Cutaneous manifestations associated with COVID-19 in children: A Systematic Review

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Systematic Review

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Abstract

Background: Cutaneous manifestation of COVID 19 in children has not yet been reviewed systematically and hence this review gives a future direction to the clinicians to be vigilant for skin presentations during such pandemic.

Methodology: The review was done as per the guidelines of PRISMA and literature search was done on PubMed database using keywords as COVID-19, children and skin in different combinations. Articles published in English with cases of age 1 month to 18 years were eligible. The outcome included varied aspects of cutaneous and COVID-19 infection. The review protocol was not registered.

Results: Of 51 publications identified, 13 studies containing 149 children met the eligibility criteria. Acrally located erythematous maculopapular lesion was the most common finding in 138 children. Erythema multiforme, varicella like exanthem and Kawasaki disease like presentations were reported in the rest of the cases. The duration of the skin lesion was 1-2 weeks in 43%. Skin biopsy done in 18 cases revealed superficial & deep perivascular and peri-eccrine lymphocytic infiltrate & lymphocytic vasculitis. RT-PCR was positive in 13.8% cases. Serological markers for HSV, parvovirus B19 analyzed across various studies, were found negative, except for mycoplasma pneumoniae in 2 of 20 cases tested.

Discussion: Clinicopathologic analysis established chilblains like lesion in 43% cases with no confirmed etiology like cold exposure, autoimmune dysfunction, drug reaction, or viral infection. The usual cephalo-caudal spread of a viral exanthem was also missing. However, a low number of discussed cases was a limitation of the study.

Conclusion: In the absence of any confirmed etiology for such cutaneous manifestations, the possibility of COVID-19 should be explored and evaluated thoroughly during such pandemic.

Introduction

The viral S protein (peplomer) of SARS-CoV-2 interacts with angiotensin-converting enzyme 2 (ACE II) receptors present on human cells and enters the host cell. ACE 2 receptors, being most abundant on alveolar type II cells is the primary site of entry. The respiratory manifestations may present as mild symptoms of flu-like illness or severe category with ARDS and multi-organ failure. [4] However, extra-respiratory involvement of COVID -19 infections is also being reported in increasing numbers.

Concurrent with the surge of COVID-19 cases, during its peak in different countries, clinicians and dermatologists started reporting a sizable number of patients presenting with a cutaneous lesion, especially in critically ill adult patients and also in asymptomatic children. [5] Diverse skin lesions typically in the form of chilblain like acral lesions, erythema multiforme mimics, and other cutaneous manifestations were noted. All these published articles are in the form of case reports and original articles and not yet been systematically reviewed, to guide the clinicians comprehensively.

The primary objective of this study is to systematically review all published literature on different spectrum of cutaneous manifestation in pediatric patients with COVID-19.

Methods

Protocol and registration:

An extensive systematic search was carried out on Medline (via PubMed) database to identify published literature on cutaneous manifestations associated with COVID-19 in pediatric patients, following the recommendations of preferred reporting items for systematic reviews and meta-analyses guidelines. [6], [7] No previously registered review protocol could be located on Prospero. The review protocol could not be registered because of the earnestness of the matter and anticipated long holding up period.

Eligibility criteria:

Studies with the following characteristics were included

(1) *Study population:*

- Cutaneous lesion
- Age group >1 month till 18 years of age
- Temporal association (Dec 2019 – 28 May 2020; in the same time frame as the peak of COVID-19 in the regions of reported studies)
- Discussing “COVID-19” in context with cutaneous lesion

(2) Intervention / Indicators: We included clinical studies discussing *cutaneous manifestations in children in context with* COVID-19.

(3) *Comparators:* There were no limitations on the type of comparators in the studies.

(4) *Outcomes:* The outcome of interest was the type of cutaneous lesion, site involved, biopsy findings, RT-PCR status of patients, antibody titer status, contact history with COVID-19 patients, the treatment offered, and any resulting sequelae.

(5) Study design: Study designs from the selected publications included Case reports, case series, prospective and retrospective cohort studies, case-control study, and clinical trials.

