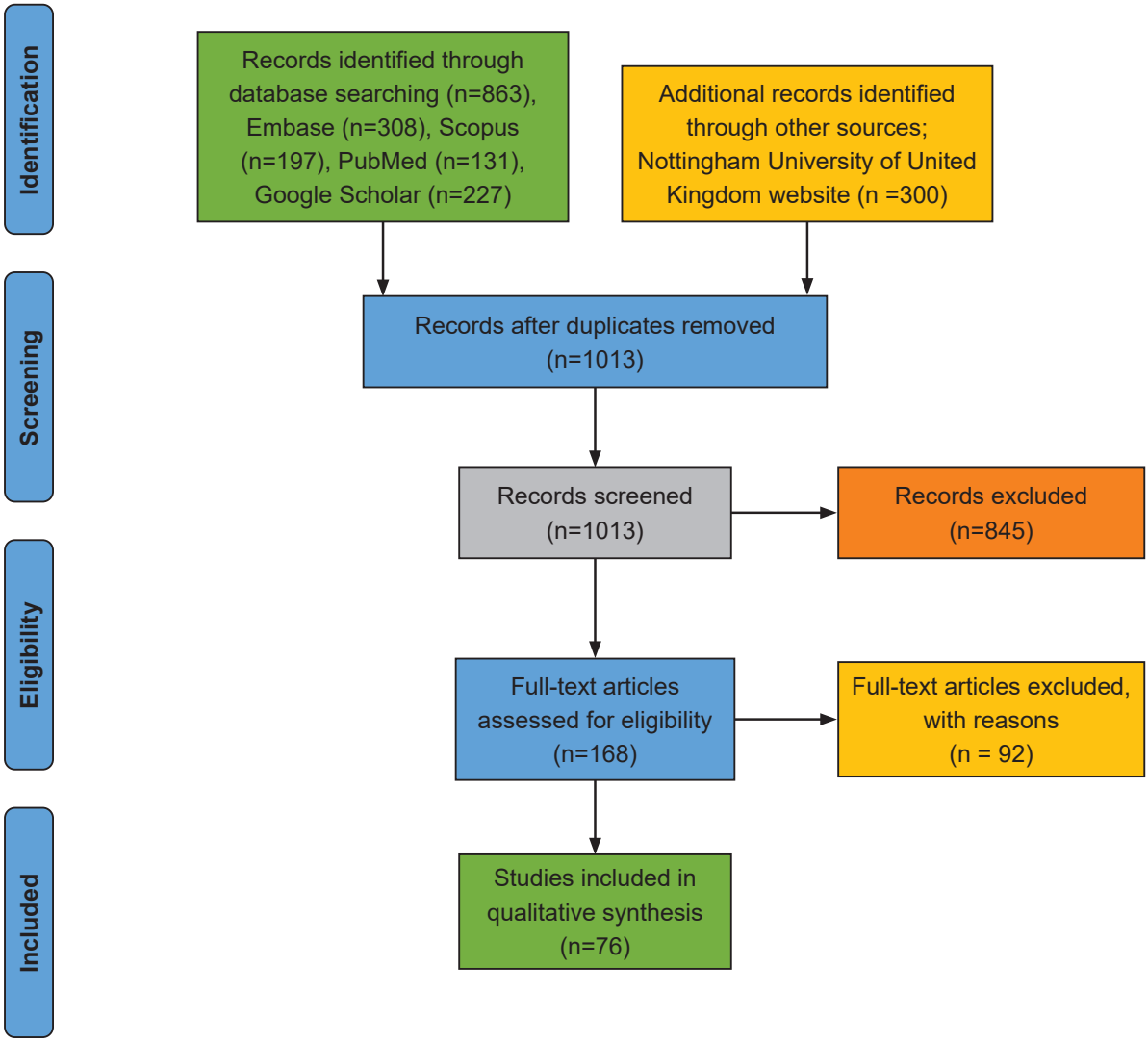

Figure 1. PRISMA flow diagram of the study.

Information sources

PubMed (http://ncbi.nlm.nih.gov/pubmed), Scopus (http://www.scopus.com), Embase (http://www.embase.com), and Google Scholar (https://scholar.google.com/) were searched for the evidence. We also used the Nottingham University of United Kingdom website (http://nottingham.ac.uk), which categorizes many valuable and trendy studies related to this work (Figure 3).

Search strategy

In this study, we used the following keywords: "pediatrics", "paediatrics", "children", "child", "baby", "newborn", "neonate", "toddler", "infant", "COVID-19", "coronavirus disease 2019", "nCoV", "2019-nCoV", "COVID-19", "COVID 2019", "Wuhan coronavirus", "novel coronavirus" and "mucocutaneous manifestation", "skin manifestation", "cutaneous reaction", "'skin reaction", "skin disease", "derm", "dermatopathology", "dermopathy", "skin and connective tissue", "skin lesion", "cutaneous inflammation", "drug side effect", "rash", "cutaneous", "drug reaction", "dermatitis", "lesion", "skin symptom", "dermatitis", "drug-related side effects", "drug-related adverse reactions", and

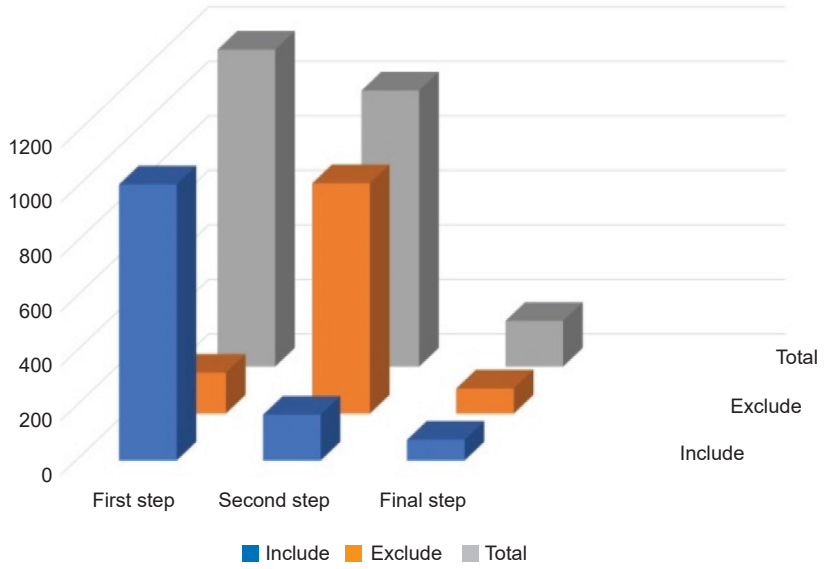

Figure 2. PRISMA chart of the study.

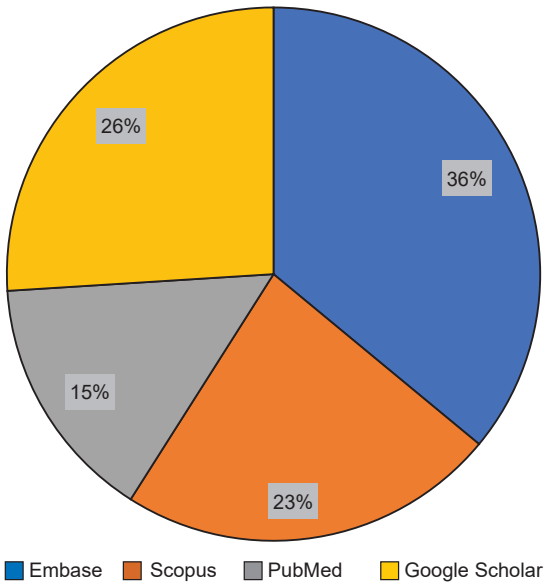

Figure 3. Percentage of records identified in different databases.

alternative names. The search was completed on September 1, 2020; the search did not limit the admissions to any condition. First, 308 articles were extracted from Embase, 197 from Scopus, and 131 from PubMed; our search on Google Scholar yielded 227 articles, bringing the total number of all retrieved articles to 863. Furthermore, 300 studies from the Nottingham University of United Kingdom website were added.

Study selection

Endnote® X8 (Clarivate Analytics, Philadelphia, USA) was used for study screening and data extraction. All articles were dispensed to the inclusion and exclusion groups. In the first step, the titles and abstracts of the articles were screened and categorized by two independent reviewers. Then, the relevant ones were taken to the second step and underwent full-text screening, where the authors checked the full texts against the eligibility criteria. Any potential conflicts were resolved by consulting a third expert reviewer. Figure 1 shows this process in the PRISMA flow diagram.

Data items

The data retrieved from each study included case characteristics, COVID-19 signs and symptoms, COVID-19 management, patient's comorbidities, type and location of skin manifestations, time of onset of reactions, managements of reactions, resolution time, sample size, mean age, sex, the incidence of skin lesions, protective equipment, skin biopsy, and outcome. The data were summarized in four tables.

RESULTS

Study selection

Eight hundred and twenty-four studies were collected from the databases, which were screened by the reviewers alongside approximately 300 articles retrieved from the Nottingham University of United Kingdom website. After screening, the included articles were divided into four categories (Tables 1-4). In total, data from 76 articles with 38,387 cases were extracted.

Study characteristics

Table 1 presents 110 cases with COVID-19-related mucocutaneous manifestations from 53 articles. This category includes 31 case reports and 22 case series.

Table 2 shows four studies with 37,794 cases, of which 16,662 reported cutaneous manifestations caused by changes in lifestyle during the COVID-19 pandemic, like protective behaviors.

In Table 3, we present one case found in a case series study that reports mucocutaneous manifestations resulting from COVID-19 treatments.

Table 4 summarizes 481 cases of suspected COVID-19 with mucocutaneous manifestations extracted from 18 articles. This table includes cohort studies and high-population case series that could not be reported case by case.

Results of individual studies

Virus-related case report studies

According to the results of the case reports/case series (with less than 10 cases), a total of 110 patients with dermatologic manifestations were identified, of whom 48 (44%) were female and 61 (55.96%) were male. Gender was not reported in one case. The male/female ratio was 1.27. We assume that the incidence of cutaneous manifestations in children with COVID-19 is unrelated to gender. The mean age of the cases was 10.79 years (range: 5 months–18 years). Among the reported comorbidities, three patients had a background of asthma [7,8,11–61].

Skin presentations

As per skin manifestations, chilblain/pernio-like lesions were the most common category identified in 57 (53.7%) patients, followed by MIS-C/Kawasaki-like syndrome-related skin lesions in 22 (20.7%), erythema multiforme-like lesions in six (5.6%), varicella-like exanthem/herpes zoster/herpetiform erosions in six (5.6%), vascular rashes within the spectrum of livedo/purpura/necrosis in six (5.6%), urticaria in five (4.7%), and unspecified erythematous rashes in four (3.7%) patients. In four cases, the exact type of skin manifestation was not reported.

Location of skin lesions

The most common location of skin lesions was the extremities, noticeably in chilblain/pernio-like lesions. Out of mucosal involvement in MIS-C/Kawasaki-like syndrome, six cases demonstrated mucosal involvement in the genital area, eyes, and tongue, and 80% of urticarial reactions were generalized.

COVID-19-related features

Fifty-five cases confirmed with RT-PCR or serology were recognized. The screening test was not mentioned in ten cases. Among the 110 patients, 67 had information related to systemic symptoms of COVID-19. Fever was the most common, reported in 50 (74.6%) patients. Other symptoms, including gastrointestinal symptoms (28, 41.7%), headache (14, 20.8%), respiratory symptoms (18, 26.8%), flu-like symptoms (22, 32.8%), loss of consciousness (3, 4.4%), and anosmia (3, 4.4%), were also described.

The onset of skin manifestations

Out of 110 patients, 67 cases provided information on the onset of skin manifestations, which occurred on average 12.47 days (incubation period: 2–60) after the onset of systemic symptoms. In nine cases (13.5%), skin lesions appeared at the same time, and in seven cases (10.5%), the skin lesions developed before other COVID-19 manifestations. In 27 (40%) cases, skin eruptions were the sole manifestation of COVID-19. In other cases, dermatologic manifestations appeared after evident systemic symptoms of COVID-19 (24 patients (36%)).

Table 1. A summary of the case reports on coronavirus disease 2019 (COVID-19)-related skin manifestations in children

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
Appearance of skin rash in pediatric patients with COVID-19: Three case presentations	8-month-old girl	Fever, rash, COVID-19 PCR: +	NM	NM	NM	Erythematous skin rash, similar to the roseola rash in appearance	Started on the face, spread to the extremities, and ended on the trunk	NM	NM	2 days
Appearance of skin rash in pediatric patients with COVID-19: Three case presentations	11-year-old girl	COVID-19 PCR: + asymptomatic	NM	NM	First presentation	Maculopapular and itchy rash	Started on the face, spread to the extremities, and ended on the trunk	NM	NM	5 days
Severe SARS-CoV-2 infection in children with suspected acute abdomen: a case series from a tertiary hospital in Spain	12-year-old boy	Fever, vomiting, diarrhea, abdominal pain, shock, dehydration, COVID-19 PCR: +, CXR: bilateral pneumonia	Norepinephrine, adrenaline, invasive mechanical ventilation, meropenem, amikacin, hydroxychloroquine, methylprednisolone (1mg/kg/day), azithromycin, lopinavir/ritonavir, tocilizumab, low-molecular-weight heparin (therapeutic dose)	NM	3days after other symptoms	Skin lesions	Genital region	Negative	NM	NM
Severe SARS-CoV-2 infection in children with suspected acute abdomen: a case series from a tertiary hospital in Spain	10-year-old boy	Abdominal pain, fever, vomiting, diarrhea, dehydration, COVID-19 serology: +	High flow cannulas, meropenem, hydroxychloroquine, methylprednisolone (1mg/kg/day), azithromycin, lopinavir/ritonavir, tocilizumab, low-molecular-weight heparin (prophylactic dose)	NM	NM	Skin lesions	Trunk, extremities	Negative	Nothing	NM
COVID toes: Digital vascular changes in patients with a COVID-19 infection	9-year-old boy	COVID-19 antibody serology: +, contact with COVID-19 patient: +, asymptomatic	NM	Attention deficit disorder, asthma	First presentation	Warm, tender erythematous nodules	Toes	Negative	Oral cephalexin (40 mg/kg/day) for 10 days, topical mometasone, local warming, acetaminophen	28 days

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
Multisystem inflammatory syndrome in children during the coronavirus 2019 pandemic: A case series	14-year-old girl	Fever, headache, diarrhea, dyspnea, shock, COVID-19 PCR: -, CXR: bilateral pulmonary infiltrates, COVID-19 serology test (IgG): +	Mechanical ventilation, epinephrine, norepinephrine, IVIG (2gr/kg), methylprednisolone (2 mg/kg/day), low-dose aspirin, cefepime, clindamycin, vancomycin, doxycycline (for 7 days)	Nothing	Same time with other symptoms	Diffuse, erythematous rash	Diffuse	Negative	Nothing	NM
Multisystem inflammatory syndrome in children during the coronavirus 2019 pandemic: A case series	12-year-old boy	Fever, abdominal pain, diarrhea, respiratory distress, altered mental status, shock, CXR: diffuse bilateral infiltrates, COVID-19 PCR: -, COVID-19 serology test (IgG): +	Noninvasive mechanical ventilation, milrinone, epinephrine, vasopressin, cefepime, clindamycin (for 7 days), vancomycin, pulse dose methylprednisolone (10 mg/kg on HD2), IVIG (2 g/kg on HD2)	Negative	Same time with other symptoms	Mucous membrane changes (fissured lips)	Lips	Negative	Nothing	NM
Multisystem inflammatory syndrome in children during the coronavirus 2019 pandemic: A case series	9-year-old girl	Fever, copious diarrhea, intermittent periumbilical pain, shock, conjunctivitis, extremity edema, COVID-19 PCR: +, CXR: pulmonary edema, cardiomegaly	Noninvasive mechanical ventilation, IVIG (2 g/kg on HD5), methylprednisolone (2 mg/kg/ day on HD5), low-dose aspirin, piperacillin/tazobactam (for 2 days), vancomycin, ciprofloxacin (for 2 days)	Negative	5 days after hospitalization	Mucosal changes (fissured lips and strawberry tongue)	Lips and tongue	Negative	Nothing	NM
Multisystem inflammatory syndrome in children during the coronavirus 2019 pandemic: A case series	5-year-old girl	Fever, conjunctivitis, swollen hands, emesis, diarrhea, irritability, nuchal rigidity, COVID-19 PCR: +, CXR: peribronchial thickening with patchy right lower lobe infiltrates, COVID-19 serology test (IgG): +	Mechanical ventilation, epinephrine, milrinone infusions, vancomycin, cefepime (for 2 days), ceftriaxone (for 5 days), IVIG (2 g/kg on HD0 and HD2), methylprednisolone (2 mg/ kg/day on HD0), anakinra (4 mg/kg/ day on HD4) and pulse methylprednisolone (30 mg/kg/day on HD4)	Negative	Same time with other symptoms (4 days before hospitalization)	Morbilliform rash, mucosal changes (fissured lips)	Lips	Negative	Nothing	NM

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven pediatric cases	11-year-old girl	Respiratory and GI involvement, COVID-19 PCR: -, contact with COVID-19 patient: +	NM	Negative	4 days before biopsy	Acral purpuric lesions (chilblains)	Feet, toes	Basal vacuolar changes, necrotic keratinocytes, spongiosis, dermal edema, superficial perivascular inflammation, deep perivascular inflammation, lymphocytic panniculitis, lymphocytic infiltration of vessels, purpura, vascular ectasia, SARS-CoV-2 spike protein (+)	Nothing	56 days
SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven pediatric cases	13-year-old girl	Respiratory involvement, COVID-19 PCR: -, contact with COVID-19 patient: +	NM	ADHD	11 days before biopsy	Acral purpuric lesions (chilblains), mild pain	Feet, toes	Basal vacuolar changes, necrotic keratinocytes, spongiosis, dermal edema, superficial perivascular inflammation, deep perivascular inflammation, lymphocytic panniculitis, lymphocytic infiltration of vessels, purpura, exocytosis, parakeratosis, fibrinoid necrosis, thrombi superficial dermis, thrombi deep dermis, dermal mucin, SARS-CoV-2 spike protein (+)	Nothing	56 days

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven pediatric cases	15-year-old girl	Respiratory involvement, contact with COVID-19 patient: -	NM	Negative	30 days before biopsy	Acral purpuric lesions (chilblains)	Feet, toes	Basal vacuolar changes, necrotic keratinocytes, spongiosis, dermal edema, superficial perivascular inflammation, deep perivascular inflammation, perieccrine inflammation, lymphocytic panniculitis, lymphocytic infiltration of vessels, purpura, fibrinoid necrosis, thrombi deep dermis, dermal mucin, SARS-CoV-2 spike protein (+)	Nothing	56 days
SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven pediatric cases	15-year-old boy	COVID-19 PCR: -, contact with COVID-19 patient: +	NM	Negative	15 days before biopsy	Acral purpuric lesions (chilblains)	Feet, toes	Basal vacuolar changes, parakeratosis, spongiosis, dermal edema, perivascular superficial inflammation, perivascular deep inflammation, lymphocytic panniculitis, lymphocytic infiltration of vessels, purpura, dermal muchin, vascular ectasia, thrombi in deep dermis, exocytosis, SARS-CoV-2 spike protein (+)	Nothing	56 days

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven pediatric cases	14-year-old boy	Respiratory involvement, COVID-19 PCR: -, contact with COVID-19 patient: -	NM	Negative	20 days before the biopsy	Acral purpuric lesions (chilblains), pruritus	Feet, toes	Basal vacuolar changes, necrotic keratinocytes, parakeratosis, spongiosis, dermal edema, superficial perivascular inflammation, deep perivascular inflammation, perieccrine inflammation, lymphocytic panniculitis, thrombi deep dermis, lymphocytic infiltration of vessels, purpura, dermal mucin, SARS-CoV-2 spike protein (+)	Nothing	56 days
SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven pediatric cases	17-year-old boy	Respiratory involvement, COVID-19 PCR: -, contact with COVID-19 patient: +	NM	Negative	20 days before the biopsy	Acral purpuric lesions (chilblains), pruritus, erythema multiforme on the elbows and knees	Feet, toes, hands, elbows, knees	Basal vacuolar changes, exocytosis, necrotic keratinocytes, spongiosis, dermal edema, superficial perivascular inflammation, deep perivascular inflammation, perieccrine inflammation, lymphocytic panniculitis, lymphocytic infiltration of vessels, purpura, dermal mucin, subcutaneous lymphocytic, SARS-CoV-2 spike protein (+)	Nothing	56 days

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven pediatric cases	15-year-old boy	COVID-19 PCR: -, contact with COVID-19 patient: +	NM	ADHD	7 days before the biopsy	Acral purpuric lesions (chilblains), pruritus	Feet, toes	Basal vacuolar changes, parakeratosis, spongiosis, dermal edema, superficial perivascular inflammation, deep perivascular inflammation, lymphocytic infiltration of vessels, purpura, vascular ectasia, SARS-CoV-2 spike protein (+)	Nothing	56 days
Chilblain-like lesions in children following suspected COVID-19 infection	11-year-old girl	Flu-like symptoms, headache, rhinitis, COVID-19 PCR: -	Negative	Nothing	14 days before symptoms	Several dusky erythematous macules with blurred edges, cyanotic and slightly atrophic lesions, erythematous plaque, coldness, and mild pain	Lateral margin of the feet and the dorsal surface of the right first, second, and third toes, plantar surface of the left first and fourth toes	Negative	Nothing	5 days
Chilblain-like lesions in children following suspected COVID-19 infection	6-year-old girl	Mild intermittent fever, localized pain on soles, COVID-19 PCR: -, contact with COVID -19 patient: +	Negative	NM	8 days after symptom	Erythematous, edematous macules, blurred edges, erythematous cyanotic central, itchy, painful	Feet (bilateral plantar surfaces)	Negative	Nothing	3 days
Chilblain-like lesions in children following suspected COVID-19 infection	5-year-old boy	Fever, cough, vascular lesions on the feet and hand, preceded by edema, localized pain. difficulty walking, COVID-19 PCR: -	Systemic antibiotics	NM	60days after symptoms	Chilblain-like lesions (several rounded macules with blurred edges)	Plantar surface of both feet, right hand	Negative	Nothing	3 days