(6) Language: Studies published in English were included.

(7) Publication status: Studies ahead of print as well as already published were both included.

The exclusion criteria to eliminate non-eligible studies were

(1) Studies that did not report cutaneous manifestations

(2) Studies that involved neonates or adults

(3) Review articles, meta-analyses, editorials, and other forms (e.g. commentary & correspondence to included published literature).

Information Source & Search strategy:

Data search was done on 28/05/2020 at 3:30 PM with key search terms as (Coronavirus OR COVID 19 OR SARS-CoV-2) AND (Paediatrics OR children) AND (skin OR dermatology OR urticaria or cutaneous) in PubMed database without any selection on the study type. The publication date was chosen to be within the last 1 year, as the first case of COVID 19 was reported towards the end of December 2019.

Study selection:

The results of our database search were sent by email to the first two reviewers and both SS &KA identified and selected the potential literature following the eligibility criteria. Full texts of the eligible studies were obtained. Disagreements were settled by discussion or consensus with the opinion of a third reviewer (AG). The study selection process is shown in figure 1.

Data collection process and data items:

To extract data from selected eligible studies, a pre-designed data extraction sheet was used. The extracted records included first authors, site of study, sample size, age, sex, type & site of skin lesion, skin biopsy findings, coexistent or proceeding history of respiratory or other systemic illness, RT-PCR & antibody status for SARS-COV2, contact history with confirmed or suspected COVID patients, the treatment offered and resulting sequelae if any.

Risk of bias*:* To reduce risk of bias included studies were independently assessed and data extraction sheets were independently prepared by 2 reviewers and then compiled by 3rd reviewer by consensus.

Summary measures and synthesis of results:

All statistical analyses were performed using SPSS version 20. Continuous variables were expressed as mean (± standard deviation). Other qualitative and epidemiological data were expressed as proportions and percentages.

Results

Initial PubMed search with the mentioned keywords identified 51 articles, of which 30 were eliminated at identification stage. Screening of these 21 articles by abstract further eliminated 3 articles. [8], [9], [10] After applying eligibility criteria, another 5 articles were eliminated. [11], [12] [13], [14] [15] Thus, a total of 13 articles met the inclusion criteria and were systematically reviewed. Out of that 5 were case series, [16], [17] [18], [19] [20] 4 were case reports, [21], [22] [23], [24] and 4 were original studies. [25], [26] [27], [28] Maximum number of

articles were reported from Italy, [16], [19] [20], [21] [22], [24] [26] followed by Spain, [17] [23], [25] France, [8] Turkey, [28] and USA. [27]

All studies were published during April &May 2020. A total of 149 different patients were analyzed & discussed. The youngest case is of 8 months female baby (28) and the oldest is an18-year male [19] with the mean patient age at 11.096 years (SD±4.56 years) Males comprised 85 cases (57%) while females accounted for 64 cases (43 %).

Table 1 summarizes cutaneous & systemic features.