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
Chilblain-like lesions in children following suspected COVID-19 infection	11-year-old girl	Intermittent fever, localized pain, COVID-19 PCR: -	NM	NM	20 days before symptom	Erythematous and dusky 5-15 mm plaques	The lateral margin of the left foot and the dorsal surface of the left second, third, and fifth toes	Dense lymphocytic perivascular cuffing, periadnexal infiltration, vasculitis in small- to medium-sized vessels with endothelial cell swelling and red blood cell extravasation, fibrin thrombus in superficial capillary vessels	Nothing	Not reported
COVID-19 and chickenpox as a viral co-infection in a 12-year-old patient: A case report	12-year-old boy	Symptoms of chickenpox, fever, such as chest pain, severe dry coughs, COVID-19 PCR: +, Serology covid-19 test (IgG): -, (IgM): +, serology VZV test (IgM, IgG):+	Acetaminophen, acyclovir, hydroxychloroquine, azithromycin	Nothing	Same time with other symptoms	Diffuse papulovesicular itchy lesions (predominance of vesicles)	Trunk, face, limbs	Negative	Nothing	NM
Case report: Systemic inflammatory response and fast recovery in a pediatric patient with COVID-19	8-year-old girl	Fever (>40 ◦C), headache, abdominal pain, vomiting, diarrhea, rash, dry cough, COVID-19 PCR: +, serology test (IgG): +, CXR: NL	Co-amoxiclav (days 3-5), ceftriaxone (days 5-6, days 8-15), Piperacillin-tazobactam (days 6-8), metronidazole (days 6-15), cotrimoxazole (days 15-17), methylprednisolone (2 mg/kg/day, tapered over 6 days, days 8-13), IVIG (400 mg/kg, day 8), prophylactic nadroparin	Juvenile idiopathic arthritis	Same time with other symptoms	Diffuse itchy maculopapular rash	Diffuse	Negative	Nothing	NM
Chilblain-like lesions on feet and hands during the COVID-19 pandemic	15-year-old-girl	Nasal congestion, mild diarrhea, COVID-19 PCR: +, contact with COVID-19 patient: +	NM	NM	7 days after symptoms	Erythematous and papular lesions became purpuric one week later	Fingers, heels	NM	NM	NM
Chilblain-like lesions on feet and hands during the COVID-19 pandemic	15-year-old-boy	CXR: mild bilateral pneumonia, COVID-19 PCR: -, rapid antibody test: -, asymptomatic	Hydroxychloroquine, azithromycin, prophylactic heparin	Asthma	First presentation	Chilblain lesions	Toes, heel	Negative	Nothing	NM

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
SARS-CoV-2-induced Kawasaki-like hyperinflammatory syndrome: A novel COVID phenotype in children	12-year-old-boy	High fever, abdominal pain, diarrhea, vomiting, COVID-19 PCR: -, CXR: NL, serology tests (IgM, IgG): +	Empiric antibiotics, methylprednisolone (2 mg/kg for 2 weeks)	Nothing	5days after symptoms	Erythema and cracked lips, mild conjunctivitis, erythema and edema, petechial elements on feet	Lips, eyes, hands, feet	NM	NM	11 days
SARS-CoV-2-induced Kawasaki-like hyperinflammatory syndrome: A novel COVID phenotype in children	7-year-old-boy	Fever, nausea, vomiting, diarrhea, abdominal pain, shock, COVID-19 PCR: -, Serology tests (IgM, IgG): +, contact with COVID-19 patient: +	Broad spectrum empiric antibiotics, noninvasive respiratory support, IVIG (2 gr/kg), methylprednisolone (2 mg/kg)	Periodic fever, PFAPA*	5 days after symptoms	Bilateral conjunctivitis, scrotal erythema, skin rash, petechial elements, de-epithelialized tongue	Eyelid, palms, soles, limbs, back, tongue	NM	NM	10 days
A case of COVID-19 with late-onset rash and transient loss of taste and smell in a 15-year-old boy	15-year-old boy	Loss of appetite, transient metallic taste, smell-related disorders, sore throat, nasal congestion, runny nose, fever, asthenia, cough, COVID-19 PCR: +, contact with COVID-19 patient: +	Acetaminophen and azithromycin (oral suspension)	Nothing	1 day after symptoms	Multiple patchy erythematous and edematous lesions, pain and itching	Lower limbs, toes	Negative	Nothing	16 days
Varicella-like exanthem as a specific COVID-19–associated skin manifestation: Multicenter case series of 22 patients	8-year-old girl	Fever, cough, COVID-19 PCR: +	NM	NM	NM	Papulovesicular lesions (predominance of papules)	Trunk, scattered	NM	NM	NM
Fever with rash is one of the first presentations of COVID-19 in children: A case report	12-month-old boy	Fever, conjunctivitis, respiratory distress, anasarca edema, COVID-19 PCR: +, third-day HRCT: patchy infiltration, pleural effusion, ground-glass opacity, and halo sign in both lungs, contact with COVID-19 patient: +	Azithromycin (single dose), ceftriaxone (40 mg/ kg, BID, day 1 to 3), hydroxychloroquine (5 mg/ kg daily), cetirizine (2.5 ml daily), IVIG (1 g/kg day 2), zinc gluconate (20 mg daily), albumin (1 g/kg of 10% solution, day 2), vitamin D (cholecalciferol 1000 IU orally daily), meropenem (30 mg/kg TDS)	Nothing	2 days after other symptoms	Erythematous maculopapular erythema multiform like targetoid rashes with faded centers, erythematous patches, mildly edematous skin	Started symmetrically from the soles and ascended to the trunk, and finally, to the face and palms	Negative	Nothing	5 days

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
Cutaneous manifestations in COVID-19: A skin rash in a child	12-year-old girl	Fever, fatigue, headache, COVID-19 PCR: +, Chest CT scan: NL, contact with COVID-19 patient: +	Paracetamol	NM	3 days after other symptoms	Purpuric eruptions and erythematous macula rashes, slightly swollen tongue and irritated with pronounced lingual papillae	Upper eyelids, above the eyebrows and in temporal region, tongue	Negative	Nothing	3 days appearance
Skin findings in the COVID-19 pandemic in the Region of Murcia	<1-year-old boy	Contact with COVID-19 patient: +, asymptomatic	NM	NM	First presentation	Rash	Trunk, upper limbs	NM	NM	NM
Skin findings in the COVID-19 pandemic in the Region of Murcia	5-year-old girl	COVID-19 PCR: -, contact with COVID-19 patient: +, asymptomatic	NM	NM	First presentation	Hives	General	NM	NM	NM
Skin findings in the COVID-19 pandemic in the Region of Murcia	1-year-old boy	COVID-19 PCR: -, contact with COVID-19 patient: +, asymptomatic	NM	NM	First presentation	Chilblain	Feet	NM	NM	NM
Skin findings in the COVID-19 pandemic in the Region of Murcia	2-year-old girl	COVID-19 PCR: -, contact with COVID-19 patient: +, asymptomatic	NM	NM	First presentation	Hives	Upper limbs	NM	NM	NM
Skin findings in the COVID-19 pandemic in the Region of Murcia	16-year-old girl	Contact with COVID-19 patient: +, asymptomatic	NM	NM	First presentation	Chilblain	Feet	NM	NM	NM
Skin findings in the COVID-19 pandemic in the Region of Murcia	5-year-old boy	Fever,COVID-19 PCR: -, contact with COVID-19 patient: +	NM	NM	2 days before symptoms	Hives	General	NM	NM	NM
Skin findings in the COVID-19 pandemic in the Region of Murcia	<1-year-old girl	Fever, respiratory symptoms,COVID-19 PCR: -, contact with COVID-19 patient: +	NM	NM	17 days after symptoms	Rash	Face	NM	NM	NM

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
Concurrent chilblains and retinal vasculitis in a child with COVID-19	11-year-old boy	COVID-19 PCR: -, serology (IgM): -, (IgG): +, retinal vasculitis	NM	NM	14 days before	Edematous and erythematous to violaceous plaques (chilblains)	Bilateral dorsal surfaces of the toes	NM	NM	NM
Therapy for probable COVID-19 associated erythema pernio-like lesions in pediatric age: Case report	15-year-old girl	NM	NM	NM	NM	Circumscribed erythematous and edematous lesions, bluish-red color	Dorsal surfaces of the toes of the left foot	Negative	Mometasone furoate cream (once a day), heparin gel (once a day)	4 days treatment
COVID-19 inflammatory syndrome with clinical features resembling Kawasaki disease	11-year-old boy	Fever, sore throat, rhinorrhea, dry cough, emesis, diarrhea, myalgia, bilateral conjunctivitis, confusion, severe headache, neck stiffness, COVID-19 PCR: +, CXR: patchy perihilar opacities in both lungs	Intubated, epinephrine, norepinephrine, vasopressin, vancomycin, ceftriaxone, acyclovir, clindamycin, doxycycline, cefepime, stress dose hydrocortisone, IVIG, IV corticosteroids (for 5 days)	Febrile seizures	2 days after other symptoms	A polymorphous rash, diffuse maculopapular rash, desquamation of fingertips	Torso, extremities, face	Negative	NM	NM
COVID-19 inflammatory syndrome with clinical features resembling Kawasaki disease	7-year-old girl	Fever, sore throat, severe abdominal pain, emesis, diarrhea, conjunctival erythema, acute and severe ileitis and colitis, altered mental status, COVID-19 PCR: +, CXR: patchy perihilar opacities	IV corticosteroids, oral glucocorticoids	Nothing	Same time with other symptoms	An erythema multiforme-like rash, cracked lips, and strawberry tongue	Face, trunk, back, lips, tongue	Negative	NM	NM

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
SARS-COV-2 infection and Kawasaki disease: Case report of a hitherto unrecognized association	6-year-old boy	Fever, sore throat, asthenia, vomiting and diarrhea, abdominal tension and pain, respiratory distress, tachypnea, oxygen desaturation, paralytic ileus, COVID-19 PCR: +, CXR: pulmonary infiltrates at the right base and minimal pericardial effusion, contact with COVID-19 patient: +	Amoxicillin+clavulanic acid, cefotaxime (IV on day 6), piperacillin/tazobactam and metronidazole (IV on day 7), high-dose IVIG 2 g/kg, high-dose acetylsalicylic acid (ASA 50 mg/kg/day), enema, polyethylene glycol, ASA 5 mg/kg/day therapy (after 48 h of apyrexia)	Nothing	On day 6 of illness	Erythematous rash in the back and hands, labial and conjunctival hyperemia	Back, hands, labia	Negative	NM	NM
Kawasaki disease features and myocarditis in a patient with COVID-19	10-year-old boy	Fever, fatigue, diarrhea, cough, rash, conjunctivitis, mild cracking of lips, erythematous oropharynx, hypotension, COVID-19 PCR: +	Ibuprofen (400 mg orally), dopamine 5 µg/kg/min and titrated up to 10 µg/kg/min	Nothing	NM	Diffuse rash, appeared mildly erythematous with blanching macules and patches	Diffuse, most prominent on extremities, trunk, palms, soles	NM	Negative	NM
A novel pediatric multisystem inflammatory syndrome during the COVID-19 pandemic	13-year-old boy	Fever, headache, red eyes, shortness of breath, diffuse abdominal pain, vomiting and diarrhea, conjunctival injection, tachycardic, hypotensive, tachypneic, SPO2:97%, COVID-19 PCR: -, CXR: cardiomegaly, COVID-19 serology: +	Vancomycin, piperacillin/tazobactam, n vasopressors, furosemide, IVIG, methylprednisolone, ceftriaxone and enoxaparin (for 7 days), ASA	Mild asthma	2 days after other symptoms	Nonpruritic rash, large circular blanching patches of erythema, smaller scattered macules, erythematous oral mucous membranes	Knee, thigh, back, neckline, mouth	Negative	NM	NM