Table 1: Cutaneous & Systemic Features

Ref. No	Cases(n)	Sex M/F	Skin lesions	Site of skin lesion	Duration of skin lesions (n)	*History	Systemic manifestations (n)	Duration of systemic illness (n)	Treatment given
16	4	2/2	Erythematous edematous macules, papules and plaques with blurred edges and a central cyanotic area with Pruritus in (n=1) and mild pain in (n=3)	Feet: 4/4	2-3 weeks (2) NR (2)	NR	Fever (3), URI (1), Pneumonia (1) None (1)	<10 days (2) > 2 months in 1	No Rx:3/4 Systematic antibiotic1/4
25	22	13/9	Erythematous to purpuric macules and violaceous swellings with Pruritus (n=9) and mild pain (n=7)	Feet: 19/22 Both: 3/22	1-28 days (22) (median 7 days)	None 22/22	URI (9/22) GI (2/22), both (10/22)	1-28 days (median 14 days)	No Rx:20/22 (Analgesics + Antihistamines + Topical steroid) 1/22 Oral short course steroid 1/22
21	1	1/0	Erythematous edematous, partially eroded, macules and plaques- asymptomatic lesion	Both :1/1	2-3 weeks (1)	None 1/1	GI (1)	>20 days	NR
26	63	30/ 33	Erythematous-edematous lesions 31/54 and blistering lesions in 23/54, Pain 17/63, itching 17/63, Both 13/63. Asymptomatic lesions 16/63	Feet 54/63 Hands 4/63 Both: 5/63	1-2week (63)	6/63 history present	Fever (4/63) URI (5/63) GI (7/63)	NR	NR
27	6	5/1	Red to violaceous macules, plaques with superficial bullae, focal hemorrhagic crust, Reticulated erythema. Pruritus and mild pain in all cases	Both: 6/6 Forearm:6	NR (6)	None 6/6	Fever (2/6) URI (2/6)	<10 days (6)	NR
17	4	3/1	Erythema multiforme like target (three rings) and targetoid (two rings), confluent macules, papules and plaques of different sizes, some with bleeding or crust at the centre. Pruritus 3/4, mild pain 1/4	Both: 4/4, Elbow: 4/4, Knee:4 /4 Ankles:3/4 Forearms:3/4 Ears :1/4 Thigh:1/4 Arms :1/4	NR (4)	NR	URI (2) GI (1) None (1)	NR	No Tt: 2/4 Topical steroid Oral steroid
22	1	0/1	Diagnosed as Viral exanthema, Erythematous papules and few vesicles scattered bilaterally and symmetrically on the trunk. The lesion had superficial vesiculation leading to crust formation.	Trunk only Limbs & mucous membranes were spared.	<1 week (1)	NR	URI (1)	<10 days (1)	NR
23	1	1/0	Erythema Multiforme like lesion with hemorrhagic purpuric eruption and vesicular blisters with itching	Feet 1/1	<1 week (1)	NR	None (1),	None	NR
18	2	2/0	Case1: Erythema Multiforme like presentation with severe erosive cheilitis, diffuse gingival erosions, bilateral conjunctivitis and multiple target lesions. Case 2: Generalized exanthema, bilateral palmar edema, glossitis, and cervical lymphadenopathy and desquamation of the extremities, diagnosed as Kawasaki disease	Case1: Both hands &feet, conjunctiva, lips & gums Case 2: Whole body, palm and tongue	Case1: <1 week (1) Case 2: NR (1)	NR	Fever (1) GI (1) Pneumonia (1)	<10 days (1)	Case1: No Rx Case2: IV Ig
19	3	3/0	Erythematous violaceous macules and papules,	Feet 3/3	2-3	NR	Fever (2),	NR	NR

			some with blisters and necrotic lesions with pain and itching in some		weeks (1) 1-2week (1) NR (1)		None (1)		
28	3	0/3	Erythematous macula popular skin rash with pruritus	Face 3/3 Both 3/3 Trunk 3/3	<1 week (3/3)	NR	Fever (1) NR (2)	NR	NR
24	1	0/1	Erythematous ulcerative chilblain-like lesions with dyschromia of the nails; with pain and itching. The lack of finger pressure clearing of the erythematous lesions suggests that the vasculitis to be of ischemic hemorrhagic nature. Pain and itching	Feet 1/1	NR (1)	None 1/1	None (1)	NR	NR
20	38	25/13	Red bluish erythematous patches with vesiculo-bullous swelling and erosion	Feet 38/38	NR (38)	NR	NR	NR	Topical steroid and antibiotic cream 38/38

Both: both hands and feet: NR: Not reported, No: absent

*** History: History of autoimmune disorders, Raynaud's phenomenon, recent addition of new drug or dosage, previous chilblain or familial chilblain, acrocyanosis**