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
A novel pediatric multisystem inflammatory syndrome during the COVID-19 pandemic	10-year-old girl	Fever, sore throat, rash, abdominal pain, vomiting, decrease appetite, tachycardic, bilateral cervical lymphadenopathy, COVID-19 PCR: -, CXR: NL, COVID-19 serology: +	Ibuprofen, 10-mL/kg bolus of 0.9% normal saline (NS), steroids, ASA	Negative	Day 2 of illness	Pruritic rash, erythematous, maculopapular lesions, erythematous, annular lesions of varying sizes on thighs, dry cracked lips	Palms of both hands, arms, thighs, lips	Negative	NM	NM
A novel pediatric multisystem inflammatory syndrome during the COVID-19 pandemic	16-year-old girl	Fever, headache, abdominal pain, vomiting, diarrhea, rash, decreased appetite and urine output, tachycardia, hypotension, tachypnea, SPO2:96%, transient ileus, COVID-19 PCR: -, COVID-19 serology: +	Normal saline (NS) bolus (15 mL/kg), methylprednisolone, IVIG, vancomycin and ceftriaxone (discontinued after 48 hours of negative cultures), enoxaparin	Negative	30 days after other symptoms	Dry mucous membranes, dry cracked lips, erythematous rash to both palms and fingers	Lips, palms, fingers	Negative	NM	NM
A novel pediatric multisystem inflammatory syndrome during the COVID-19 pandemic	4-year-old girl	Fever, abdominal pain, rash, headache, throat pain, decrease in oral intake, tachycardic, tachypnea, SPO2:95%, COVID-19 PCR: +, COVID-19 serology: +	Acetaminophen, normal saline (NS) bolus 20 mL/kg, piperacillin/ tazobactam, vancomycin, IVIG, methylprednisolone, ASA, ceftriaxone	Negative	30 days after other symptoms	Pruritic rash started diffuse, patchy, blanching erythematous rash, erythematous tongue	Arms, legs, face, torso, extremities sparing palms and soles, tongue	Negative	NM	NM
COVID-19 and Kawasaki disease: Novel virus and novel case	6-month-old girl	Fever, fussiness, refusal to eat, mild congestion, tachycardia, tachypnea, SPO2:100%, limbic-sparing conjunctivitis, irritability, mild subcostal retractions, CXR: faint opacity in the left midlung zone, COVID-19 PCR: +	Single dose of 2 g/ kg IVIG, high-dose acetylsalicylic acid (ASA 20 mg/kg four times daily)	Nothing	2 days after other symptoms	An erythematous, pruritic, blotchy rash, dry cracked lips, a blanching, polymorphous, maculopapular rash, swelling, tongue papilla	Lips, hands and lower extremities prominent, tongue	Negative	NM	NM

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
Multisystem inflammatory syndrome in children (MIS-C) associated with 2019 novel coronavirus (SARS-CoV-2) infection	10-year-old girl	Fever, diffuse abdominal pain, multiple episodes of watery, non-bloody, nonmucoid stools, pink eyes, lethargy, conjunctival injection, hypotension, COVID-19 PCR: +	Norepinephrine, IV antibiotics (ceftriaxone and linezolid) for a total of 2 days, IVIG (2 g/Kg), steroids, enoxaparin	Nothing	4 days after other symptoms	A generalized blanching rash	Generalized	Negative	NM	NM
Multisystem inflammatory syndrome in children (MIS-C) associated with 2019 novel coronavirus (SARS-CoV-2) infection	6-year-old girl	Fever, headache, vomiting, abdominal pain, diarrhea, conjunctivitis, hypotension, respiratory failure, COVID-19 PCR: -, COVID-19 serology (IgG): +, contact with COVID-19 patient: +, Chest CT scan: bilateral infiltrates with small pleural effusion	Pressor support, intubation and mechanical ventilation, broad-spectrum IV antibiotics (meropenem and linezolid), IVIG (2 g/kg), methylprednisolone, enoxaparin, tocilizumab (one dose of 12 mg/kg) on day 4 of hospitalization	Nothing	4 days after other symptoms	Rash	NM	NM	NM	NM
Incomplete Kawasaki disease as presentation of COVID-19 infection in an infant: A case report	5-month-old boy	High-spiking fever, bilateral non-purulent conjunctivitis, irritability, COVID-19 PCR: +, CXR: mild opacity in right middle lung zone, COVID-19 PCR of both parents: +	IV cephalosporin and paracetamol, IVIG (2 g/kg), oral aspirin (30 mg/kg reduced to 3 mg/kg/day after 48 hour) and azithromycin (10 mg/kg/day continued for 5 days)	Nothing	Day 3 of illness	Non-pruritic maculopapular rash	Upper limbs, trunk	Negative	NM	NM
A child confirmed COVID-19 with only symptoms of conjunctivitis and eyelid dermatitis	2-years-old boy	Conjunctivitis, COVID-19 PCR: +, contact with COVID-19 patient: +, COVID-19 serology (IgG): +, chest CT scan: NL	NM	NM	7 days after positive PCR	Eyelid dermatitis	Eyelid	Negative	NM	5 days

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
Hyper-inflammatory syndrome in a child with COVID-19 treated successfully with intravenous immunoglobulin and tocilizumab	8-year-old boy	Fever, cough, throat pain, intercostal retractions, tachycardia, hypotension, warm extremities, non-purulent bulbar conjunctivitis, tender hepatomegaly, abdominal distention, CXR: right upper and middle lobe infiltrates, COVID-19 RT-PCR: +	Ceftriaxone and azithromycin (Days 4-7), piperacillin-tazobactam, doxycycline, HFNC, meropenem, vancomycin, clindamycin, IVIG (2 g/kg), aspirin (75 mg once a day), tocilizumab (8 mg/kg IV over 2 hours)	Nothing	7 days after other symptoms	Generalized non-pruritic erythematous skin rash, periungual peeling of skin, cracked lips, strawberry tongue, edema of limbs	Generalized, lips, tongue, limbs	Negative	NM	14 days
Kawasaki-like syndrome as an emerging complication of SARS-CoV-2 infection in young adults.	18-year-old boy	Abdominal pain, fever, vomiting and diarrhea, increased CRP, thrombocytopenia, hyperlactatemia, SARS-CoV-2 PCR: +	Norepinephrine (0.5 µg/kg/min) crystalloids/ dobutamine was initially titrated to 7.5 µg/kg/min, piperacillin/tazobactam, vancomycin and clindamycin	HTN, AKI	3 days after other symptoms	Erythematous maculopapular rash	Torso, head, neck and upper limbs	NM	NM	2 days

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
Cutaneous endothelial dysfunction and complement deposition in COVID-19	15-year-old boy	He remained afebrile and asymptomatic, SARS-CoV-2 PCR: +	NM	Nothing	First presentation	2 acral necrotic lesions	On the fourth and fifth fingers of the left hand	Infiltrate of neutrophils and lymphocytes of the perivascular zone and in the adjacent tissue. The vascular walls were thickened by exudation of fibrin and inflammatory cells, with degeneration of endothelial cells. thrombosis of vessels, with luminal fibrin deposits with focal necrosis. The dermis showed edema, inflammatory infiltrates, and perivascular hemorrhage. There was extravasation of red cells, nuclear dust, and deposits of fibrin within the vessels.	NM	NM
Livedo reticularis and acrocyanosis as late manifestations of COVID-19 in two cases with familial aggregation. Potential pathogenic role of complement (C4c).	12-year-old boy	Catarrh, dry cough, fever, RT-PCR for SARS-CoV-2 and other respiratory viruses: -, SARS-CoV-2 IgA: +	NM	NM	21 days after other symptoms	Acrocyanosis and livedo reticularis	Extremities	Chronic perivascular inflammatory infiltrate with prominent endothelium	NM	NM
Livedo reticularis and acrocyanosis as late manifestations of COVID-19 in two cases with familial aggregation. Potential pathogenic role of complement (C4c).	14-year-old boy	Headache, a fever of up to 38.5°C, general malaise, a dry cough, and diarrhea, SARS-CoV-2 IgG: +, SARS-CoV-2 PCR: -	NM	NM	14 days after other symptoms	Acrocyanosis	Extremities	NM	NM	NM

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
Livedo reticularis and acrocyanosis as late manifestations of COVID-19 in two cases with familial aggregation. Potential pathogenic role of complement (C4c).	10-year-old girl	Fever, a dry cough, asthenia, and headache, RT-PCR for SARS-CoV-2:-, SARS-CoV-2 IgA: +, IgM: +	NM	NM	7 days after other symptoms	Livedo reticularis	Extremities	Chronic inflammatory component	NM	NM
Skin manifestations in COVID-19: A case series of 5 patients from ElazIĞ, Turkey.	18-years-old boy	Fever, headache, sinus pressure, anosmia,	NM	Nothing	NM	Purple, erythematous macules	On the left four toes	NM	NM	Few days
Skin manifestations in COVID-19: A case series of 5 patients from ElazIĞ, Turkey.	10-months boy	Asymptomatic	NM	NM	First presentation	Widespread erythematous rash	Body and arms	NM	NM	10 days
Herpes zoster ophthalmicus in COVID-19 patients.	7-years-old girl	Fever, malaise, and dry cough, COVID-19 PCR: +	NM	NM	5 days after other symptoms	Blepharitis and conjunctivitis	Face	NM	Acyclovir 20 mg/kg/5 times/ day/7 days	NM
Herpes zoster ophthalmicus in COVID-19 patients.	9-years-old boy	Fever, diarrhea, and dry cough, COVID-19 PCR: +	NM	NM	4 days after other symptoms	Blepharitis with lid edema and conjunctivitis	Face	NM	Acyclovir 20 mg/kg/5 times/ day/7 days	NM
Varicella-like exanthem associated with COVID-19 in an 8-year-old girl: A diagnostic clue?	8-year-old girl	Mild cough, thrombocytopenia (platelet count: 105,000/µL), mild fever, COVID-19 PCR: +	Nothing	NM	3 days after other symptoms	Papulovesicular skin eruption	Trunk	Refused a skin biopsy	Nothing	7 days
Urticaria in an infant with SARS-CoV-2 positivity.	6-month-boy	Asymptomatic, COVID-19 PCR: +	Betamethasone (soluble tablets, 0.5 mg/d for 7 days)	NM	14 days after other symptoms	Giant urticaria, with multiple lesions	Trunk and limbs	NM	NM	NM