Acrally located erythematous to violaceous maculopapular lesion having blurred edges, occasionally with superficial bullae and focal hemorrhagic crust was the most common finding in 127 children. [16], [20], [24], [25], [26] A similar but larger lesion as erythematous to purpuric plaques with occasional macules was reported in 11 cases. [16], [19] [21], [27] Erythema multiforme like lesion observed in 6 cases, consisted of target and targetoid, confluent macules, papules and plaques of different sizes, few with bleeding and crust at the center with the involvement of conjunctiva in one and mucous membrane in one patient each. [17] [18], [23] Bilaterally symmetrical varicella like exanthem presented as erythematous papules & vesicles with superficial vesiculation & crust formation, on the trunk, in an 8-year female child. However, the limbs, face, genitals, and mucous membranes were spared. [22] Generalized exanthematous lesion with palmer edema, cervical lymphadenopathy, glossitis and desquamation of extremities; Kawasaki disease like presentation, was reported in a 3 years male child with negative RT PCR but ground glass consolidation in CT chest suggestive of COVID pneumonia. [18] Additionally, Bursal et al reported non-acral erythematous maculopapular rash starting on the face and extending to trunk and extremities in 3 of their COVID positive patients. [28]

The site of lesion was feet alone in 120 cases, mostly at the dorsal surface of toes & sometimes on the lateral margin of feet. Plantar surface & heel was also involved occasionally, more so in erythema multiforme type lesion. Hands alone were involved in 4 cases, affecting the dorsal surface of fingers and periungual region. The involvement of both hands and feet were reported in 23 cases. Duration of skin lesion (n=96) was <1 week in 6, 1-2 weeks in 64 (43%), and 2-3 weeks in 4 cases. Further Andina et al mentioned in their study that 22 children reported a median of 7days with a range of 1-28 days. [25]

Systemic manifestations like fever, upper respiratory tract infection (URI) and Gastro Intestinal (GI) symptoms were present in 11, 20, and 22 cases respectively. Upper respiratory tract infection (URI) in the form of mild flu & rhinorrhea while GI symptoms included loss of taste, diarrhea, nausea & vomiting. URI and GI symptoms together were present in 10 cases. Radiologic evidence of pneumonia was present in 2 patients; both were under 5 years of age and negative for RT PCR (16, 18). The incubation period varied from less than 10 days (n=10) to 30 days (n=32) with more than 60 days in a 5-year-old boy having pneumonia but negative RT PCR. [16]

Symptomatic treatment with antihistaminic, topical steroid or antibiotic was given in 41, Oral short course steroid in 2 and IV immunoglobulins in one patient with Kawasaki Disease like presentation. No cutaneous sequelae were reported in any study.

Table 2 depicts the histopathology of the skin biopsy and other laboratory evaluation

Table 2: Histopathology & Laboratory Evaluation

Ref. No.	RT PCR test	** Ab	Contact history	Skin Biopsy (n=18)	Routine Blood test(CBC, LFT, KFT, ANA)	Coagulation profile	CRP, Ferritin Fibrinogen IL6	d Dimer (<500 µg/L normal range)
16	-ve 4/4	NR	SC: 4/4	Lymphocytic perivascular and peri adnexal infiltration with signs of vasculitis and fibrin thrombus in superficial capillaries 2/2	Thrombocytosis & monocytosis 1 /4	N 4/4	N (4/4)	1/1: 723 µg/L
25	+ve 1/19	NR	CC:1/22 SC:12/22	Lymphocytic vasculopathy, superficial and deep angiocentric and eccrinotropic lymphocytic infiltration, papillary dermal edema, vacuolar degeneration of the basal layer 6/6	N:22/22	N 18	NR	1/16 high (900 ng/ml)
21	+ve 1/1	NR	CC: 1/1	Superficial and deep lymphocytic infiltrate in a perivascular and peri eccrine pattern, no endothelial damage 1/1	ANA +ve1 Cryoglobulin present 1	N1	NR	NR
26	+ve 2/11	+ve 2/6	CC: 2/63 SC: 8/63	NR	ANA +ve in 1/22	N 22	N 22	NR
27	-ve 6/6	-ve 6/6	SC: 6/6	Superficial and deep lymphocytic infiltrate, perivascular and peri eccrine distribution, Mucin deposition in both the reticular and peri adnexal dermis. Hemorrhagic parakeratosis at stratum corneum. Direct immunofluorescence was negative for immunoreactant deposition 6/6	NR	NR	NR	NR
$17	+ve 1/4	NR	SC:1/4 NC:3/4	2/2; A superficial and deep perivascular and peri eccrine lymphocytic infiltrate with lymphocytic vasculitis and vascular ectasia, epidermis spared, no eosinophils were seen in the infiltrate. fibrinoid necrosis and thrombosis absent. Necrotic keratinocytes also absent in both samples. IHC positive for SARS-CoV-2 spike protein	N:2/2	N 3/3	NR	2/2 N
22	+ve 1/1	NR	CC:1/1	NR	Thrombocytopenia1/1	NR	N 1 (CRP)	NR
#23	-ve 1/1	-ve 1/1	NC:1/1	Partial epidermal necrosis and perivascular lymphoid infiltrate in superficial and deep dermis, capillaries in papillary dermis had microthrombi, with extravasation of RBC. Vasculitis changes were present in relation to the lymphoid component but not in the thrombotic one.	N:1/1	NR	N 1 (CRP)	NR
18	+ve 1/1 -ve 1/1	NR	CC: 1/2 SC:1/2	NR	N:2/2	NR	High CRP High TLC	NR
19	+ve 3	NR	CC:2/3 NC:1/3	NR	NR	NR	NR	NR
28	+ve 3	NR	NC :3/3	NR	NR	NR	NR	NR
24	-ve	+ve	NR	NR	N:1/1	N	C3, C4, IL6	N
20	-ve	NR	NR		NR	NR	NR	NR