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
Special dermatological presentation of pediatric multisystem inflammatory syndrome related to COVID-19: erythema multiforme.	13-year-old boy	Fever along with abdominal and thoracic pain, odynodysphagia., COVID-19 PCR: -, COVID-19 serology (IgA, IgG): +, chest CT scan: bibasal pneumonia	Paracetamol started on day 1, azithromycin started on day 2	Nothing	Same time with other symptoms.	Four isolated round papular lesions	Left shoulder	NM	NM	7 days
Erythema multiforme-like lesions in children and COVID-19.	12 years old boy	Asymptomatic, COVID-19 PCR= -	NM	NM	First presentation	Erythema multiforme lesions	Elbows, knees, forearms, ankles, dorsal and lateral feet, hands, ears	Interface dermatitis with superficial and deep perivascular lymphocytic inflammation, Moderate exocytosis with vacuolar changes and spongiosis	Topical corticosteroids	7-21 days
Erythema multiforme-like lesions in children and COVID-19.	17 years old boy	Mild respiratory symptoms, COVID-19 PCR: -	NM	NM	NM	Erythema multiforme lesions	Elbows, knees, dorsal feet, hands	Superficial and deep perivascular inflammation and vascular ectasia, mild exocytosis, vacuolar changes, and spongiosis	Oral corticosteroids	7-21 days
Erythema multiforme-like lesions in children and COVID-19.	11-years-old girl	Mild GI symptoms, COVID-19 PCR: +	No treatment	NM	NM	Erythema multiforme lesions	Elbows, knees, thighs, arms, forearms, legs, ankles, dorsal feet and hands	No biopsy	No treatment	7-21 days
Erythema multiforme-like lesions in children and COVID-19.	15-years-old boy	Mild respiratory symptoms, COVID-19 PCR: -	No treatment	NM	NM	Erythema multiforme lesions	Elbows, knees, forearms, ankles, dorsal feet, hands	No biopsy	No treatment	7-21 days
Atypical erythema multiforme palmar plaques lesions due to Sars-Cov-2.	17-year-old patient	Mild COVID -19 symptoms	Vitamin C	Nothing	15 days after	Erythematous maculopapular, atypical targetoid, eruption (erythema multiforme)	Palms	NM	NM	NM
Dermoscopy of chilblain-like lesions during the COVID-19 outbreak: A multicenter study on 10 patients	11-year-old boy	Some systemic symptoms, COVID-19 PCR: -	NM	Nothing	33 days after	Erythematous-edematous	Feet	Dermoscopy: background: erythematous, vessels: linear	NM	NM

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
Dermoscopy of chilblain-like lesions during the COVID-19 outbreak: A multicenter study on 10 patients	13-year-old boy	Some systemic symptoms, COVID-19 PCR: -	NM	Nothing	34 days after	Blistering	Feet	Dermoscopy: background: coppery red, vessels: hemorrhagic dots, linear	NM	NM
Dermoscopy of chilblain-like lesions during the COVID-19 outbreak: A multicenter study on 10 patients	12-year-old girl	Some systemic symptoms, COVID-19 PCR: -	NM	Nothing	12 days after	Erythematous-edematous	Feet	Dermoscopy: background: coppery red, vessels: hemorrhagic dots	NM	NM
Dermoscopy of chilblain-like lesions during the COVID-19 outbreak: A multicenter study on 10 patients	14-year-old girl	Some systemic symptoms, COVID-19 PCR: -	NM	Nothing	10 days after	Erythematous-edematous, crusts, unstructured purple bullae	Feet	Dermoscopy: background: coppery red, vessels: hemorrhagic dots	NM	NM
Dermoscopy of chilblain-like lesions during the COVID-19 outbreak: A multicenter study on 10 patients	13-year-old boy	Some systemic symptoms, COVID-19 PCR: -	NM	Nothing	12 days after	Blistering, crusts, unstructured purple areas	Feet	Dermoscopy: background: coppery red, vessels: hemorrhagic dots, glomerular vessels,	NM	NM
Dermoscopy of chilblain-like lesions during the COVID-19 outbreak: A multicenter study on 10 patients	11-year-old girl	Some systemic symptoms, COVID-19 PCR: -	NM	Nothing	10 days after	Erythematous-edematous, unstructured purple areas	Hands, feet	Dermoscopy: background: coppery red irregular linear vessels, cuticular vessels, vessels with branches, multiple short vessels arranged perpendicularly	NM	NM
Dermoscopy of chilblain-like lesions during the COVID-19 outbreak: A multicenter study on 10 patients	13-year-old girl	Some systemic symptoms, COVID-19 PCR: -	NM	Nothing	15 days after	Erythematous-edematous	Hands	Dermoscopy: background: erythematous, vessels: hemorrhagic dots, irregular dots, cuticular vessels	NM	NM

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
Dermoscopy of chilblain-like lesions during the COVID-19 outbreak: A multicenter study on 10 patients	12-year-old boy	Some systemic symptoms, COVID-19 PCR: -	NM	Nothing	6 days after	Erythematous-edematous, round, brown unstructured area with a halo	Feet	Dermoscopy: background: coppery red, vessels: hemorrhagic dots, irregular linear vessels	NM	NM
Dermoscopy of chilblain-like lesions during the COVID-19 outbreak: A multicenter study on 10 patients	13-year-old boy	Some systemic symptoms, COVID-19 PCR: -	NM	Nothing	17 days after	Erythematous-edematous	Feet	Dermoscopy: background: erythematous dotted	NM	NM
Acro-ischemic lesions associated with extremely elevated D-Dimer in a child during the COVID-19 pandemic	10-year-old boy	Dry cough, fever, RT-PCR and a SARS-CoV-2 IgM/IgG: -	NM	Nothing	Same time with other symptoms	Acral lesions similar to acro-ischemia, Erythematous–purpuric lesions and superficial crusts	Toes of both feet	Vacuolar degeneration in the basal epidermal layer, superficial and deep perivascular lymphocytic infiltrates, swollen endothelium, edema, fibrin and extravasation of red, blood cells in the papillary dermis.	NM	28 days

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
The differing pathophysiologies that underlie COVID-19associated perniosis and thrombotic retiform purpura: A case series	16-year-old boy	COVID-19 PCR: -	NM	NM	First presentation	Bilateral painful perniotic-like plaques, areas of ulceration and focal targetoid areas	Toes of both feet	Papillary dermal edema, dense superficial and deep angiocentric lymphocytic, histiocytic infiltration and mononuclear-cell-dominant interface dermatitis surrounded and infiltrated the blood vessels and were adjacent to the eccrine coil, ducts and glands. Reniform and serpiginous nuclei and intracytoplasmic cellular debris in histiocytes. Fibrin deposition, reticular dermal-based blood vessels.	NM	NM
Comment on 'two cases of COVID-19 presenting with a clinical picture resembling chilblain: first report from the Middle East': pernio unrelated to COVID-19	16-year-old girl	Asymptomatic PCR and serology: -	NM	NM	First presentation	Erythematous–violaceous papules	Distal joints	No biopsy	NM	1 week
Comment on 'two cases of COVID-19 presenting with a clinical picture resembling chilblain: first report from the Middle East': pernio unrelated to COVID-19	16-year-old boy	Asymptomatic PCR and serology: -	NM	NM	First presentation	Erythematous macules and reddish papules with an orange hue, slight edema, discrete blanching	Hands, fingers	No biopsy	NM	1 week

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
Skin signs resembling vascular acrosyndromes during the COVID-19 outbreak in Italy	16-year-old girl	Pharyngodynia	NM	Alopecia areata universalis	2 weeks after	Painful erythematous plaques	Both heels	No biopsy	Emollients and oral paracetamol.	NM
Skin signs resembling vascular acrosyndromes during the COVID-19 outbreak in Italy	18-year-old girl	Asymptomatic	NM	Negative	First presentation	Erythematous plaques, erythematous confluent papules, itching and pain	Extensor surface of her toes, both heels	No biopsy	Emollients and oral paracetamol	NM
Management of pernio-like cutaneous manifestations in children during the outbreak of COVID-19	5-year-old boy	Fever, COVID-19 PCR and serology: -	NM	NM	3 weeks after	Itchy swelling, redness, flaking	Toes	NM	NM	NM
Management of pernio-like cutaneous manifestations in children during the outbreak of COVID-19	12-year-old girl	Fever, COVID-19 PCR and serology: -	NM	NM	3 weeks after	Purple hand injuries, painless	Hand	NM	NM	NM
Management of pernio-like cutaneous manifestations in children during the outbreak of COVID-19	11-year-old boy	Fever, COVID-19 PCR and serology: -	NM	NM	4 days after	Purple, painless, itchy hands lesions	Hands	NM	NM	NM
Management of pernio-like cutaneous manifestations in children during the outbreak of COVID-19	11-year-old boy	Chills, asthenia, COVID-19 PCR and serology: -	NM	NM	3 weeks after	Purple skin lesions, painfulness	Toes of both feet and heels	NM	NM	NM
Management of pernio-like cutaneous manifestations in children during the outbreak of COVID-19	8-year-old girl	Asymptomatic, COVID-19 PCR and serology: -	NM	NM	First presentation	Petechial skin lesions	Heels	NM	NM	NM
Management of pernio-like cutaneous manifestations in children during the outbreak of COVID-19	13-year-old girl	Asymptomatic, COVID-19 PCR and serology: -	NM	NM	First presentation	Purple, painless, itchy	Toes and heels	NM	NM	NM

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
Management of pernio-like cutaneous manifestations in children during the outbreak of COVID-19	14-year-old girl	Nasal congestion, COVID-19 PCR and serology: -	NM	NM	Same time with other symptoms	Itching, burning, purple lesion with pain	Feet	NM	NM	NM
Management of pernio-like cutaneous manifestations in children during the outbreak of COVID-19	15-year-old boy	Asymptomatic, COVID-19 PCR and serology: -	NM	NM	First presentation	Purple, painful lesions	Fingers of both hands	NM	NM	NM
Management of pernio-like cutaneous manifestations in children during the outbreak of COVID-19	14-year-old girl	Fever, chest pain, dyspnea, COVID-19 PCR and serology: -	NM	NM	1 week after	Purple, painful lesion	First and second toes, on sole of both feet	NM	NM	NM
SARS-CoV-2-related chilblains	16-year-old girl	Asymptomatic PCR: -, IgG and IgA Antibody: +	NM	Nothing	First presentation	Painful, red-violaceous papules	Left third toe, right fifth toe, right index finger	Superficial and deep dermal lymphocytic inflammation with subepidermal edema	Topical corticosteroids	3 weeks
Chilblains-like dermatologic manifestation of COVID-19 diagnosed by serology via multidisciplinary virtual care	7-year-old boy	Fever, pharyngitis, and cough, PCR: -, IgG antibodies: +	NM	NM	6 weeks after	Pain, swelling, erythema and mild edema, localized violaceous, mild pruritus, erosions,	Plantar and dorsal feet, toes	Vesicular changes	NM	NM
Oral vesicles and acral erythema: report of a cutaneous manifestation of COVID-19	9-year-old girl	Profound weakness, loss of appetite, high fever (maximum temperature of 39.6 °C), abdominal pain, diarrhea, dry cough, shortness of breath with tachypnea, hypoxia, somnolence, PCR: +, CXR=ground glass densities involving both lungs	Hydration and supplemental oxygen therapy as needed at home	Nothing	3 days before	Vesicular, herpetiform erosions, oral eruption, acral deep red, edematous, erythematous papules and plaques	Lips, anterior tongue, and buccal mucosa, dorsal hands and feet	NM	NM	1 week