NR: Not reported, SC: Suspected Covid, CC: RT PCR Confirmed Covid, NC: No contact, N: Normal, Ab: SARS-COV antibody

[$]Immunohistochemical stain with Ab against SARS-CoV/SARS-CoV-2 spike protein showed granular positivity in endothelial cells and epithelial cells of eccrine glands (2/2). but both -ve for RT PCR

* Viral markers were done for CMV, EBV, parvovirus B19 in 21 cases and were found negative. Serology for mycoplasma pneumoniae done in 20 cases but was positive in 2 cases only.

† HSV, measles, rubella, parotitis, HIV and hepatitis B and C, enterovirus were done in and all found negative.

Skin biopsy done in 18 cases revealed superficial & deep perivascular and peri eccrine lymphocytic infiltrate (18/18), lymphocytic vasculitis (18/18), vacuolar degeneration of basal layer (12/18), mucin deposition at reticular and peri adnexal dermis (6/18), hemorrhagic parakeratosis (6/18) and fibrin thrombus in (2/18) cases.

In terms of COVID-19 diagnosis, 13/94 were positive for RT PCR and antibody was positive in 3/14 cases. Complete blood count (n=43), LFT and RFT (n=35) did not reveal any abnormality. Viral markers (Parvovirus B19, HSV, CMV, EBV, Measles, Rubella, HIV, Hepatitis B & C, Enterovirus) analyzed across various studies were found negative. Serology for mycoplasma pneumoniae was positive in 2 of 20 cases. [26], [27]

Discussion

This systematic review describes cutaneous manifestations, histopathologic and laboratory evaluation along with the possibility of a causal association with COVID- 19 in terms of either positive RT PCR or history of contact with suspected or confirmed COVID-19 patients. All the included studies reported a surge in children seeking dermatology consultations in the same time frame as the peak of COVID-19 infection in their respective regions.

SARS-CoV-2, the causative agent of COVID-19 enters host cells via ACE II and the transmembrane serine protease 2 (TMPRSS2) receptors, both being co-expressed in type II alveolar cells of lungs, upper epithelial & gland cells of esophagus and enterocytes of the ileum and colon (29). The common presenting feature is mild flu in the majority of cases, followed by GI symptoms. [30] Atypical presentations at the forefront, like cutaneous lesions, neurological abnormalities, anosmia, ocular involvement, and venous thromboembolism are not infrequent. [5], [31] [32], [33] [34] We found systemic manifestations in 65 cases (43.6%) as described.

The varied cutaneous presentations, histopathological findings, and other details are tabulated in table 3.