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
Histologic features of long-lasting chilblain-like lesions in a pediatric COVID-19 patient	16-year-old boy	Transient dysgeusia and mild diarrhea, RT-PCR: +	NM	NM	20 days before	Multiple asymptomatic erythemato-edematous, partially eroded macules and plaques	Dorsal aspects of the fingers, second right toe, palmar aspect of the fifth finger	Peri-vascular and peri-eccrine pattern superficial and deep lymphocytic infiltration, edema of the papillary dermis	NM	NM
Histological findings in chilblain lupus-like COVID lesions: in search of an answer to understand their etiology	17-year-old boy	Asymptomatic PCR: +, serology: positive IgG with negative IgM	NM	NM	First presentation	Acral lesions, periungual erythema	Second and third finger toe	Hydropic degeneration in the basal layer, necrotic keratinocyte, moderate lymphocyte infiltration in the papillary and reticular dermis around the vessels, dense perieccrine infiltration without fibrinoid necrosis	NM	NM
Recent outbreak of chilblain-like lesions is not directly related to SARS-CoV-2 infection	11 –year-old boy	Asthenia, headache, Serology: -	NM	Nothing	28 days after	Erythematous purplish patches, papules with superficial erosion, post-inflammatory scaling	Dorsal surface of the toes (both sides I and II)	Epidermal lesions (mild spongiosis and parakeratosis, basal layer vacuolation, apoptotic keratinocytes, epidermal necrosis), perivascular and periadnexal lymphohistiocytic infiltrate, upper dermis edema, vascular lesions (capillarectasy and fibrinoid thrombi, angiocentrism, angiotropism and endothelium swelling)	NM	27 days
Recent outbreak of chilblain-like lesions is not directly related to SARS-CoV-2 infection	18-year-old boy	Asymptomatic COVID-19 PCR and serology: -	NM	Nothing	First presentation	Erythematous, livedoid, purplish, patches, papules, with superficial erosion	Dorsal and lateral sides of the toes (left I, II, III, V) and fingers		NM	27 days
Recent outbreak of chilblain-like lesions is not directly related to SARS-CoV-2 infection	14-year-old boy	Cough, asthenia, headaches, myalgia, arthralgia, serology and PCR: -	NM	Nothing	35 days after	Erythematous, livedoid, purplish patches, papules with post-inflammatory pigmentation and scaling	Dorsal surface and fingertips of all toes		NM	43 days
Images in practice: painful cutaneous vasculitis in a SARS-Cov-2 IgG-Positive Child	11-year-old girl	Asymptomatic COVID-19 PCR:-, serology:+	NM	Nothing	First presentation	Erythematous chilblain-like, several ulcerative lesions with dyschromia of the nails, pain, itching, and purulent discharge	Feet, nails	NM	Paracetamol 750 mg 4 times/ day, mupirocin 2% ointment TID	15 days

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
Silent COVID-19: what your skin can reveal	14-year-old boy	Asymptomatic PCR: +	NM	NM	First presentation	Erythematous-violaceous lesions, red macules and papules, small ulcer	Dorsum of all digits of both feet, lateral and plantar aspects of both feet	NM	NM	7 days
Silent COVID-19: what your skin can reveal	14-year-old boy	Asymptomatic, PCR: +	NM	NM	First presentation	Small erythematous-violaceous lesions, necrotic aspects with blackish crusts	Dorsum of all digits of the feet	NM	NM	20 days
Silent COVID-19: what your skin can reveal	18-year-old boy	Fever, PCR: +	NM	NM	2 days after	Chilblain-like lesions	Distal part of all digits of the feet	NM	NM	10 days
Acral purpuric lesions (Erythema multiforme type) associated with thrombotic vasculopathy in a child during the COVID-19 pandemic	12-year-old boy	Asymptomatic, COVID-19 PCR: -, COVID-19 serology: -	NM	NM	First presentation	Pruriginous, hemorrhagic purpuric eruption and vesicular blisters	Heels of both feet	Partial epidermal necrosis, perivascular lymphoid infiltrate in superficial and deep dermis, microthrombi with extravasation of red blood cells in some capillaries in papillary dermis. Vasculitis changes in relation to the lymphoid component but not in the thrombotic one	NM	NM
Giant urticaria and acral peeling in a child with COVID-19.	6-year-old girl	Fever and pharyngodynia, PCR=+	NM	Nothing	1 day before	Fleeting urticarial lesions and migrant appearance with polycyclic contours, desquamation of the distal phalanges and cyanosis of the apical portion of the nail bed, pruritic (acute viral giant urticarial)	All the body, phalanges of the hands and feet	NM	Antihistamine	4 days

Table 1. Continued

Title	Case characteristic	COVID-19 signs and symptoms	COVID-19 management	Patient's comorbidities	Time of onset of reaction	Type of skin manifestation	Location of skin manifestation	Skin biopsy	Management of reactions	Resolution time
Skin involvement in SARS-CoV-2 infection: Case series.	12-year-old girl	Asymptomatic, PCR=+	NM	Nothing	First presentation	Erythematous-edematous purple lesions and clear demarcation from the remaining skin of the feet (chilblain-like lesions)	Distal phalanges of all 10 toes	NM	NM	NM
Skin involvement in SARS-CoV-2 infection: Case series.	8-year-old boy	Asymptomatic	NM	NM	First presentation	Chilblain-like lesions	Toes	NM	NM	NM

*NM: Not mentioned
*PFAPA syndrome: Periodic fever, aphthous stomatitis, pharyngitis and adenitis
*IV: Intravenous
*IVIG: Intravenous immunoglobulins
*HFNC: High-flow nasal cannula
*AKI: Acute kidney injury
*CRP: C-reactive protein

Management

It took 2–56 days on average for skin lesions to resolve. The results of these case reports demonstrated that most of the children's skin lesions in the setting of COVID-19 healed spontaneously without any treatment. In SARS-CoV-2-induced Kawasaki-like hyper-inflammatory syndrome, aspirin, intravenous immunoglobulin, and systemic corticosteroids were prescribed. Finally, in two cases with ophthalmic herpes zoster, acyclovir was administered.

Skin lesions related to protection equipment

The indirect influence of changes in lifestyle during the coronavirus pandemic on the incidence of skin lesions has recently been documented. Four studies fell in this category. Three studies were related to irritant contact dermatitis caused by handwashing, disinfectants, and hand sanitizers. A history of atopic dermatitis had long-term consequences on the development of hand eczema. There were no differences between the two genders. In a case series, seven children presented with acral dermatosis; a long-lasting period of sitting in an inappropriate position on the floor during lockdown was the predisposing factor [62–65].

A drug-related mucocutaneous manifestation

In one case series, a 17-year-old girl presented with maculopapular eruptions after three days of hospitalization, correlating with using hydroxychloroquine (HCQ) treatment for COVID-19 [7].

Studies with a large number of cases of mucocutaneous manifestations related to COVID-19

In this category, 18 studies met the eligibility criteria for inclusion. Two studies were cohorts, and the rest were case series with a large number of cases, totaling 482 patients. The study population consisted of 255 boys (58.3%) and 182 girls (41.6%), with a boy/girl ratio of 1.4; one study did not mention gender. The mean age of the participants was 12.4 years. The age range was not available in one study [47,66–82].

Table 2. Studies that reported skin lesions in children related to protective equipment used for protection against coronavirus disease 2019 (COVID-19)

First author	Title	Type of article	Number of patients	Gender	Age (year)	Incidence of skin lesions	Protective equipment	Patient's comorbidities	Time of onset of reaction	Type of skin reaction	Location of skin reaction
Borch, L.	COVID-19 reopening causes high risk of irritant contact dermatitis in children	Cohort	6,273 children	Boy=3,174 (50.6%) Girl=3,099 (49.40%)	Mean: 6.70 ± 3.12, Range:0-12	42.4% (N=4,496)	Handwashing and disinfection	Known allergy: 491 (7.83%), Atopic dermatitis: 1334 (21.27%)	NM	Irritant contact dermatitis	Hand
A B Simonsen	High incidence of hand eczema in Danish school children following intensive hand hygiene during the COVID-19 pandemic - a nationwide questionnaire study	Cohort	25,672 children	Boy=12,962 (50.4%), Girl=12,710 (49.5%)	Range: 5-13	40.9% (N=10,491)	Handwashing and disinfection	Atopic dermatitis	NM	Irritant contact dermatitis	Hand
N Bodak	COVID-19 lockdown induced acral dermatosis in children	Case series	7 children	Boy=3 (42.8%), Girl=4 (57.1%)	Mean: 6 Range:5-8	100% (N=7)	Friction and rubbing (playing activities on the floor)	Healthy children	Sixth week of the lockdown	Rounded pad-like hyperkeratotic, frictional dermatosis, initially erythematous and then slightly hyperpigmented	Feet and knees
Anne B Simonsen	Increased occurrence of hand eczema in young children following the Danish hand hygiene recommendations during the COVID-19 pandemic	Cohort	5,842 children	Boy=2,987 (51.1%) Girl=2,855 (48.8%)	Mean: 3.4 ± 1.37, Range:0-7	28.6% (N=1668)	Handwashing and disinfection	Atopic dermatitis, asthma, hay fever	NM	Irritant contact dermatitis	Hand

Table 3. Drug-related mucocutaneous manifestations in children with coronavirus disease 2019 (COVID-19)

First author	Title	Case characteristics	COVID-19 signs and symptoms	Patient's comorbidities	COVID-19 drug	Time of onset of reaction	Type of skin reaction	Location of skin reaction	Skin biopsy	Management of reactions	Resolution time	Outcome
Bursal Duramaz	Appearance of skin rash in pediatric patients with COVID-19: Three case presentations	17-year-old girl	COVID-19 PCR: positive	NM	Hydroxychloroquine	On the 3rd day of treatment	Maculopapular mild itchy rash	Started on the face, continued on the extremities, and ended on the trunk	NM	NM	NM	Resolved

Table 4. Studies with a large number of cases of mucocutaneous manifestations related to coronavirus disease 2019 (COVID-19) in children

Title	No. of patients	Percentage of skin lesions	Skin lesion characteristics	Accompanying COVID-19 symptoms	PCR	Location of skin lesions	Accompanying local symptoms	Age (year)	Gender ratio	Duration of skin lesions (days)
Outbreak of chilblain-like acral lesions in children in the metropolitan area of Milan, Italy, during the COVID-19 pandemic	30	100%	Erythematous-violaceous patches or slightly infiltrated plaques, associated with edema in 3 cases	Fever (n = 9/13; 69.2%), followed by cough (n = 6/13; 46.2%), coryza (n = 3/13; 23.1%), pharyngodynia (n = 2/13; 15.4%), weakness (n = 2/13; 15.4%), dyspnea (n = 2/13; 15.4%), abdominal pain (n = 1/13; 7.7%), and headache (n = 1/13; 7.7%)	PCR was negative in all 6 patients tested	Twenty-six patients (86.7%) had foot lesions, 2 involving only the ankle, and 4 had hand lesions, including 2 with foot involvement. Lesion distribution was unilateral in 4 cases (13.3%).	Moderate itching (median visual analog scale score 4.5) was recorded in 14 patients (46.7%) and pain in 5 (16.7%; median visual analog scale score 3).	Mean: 11, range: 2-17	Boys: N=17 (56.7%)	Mean: 7, range: 1-23
Chilblain-like lesions in pediatrics dermatological outpatients during the COVID-19 outbreak	27	100%	Chilblain-like 25/27 (92.6%) Erythema multiforme-like 2/27 (7.4%)	No respiratory symptoms, just 1 case has diarrhea	PCR negative (n=2), IgM negative (n=9), IgA negative (n=9), IgG negative (n=9)	Hands 22% (n = 6) Feet 74% (n = 20) Both 4% (n = 1)	Asymptomatic: 67% (n=18), pruritus: 11% (n=3), mild pain: 22% (n=6)	Mean: 14.4, range: 0-16	Boys: N=18 (66%)	Mean: 14.6
A clinical, histopathological and laboratory study of 19 consecutive Italian pediatric patients with chilblain-like lesions: lights and shadows on the relationship with COVID-19 infection	19	100%	Toe swelling and erythema in all patients, erythemato-violaceous roundish macules and purpuric lesions in 12 cases (63%). Some patients also presented pustules and erosions covered by crusts	Five patients (26%) reported fever and cough 1–2 months prior to development of skin lesions, one patient presented diarrhea one week after skin manifestation onset	PCR negative (all of them); IgA positive in 6 patients and borderline in 3; IgG negative	Feet in all cases 9 cases have lesions on soles, heels, and toes	Eleven patients (57.8%) reported pain and/or itching	Mean: 14.0, range: 11–17	Boys: N=14 (73.68%)	14 days after screening, cases still had the lesions
Pediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort	16	n=15, 94%	Mucocutaneous involvement (n=15, 94%), skin rash 13 (81%), Hands and feet erythema/edema 11 (68%), dry cracked lips 14 (87%)	Fever 16 (100%), respiratory signs 2 (12%), gastrointestinal signs 13 (81%), anosmia 1 (6%), neurological signs 9 (56%), conjunctivitis 15 (94%), cervical lymphadenopathy 6 (37%), arthritis 1 (6%), hemodynamic failure 11 (69%)	RT-PCR was positive in 11 patients (100%), IgG was positive in 7/8 (87%) patients, IgM was positive in 5 patients	Diffuse skin rash (n=13, 81%), rash/edema of hands and feet (n=11, 68%), conjunctivitis (n=15, 93%), dry cracked lips (n=14, 87%), cervical lymphadenopathy (n=6, 37%) and arthritis (n=1, 6%)	NM	Median: 10, IQR: 4.7-12.5	Boys: N=8 (50%)	Mean: 30
Assessment of acute acral lesions in a case series of children and adolescents during the COVID-19 pandemic	20	100%	Acral erythema (6 patients), dactylitis (4 patients), purpuric maculopapules (7 patients), and a mixed pattern (3 patients).	Asymptomatic	2 (10%) had positive results for antinuclear antibodies (titers of 1/160 and 1/1280, respectively)	14 feet, 2 hands, 4 hands and feet	No patient had any clinical signs	Mean: 12.3 ± 4.3, range:1-18	Boys: n=13 (65%)	NM