Table 3: Pattern of Skin lesions with different characteristics

Type	Acral Chilblain like lesion (n=138) (79M/59F)	Erythema multiforme (n=6) (5M/1F)	Varicella like exanthema (n=1) (1F)	Kawasaki disease like presentation (n=1) (1M)	Non acral erythematous maculopapular rash(n=3)
Reference	[16],[19],[20],[21],[24],[25],[26],[27]	[17], [18], [23]	[22]	[18]	[28]
Skin lesion	Erythematous, violaceous or purpuric macules, papules and plaques with blurred edges, few with superficial bullae and focal hemorrhagic crust	Target (3 rings) and targetoid (2 rings), confluent macules, papules and plaques of different sizes, some with bleeding or crust at centre.	Erythematous papules and few vesicles with superficial vesiculation and crust formation.	Generalized exanthema with desquamation, palmar edema, glossitis and cervical lymphadenopathy.	Erythematous maculopapular rash with pruritus
Site involved	Feet: 120, Hands: 4, *Both: 15, Forearm :10	Feet: 1, ¶Both:5, Elbow: 4 Knees: 4, Forearms: 3 Ankles: 3/6 cases Ears :1, Conjunctiva:1, Lips:1/6 case	Trunk only (bilaterally symmetrical) Mucous membranes spared.	Whole body, palm and tongue	HCQ received (n=3), Rash starting on face and then extended to extremities and trunk after HCQ(n=1), Face: 3/3.*Both: 3/3, Trunk: 3/3
Duration of skin lesion	<1week: 1, 1-2 weeks :65 2-3 weeks: 7, NR:44	<1week: 2 NR: 4	<1 week :1/1	NR	<1week: 3
Skin biopsy	Superficial and deep perivascular and peri eccrine lymphocytic infiltrate (15/15), Lymphocytic vasculitis with endothelial cell swelling and RBC extravasation (14/15), Vacuolar degeneration of basal layer (12/15), Mucin deposition at reticular and peri adnexal dermis (6/15), Hemorrhagic parakeratosis at stratum corneum (6/15), Fibrin thrombus (2/15) Direct immunofluorescence was negative for immunoreactant deposition (6/6)	Superficial and deep perivascular and peri eccrine lymphocytic infiltrate 3/3, Lymphocytic vasculitis 3/3, Partial epidermal necrosis in 1/3, No eosinophils in the infiltrate, no fibrinoid necrosis and no thrombosis. IHC stain with Ab against SARS-CoV-2 spike protein showed granular positivity in endothelial and epithelial cells of eccrine glands in 2 cases, though both are PCR negative for SARS CoV2.	NR	NR	NR
History of Autoimmune dis./Raynauds phenomenon/	Present 6/87- (Autoimmune dis.)	NR	NR	NR	NR

Drug					
RT PCR	+ve 7/87	+ve 2/6	+ve 1/1	+ve 1/1	+ve 3/3
Contact history	CC: 6/85 SC: 30/85 NC: 49/85	SC: 2/6 NC: 4/6	CC: 1/1	NC: 1/1	NC:3/3
Systemic illness	Fever 11, URI 20, GI 11, Both 10 Pneumonia 1	URI 3, GI 1	URI	Fever: 1 Pneumonia:1	Fever:1 NR: 2
Duration of Systemic illness	1-4 weeks: 30 (median 14 days) >2 months: Pt having pneumonia	NR	6 days	<10 days -1	NR

CC; Confirm contact. SC: suspected contact, NC: No contact, NR: Not reported, ¶Both: both hands and feet

The majority of the children showed erythematous maculopapular eruptions, which is generally the commonest cutaneous presentation in any viral illness, however, a closer look in our study subjects throws up several contradicting observations. For instance, instead of general cephalocaudal distribution in any viral exanthem, here the cases showed involvement of acral region of feet and hands. The maculopapular viral exanthem always heals with exfoliation, but the majority of our study population showed secondary changes like erosion, vesiculation, and crusting. These unusual accompaniments may be used as a clue to suspect COVID-19 association particularly, in absence of usual causative agents.