Table 4. Continued

Title	No. of patients	Percentage of skin lesions	Skin lesion characteristics	Accompanying COVID-19 symptoms	PCR	Location of skin lesions	Accompanying local symptoms	Age (year)	Gender ratio	Duration of skin lesions (days)
Immunological and virological profile of children with chilblain-like lesions and SARS-CoV-2.	30	100%	Total/feet/hands/both, eccrine hidradenitis, maculopapular rash, urticaria, livedo, targetoid lesions, vascular, ecchymosis purpure, erythema nodosum, mucosal manifestations, chilblain-like lesions, eccrine hidradenitis, maculopapular rash, urticaria, livedo, targetoid lesions, vascular/ ecchymotic purpure, erythema nodosum, mucosal manifestations	Fever: 13 (43.33%), influenza-like symptoms: 20 (66.67%), respiratory symptoms: 16 (53.33%), ENT symptoms/ anosmia:17 (56.67%), digestive symptoms: 10 (33.34%)	IgG positive, all PCR: negative, IgG positive:1/26 (4%) ELISPOT:11/11 (100%)	Feet:14, hands:2, both:1	Pruritus n=11 (30%), Pain n=9 (27%)	Mean: 9.5 ± 0.5range: 1.8-17.3	Boys: n=20 (66%)	Mean: 22
All that glisters is not COVID: Low prevalence of seroconversion against SARS-CoV-2 in a pediatric cohort of patients with chilblain-like lesions	24	100%	Twenty-two patients presented with chilblains; six patients developed blistering lesions	Fever 4 (16.7%), cough 10 (41.7%), conjunctivitis 3 (12.5%), GI symptoms 5 (20.8%)	Fecal PCR: Negative in all, rectal swab: positive in 1, enzyme-linked immunosorbent assay and chemiluminescence: positive in3 patients (12.5%)	Twenty-two patients' toes, 2 patients' heels	NM	Mean: 13, range: 6-17	Girls: n=15 (62.5%)	83% of lesions lasted more than 14 days
Chilblain-like lesions during the COVID-19 pandemic: a serological study on a case series	12	100%	Chilblain-like, acral skin lesions	NM	IgG positive in1/12, All of them were negative IgM	Feet: 9, hand:2, both: 1	NM	Mean: 13.5 range: 9-19	Girls: n=8 (66.66%)	NM
No evidence of SARS-CoV-2 infection by polymerase chain reaction or serology in children with pseudo-chilblain	38	100%	Pseudo-chilblain skin lesions (multifocal and asymmetric purpuric–ecchymotic patches and/ or 'pernio-like' lesions or ecchymotic lesions)	Eight patients had associated symptoms: six had fever about one month before, and two had diarrhea	PCR, IgM, IgG and IgA: Negative	Sole, heel and/ or plantar aspect of a single toe or dorsal aspect of the hands	Swelling and erosion	Media: 13.5, range: 7-18	Boys: n=22 (58%)	Few days
The management of the outbreak of acral skin manifestations in asymptomatic children during COVID-19 era	38	100%	Acral rash, multifocal and asymmetric purpuric-ecchymotic and/or "pernio-like" lesions with vesiculo-bullous swelling and erosion	Asymptomatic	All had negative COVID-19 PCR	Feet, hands, and other distal sites (such as ears)	Swelling and erosion	Mean: 10.6, range: 5-16	Boys: n=25 (65.8%)	Mean: 14

Table 4. Continued

Title	No. of patients	Percentage of skin lesions	Skin lesion characteristics	Accompanying COVID-19 symptoms	PCR	Location of skin lesions	Accompanying local symptoms	Age (year)	Gender ratio	Duration of skin lesions (days)
Chilblain-like lesions during COVID-19 epidemic: a preliminary study on 63 patients	63	100%	Erythematous–edematous lesions, blistering lesions	Gastrointestinal symptoms (11.1%) (median duration: 7 days with an IQR of 1–9), respiratory symptoms (7.9%) (median duration: 7 days with an IQR of 3–10), fever (4.8%) (median duration: 4 days, with an IQR of 3–8, 5)	Two from six serology tests were positive.	Feet (85.7%), feet/hands together (7%), hands alone (6%)	Pain 27%, itch 27%, pain/itch together 20.6%, Asymptomatic lesions 25.4%	Median:14, IQR: 12–16	Girls:57.4%	NM
Major cluster of pediatric 'true' primary chilblains during the COVID-19 pandemic: a consequence of lifestyle changes due to lockdown	8	100%	Multiple red-purple macules and/or patches (8/8) (100%), nodules (4/8) (50%) and bullae (3/8) (37.5%)	All patients were asymptomatic	RT-PCR &IgM and IgG negative in all cases	Toes (8/8) (100%), soles and heels (3/8) (37.5%) and fingers (3/8) (37.5%)	Itching (5/8) (62.5%), pain (3/8) (37.5%) and heel tingling (1/8) (12.5)	Range: 11-15	Girls: n=5 (62.5%)	Range: 28-35
Chilblains in children in the setting of COVID-19 pandemic	22	100%	erythematous to purpuric macules and violaceous swellings	Respiratory symptoms (cough or rhinorrhea) 9 (41%), GI symptoms (abdominal pain or diarrhea) 2 (9%), Shortness of breath 0 (0%), Fever 0 (0%)	PCR positive: in 1 case.	Feet 22 (100%), Hands 3 (14%)	Local pruritus 9 (41%), Local pain or tenderness 7 (31%)	Range: 6-17, median: 12	Boys: n=13 (59%)	Range: 21-35
Clustered cases of acral perniosis: Clinical features, histopathology, and relationship to COVID-19	6	100%	Dusky purpuric patches and focal lesions	Two cases of rhinorrhea, congestion, sore throat, and subjective fevers one week before the onset of skin lesions.	All PCR, IgM and IgG tests were negative	Heels, soles and distal aspect of the dorsal feet and lateral foot, flexor surfaces of the forearms, the dorsal hands	Itching 6 (100%), tenderness	Range: 12-17	Boys: n=5 (83.33%)	NM
Chilblains in children in the time of COVID-19: New evidence with serology assay	45	100	Red to violaceous macules and dusky, purpuric plaques	Low-grade fever and systemic symptoms (cough and gastrointestinal disorders) were frequently reported	One positive IgG in 8 cases.	Heels, soles and lateral margin of the feet	Painful edema, consistent with chilblains	NM	NM	NM
Acral lesions in a pediatric population during the COVID-19 pandemic: a case series of 36 patients from a single hospital in Spain	36	100%	Erythematous papules: n=24 (66.67%), purpuric macules: n=16 (44.44%), both: n=4 (11.11%), erosion: n=5 (13.8%), swelling: n=6 (16.67%)	Cough: n= 7 (63.64%), fever: n=3 (27.27%), diarrhea, nausea and vomiting: n=3 (27.27%), asthenia and myalgia: n=2 (18.18%)	All PCR, IgM and IgG tests were negative.	Hands: n=2 (5.55%), feet: n=35 (97.22%), both: n=1 (2.78%)	Pruritus: n=14 (38.89), pain: n=8 (22.22), asymptomatic: n=18 (50.00)	Mean: 11.11, range: 0-14	Boys (63.8%)	NM

Table 4. Continued

Title	No. of patients	Percentage of skin lesions	Skin lesion characteristics	Accompanying COVID-19 symptoms	PCR	Location of skin lesions	Accompanying local symptoms	Age (year)	Gender ratio	Duration of skin lesions (days)
A new dermoscopic pattern for chilblain-COVID-19elike skin lesions in adolescents	15	100%	Erythematous purpuric papules and macules, with possible bullous and crusty evolution or digital swelling	Six patients (40%) reported having had a history of COVID-19–like symptoms in the previous 4 months.	The nasopharyngeal and oropharyngeal swab specimens for examining SARS-CoV-2 infection were negative in all the patients (100%)	Toes (100%, n=15), heels (26.67%, n = 4)	Itching and burning	Mean: 13 ± 2.08, range: 8-17	Girls: n=6 (40%)	NM
Therapy for probable COVID-19 associated erythema pernio-like lesions in pediatric age. Case report	33	100%	Circumscribed erythematous edematous elements, with a purplish red color, similar to chilblains/erythema pernio	Dry and irritating cough, sore throat and fever in three patients	NM	Feet, especially at the dorsal surfaces, and to a lesser extent on the hands and face	Swelling (nine cases), itching (eight cases), pain (six cases), and burning (two cases). No symptoms in 18 cases.	Mean: 12.84, range: 0-54	Girls: n=11 (33.33%)	Range:8-16

Skin presentations

Most of the studies were related to acral lesions and chilblain-like lesions. Also, 481 patients out of 482 had skin lesions, most of whom (451, 93.7%) struggled with pernio-like/chilblain-like lesions. Fifteen (3.1%) children out of 16 MIS-C cases developed Kawasaki-like lesions. A maculopapular rash was described in eight (1.6%) patients, and four (0.8%) cases presented with erythema-multiforme-like lesions. Hidradenitis was reported in two cases (0.4%), livedo-like lesions in two (0.4%), vascular/ecchymosis purpura in two (0.4%), erythema nodosum in one (0.2%), and urticaria in one (0.2%).

The majority of skin manifestations were asymptomatic or minimally symptomatic, with the main complaint of significant pruritus and pain. Most rashes disappeared after 1–35 days.

Location of skin lesions

Skin lesions were most often found in acral sites like the hands and feet, while Kawasaki-like lesions were diffusely distributed.

COVID-19-related features

Respiratory symptoms (n = 84, 42%) and fever (n = 58, 29%) were the most common presentations; other symptoms were gastrointestinal symptoms (n = 38, 19%), anosmia (n = 18, 9%), and myalgia (n = 2, 1%).