Acral chilblain like lesion, rather an unusual feature during the months of March-May, when the temperature was not unbearably cold or humid, a prerequisite for developing chilblains advocates possible association of coronavirus infection. Negative history for autoimmune disorders, Raynaud's phenomenon, familial chilblains, and absent immune-reactants in skin biopsy further excludes the possibility of secondary causes of chilblains.

No significant drug history refutes the possibility of a drug-induced skin lesion in the majority of children; however temporal co-relation with HCQ was argued in one patient where lesion appeared after starting HCQ and subsided after its withdrawal.

A normal coagulation profile ruled out disseminated intravascular coagulation or coagulation derangements as a cause for the cutaneous features, as opposed to a prevalent procoagulant state reported in the acral ischemic lesion in adults. [35]

In a substantial number of the described patients, negative viral serology for Herpes Simplex Virus and Mycoplasma pneumoniae, the most common causes for erythema multiforme, suggests the COVID -19 associated pathogenesis in these cases. Similarly, the presence of negative viral markers for Parvovirus B19, CMV, and EBV among others eliminates the possibility of these usual viruses as a causative factor for viral exanthema and viral skin lesions. Additionally, a normal complete blood count in the majority of cases excluded the likelihood of any hematologic etiology.

The exact mechanism of cutaneous involvement in COVID-19 is not clear, but the pathogenesis probably involves high interferon. Viral infection causes the release of type I interferon which activates the JAK-STAT signaling pathway, resulting in increased expression of genes, which inhibits viral proliferation and thus helps in the elimination of virus and immunity against viral disease. [36] Chilblain like lesions has been reported in patients with high type I interferon. [37] So, there is a possibility that these children had high IFN initially, which helped in the early elimination of the virus and development of skin lesions in the convalescent phase. It is proposed that erythema multiforme type lesion in COVID-19 occurs secondary to activation of the complement pathway in a setting of prevailing pro-coagulant state, causing thrombogenic vasculopathy. [38]

The low positivity rate for RT-PCR (13.8 %) can be explained in terms of faster clearance of virus from the nasopharyngeal site in children, a lower viral load, false-negative test reports or delayed development of cutaneous lesions in late convalescent phase by which the children might have eliminated the virus. Serological testing in these cases can confirm previous infections, but the sensitivity and specificity of the available tests are yet to be validated. The fact that immune histochemical staining (IHC) with Ab against SARS-CoV/SARS-CoV-2 spike protein was positive in 2/2 cases, with negative RT PCR reports, advocates a definite causal role of SARS-CoV-2. [17]

Limitations *of the study*: The study sample is less looking at the pandemic nature of the disease to give any concrete comment on the path physiology and pattern of presentation of the disease process.

Strength of the study: The author has tried to screen all published data with all possible keywords and analyzed the available literature on case to case basis.

Conclusion

In the setting of prevalent COVID-19 infection, in absence of any confirmed etiology for the cutaneous involvement, a reasonable association of cutaneous manifestations with COVID-19 can be argued. The fact that IHC stain was positive in skin biopsy in patients with negative RT PCR, establishes the possible presence of COVID-19 infection. Nonetheless, in the absence of case reports from this subcontinent, with the pandemic still continuing, this review will help clinicians to look for COVID-19 association, in unexplained dermatologic presentations and advocates early isolation of the patient to eliminate the threat of cross-infection or spread to fellow patients.

Declarations

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Author contributions: SS conceived, designed the study, and prepared the manuscript. KA and RN retrieved & analyzed the data. SG helped in data extraction, analysis, and interpretation of the data EM & AG revised the manuscript critically. All authors approved the final manuscript.

Research Quality and Ethics Statement

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting, and reproducibility guidelines set forth by the EQUATOR Network (PRISMA Guidelines for systematic review). The authors also attest that this clinical investigation was not determined to require the Institutional Review Board / Ethics Committee review, and the corresponding protocol/approval number is not applicable. We also certify that we have not plagiarized the contents in this submission and have done a Plagiarism Check.