Risk of bias

The risk of bias was determined based on the quality of the methodology. We used Cochrane Handbook guidelines for the quality assessment. Seven domains, namely bias due to confounders, representative spectrum reference standard, partial verification, clear definition, free of selective reporting, and missing data, were reviewed to assess the quality of each study [20,21]. Results of quality assessment based on the Cochrane Handbook are shown in Figure 4.

DISCUSSION

Summary of evidence

There are some systematic review studies

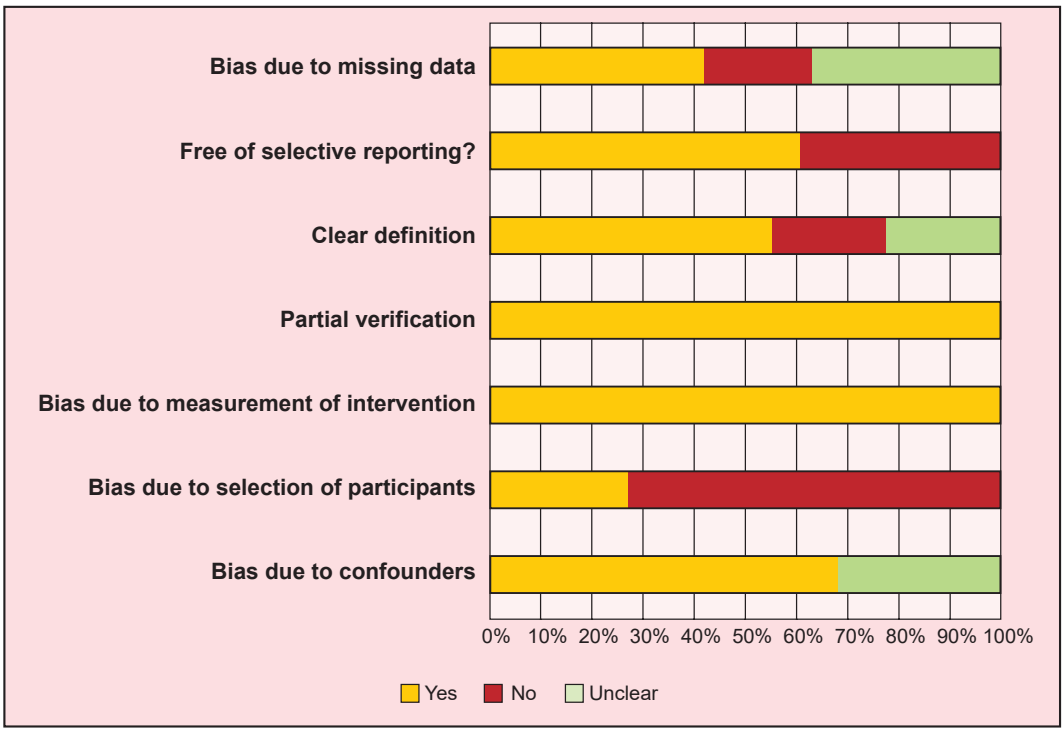

Figure 4. Quality assessment of articles included in this systematic review.

regarding primary and secondary dermatologic presentations of COVID-19 [85–94], including COVID-19-related drug eruptions and special dermatologic concerns, like the mutual impacts of specific dermatologic disorders and COVID-19 on each other during the pandemic [95–108]. The majority of these studies focused on adult patients, while the disease can also affect children, indicating the need to also focus on this age group. The prevalence of dermatological manifestations of COVID-19 is estimated to be between 0.25% and 3% in children and adolescents, although the range is highly variable [109]. It should be noted that a primary virus-related dermatologic presentation can be seen in roughly 20% of adults. In adults, the range of COVID-19-related dermatologic manifestations—regardless of the exact etiology—could be even up to 45% in the peri-infection period [86]. Children can be carriers and transmit the infection to other family members; thus, early diagnosis of the disease in children is of great importance. In children, the mucocutaneous presentations of COVID-19 can be a precursor to or concomitant with other signs and symptoms of the disorder. Getting more familiar with these dermatologic clues, as visible signs, helps diagnose the disease earlier and prevent its spread.

Based on our study, chilblain/pernio-like lesions were the most common dermatologic presentation of pediatric patients affected by COVID-19, followed by MIS-C/Kawasaki-like syndrome-related mucocutaneous lesions. The reported percentages of these presentations varied based on different studies; however, it appears that the percentage of acral vasculopathy lesions is more than 50%, even up to 90%. For MIS-C/Kawasaki-like syndrome presentations, the percentage is more than 3%, even up to 20%. The mean age of children with COVID-19 and dermatologic manifestations was more than 10 years, and presentation rates were insignificantly higher in the male gender. Regarding the onset of dermatologic manifestations in children with COVID-19, the mean time was about 12.47 days after the onset of systemic symptoms. Most patients were either asymptomatic or had few general symptoms. This shows that dermatologic signs and symptoms can often be the sole clue to COVID-19 in pediatric patients. Therefore, dermatologic clues can warn of COVID-19 and should be considered for earlier diagnosis and

transmission prevention.

Cutaneous lesions resolved spontaneously or by using topical or systemic corticosteroids in 3 to 88 days without any sequela. Documented skin manifestations were chilblain-like (pseudo chilblain) lesions, erythema multiforme-like lesions, dactylitis, acral erythema, acute urticaria, livedo reticularis, mottling, acro-ischemia, generalized maculopapular lesions, eyelid dermatitis, miliaria-like lesions, varicelliform lesions, and petechiae and/or purpura. We found acral vasculopathy to be the common dermatologic presentation.

Exanthematous rash, urticaria, and acral vascular lesions are the most reported lesions as primary dermatologic manifestations of COVID-19. The most common primary rashes were chilblains/pernio-like lesions (51.5%), erythematous maculopapular eruptions (13.3%), and viral exanthem (7.7%).

The mean age for dermatologic eruptions was 12.9 years in children and 34.2 years in adults. The mean latency from the time of upper respiratory illness symptoms to cutaneous findings was 1.5 days in children and 7.9 days in adults. About 10% of the patients in both populations were asymptomatic, which means they presented with only dermatologic findings. Moreover, 13.3% of children and 5.3% of adults presented with skin eruptions, which were followed by systemic signs and symptoms later.

In this pandemic, a significant association was observed between COVID-19 and Kawasaki-type disorders; thus, pediatricians should be alert about children with atypical or incomplete forms of Kawasaki disease (Kawasaki-like) for early diagnosis of COVID-19. Patients with Kawasaki-like syndrome affected by COVID-19 had more complications and showed cardiogenic shock, neurological symptoms, lymphocytopenia, and thrombocytopenia more frequently in comparison with classic Kawasaki's disease [110,111].

Interestingly, based on our results, patients with COVID-19 with a rash had less frequent respiratory symptoms, pediatric intensive care unit (PICU) admission, and invasive ventilation, as well as shorter hospitalization days in comparison with those without a rash. Regarding prognosis, MIS-C patients with a rash had less frequent PICU admission, shock, and ventilator need. Regarding the laboratory data, lower levels of CRP, ferritin, D-dimer, and troponin may be expected vs. MIS-C without a rash. It is known that the neutrophil-to-lymphocyte ratio is similar in MIS-C cases with or without a rash.

In a three-part study by Andina *et al.* [112], the authors focused on the most widespread cutaneous manifestations of COVID-19 in children, namely chilblain-like lesions erythema multiform, urticaria, and Kawasaki disease-like inflammatory multisystemic syndrome [113], and the histological findings of COVID-19 manifestations were also discussed [114,115]. Although the exact pathomechanism of acral vasculopathy (chilblain-like lesions) and COVID-19 is not fully recognized, these presentations may be frequently seen in definite or suspected cases of COVID-19 [109]. Erythema multiform-like lesions may occur in association with chilblains in suspected pediatric cases of COVID-19. Urticaria was reported in 10–20% COVID-19 cases. COVID-19 may be underestimated in children, and vesicular rashes can also be seen; however, they are more prevalent in adults. Pediatric inflammatory multisystem syndrome (PIMS) is a rare but severe form of COVID-19 that may present as a Kawasaki-like disorder. Maculopapular exanthems, pityriasis rosea-like lesions, and oral mucosal involvement are among the other probable presentations [61]. In part 3, the authors reported that the histopathology of COVID-19-related chilblains is similar to that of classic primary chilblains. The sensitivity and specificity of PCR and serology tests in children are low, and epidemiological data have a key role in the diagnosis of COVID-19 in children. Moreover, more than 90% of children have an asymptomatic or mild-moderate COVID-19 course [114].

Coagulation disorders or hypersensitivity reactions might be the main culprits that potentially invert an innocent chilblain-like lesion to a sign of life-threatening internal organ involvement. In one case, retinal vasculitis and chilblains presented concurrently [48], indicating that children require special attention in the primary stage of infection.

A study by Federico Diotallevi *et al.* [11] suggests that urticarial rash, exanthemas, and chickenpox-like vesicles indicate the early phase of the infection, related to the viral replication or cytokine storm, whereas chilblain-like lesions are the late presentation, related to the secondary cell-mediated immune response.

Little data exists on treatment-induced

mucocutaneous eruptions in children with COVID-19, which may be due to more conservative or different therapeutic approaches, contrary to adult patients for whom the number of reports on drug eruptions, even life-threatening and severe reactions, is growing. Until this systematic review was in writing, there was only one reported hydroxychloroquine-induced drug reaction in a 17-year-old patient, while the last published systematic review on dermatologic drug reactions in patients with COVID-19 only focused on adult patients.

The authors of this study focused on various dermatologic concerns during the pandemic, including different age populations; however, there is currently a great need for a deep focus on dermatologic manifestations of COVID-19 in children. In order to achieve a better diagnosis and optimize management strategies of dermatologic features of COVID-19 in patients under 18 years of age, we need systematic studies with a wider range of topics to focus on virus-related and drug-related dermatoses as well as secondary environmental-induced dermatoses related to hygiene issues or protective gear, masks, and devices in this certain age group.

CONCLUSION

Dermatologic clues can help promptly diagnose COVID-19 and prevent its transmission. Chilblain/pernio-like lesions appear to be the most common dermatologic presentation in children, followed by MIS-C/Kawasaki-like syndrome-related mucocutaneous lesions, erythematous maculopapular eruptions, and viral exanthema. Regarding the management of the most prevalent dermatologic presentations in children, an adequate targeted therapy can shorten the disease course, although these lesions heal spontaneously in most cases. Dermatologic clues may be prognostic in children affected by COVID-19; children with a rash usually develop less severe disease with better outcomes. MIS-C shows a better prognosis and better laboratory data in children when a rash is present rather than when it is absent. Dermatologic signs may be evident before/during/after other manifestations of COVID-19, and in 40% of the affected children, these signs are the sole presentation of COVID-19. During the pandemic, each new mucocutaneous event in children—especially acral lesions with a vascular color—should be kept in mind as a probable clue of COVID-19. The mucocutaneous presentations of COVID-19 in pediatrics are, to some extent, different from what is seen in adults, especially in some characteristic presenting features, aspects of the disease course, and the prognostic role of some rashes. All of these factors mandate better evaluation of dermatologic signs and symptoms in children.

Limitation

There is a paucity of data regarding treatment-induced mucocutaneous eruptions in children with COVID-19, meaning that this topic should be explored in future studies. Also, COVID-19 is an ongoing disease accompanied by ever-increasing novel strains. Furthermore, our title covered and extended over a great area of skin eruptions in children, so the limited search interval is another limitation of this article

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