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Figures

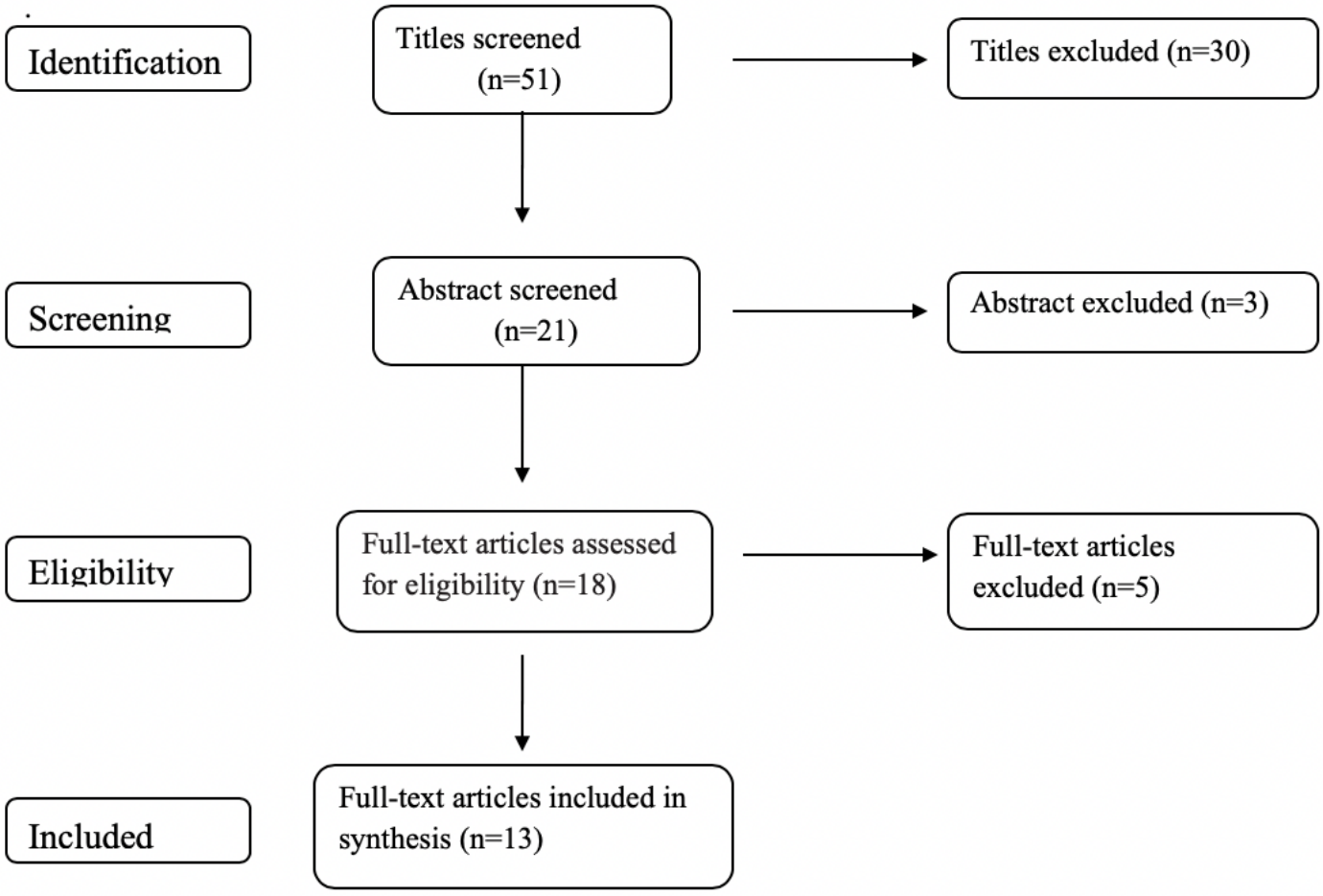

Figure 1

The final inclusion of a total of 13 studies from an initial search of 51 studies is depicted in the PRISMA flow diagram.

Supplementary Files

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- PRISMA2009ChecklistMSWord.doc