

“COVID toes”: A meta-analysis of case and observational studies on clinical, histopathological, and laboratory findings

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Abstract

Background: Coronavirus disease (COVID-19) is related to several extrapulmonary disorders; however, little is known about the clinical, laboratory, and histopathological characteristics of pernio-like skin lesions associated with COVID-19 infection.

Objective: To evaluate and summarize the clinical, laboratory, and histopathological characteristics of pernio-like lesions reported in the literature.

Methods: We conducted a search of the PubMed, SciELO, and ScienceDirect databases for articles published between January 1, 2020 and November 30, 2020, following the PRISMA recommendations (PROSPERO registration ID: CRD42020225055). The target population was individuals with suspected or laboratory-confirmed COVID-19 with pernio-like lesions. Observational studies, research letters, and case/series reports were all eligible for inclusion. Observational studies were evaluated using a random-effects model to calculate the weighted mean prevalence, overall mean, and 95% confidence interval. We evaluated case studies using the chi-square test for dichotomous variables and the Mann-Whitney test for continuous variables.

Results: A total of 187 patients from case reports and 715 patients from 18 observational studies were included. The mean age of patients was 16.6 years (range 14.5–18.8). Feet were affected in 91.4% (87.0–94.4%) of patients in observational studies. The proportion of patients with a positive RT-PCR test was less than 15%. Lesion topography and morphology were associated with age.

Conclusion: Lesions mostly occurred in pediatric patients, and the morphological characteristics tended to differ between pediatric and non-pediatric populations. There is a possible multifactorial component in lesion pathophysiology. The non-positivity of laboratory tests does not exclude an association with COVID-19. Pernio-like lesions may be a late manifestation of COVID-19.

KEYWORDS

chilblains-like, coronavirus, COVID-19 toes, pernio-like

1 | INTRODUCTION

Several extrapulmonary manifestations are associated with infection with severe acute respiratory syndrome coronavirus 2

(SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19). Of the described cutaneous manifestations, chilblain- and pernio-like lesions are among the most controversial.¹ Perniosis (chilblains) is commonly defined as an acral skin lesion caused by

poor blood circulation due to prolonged cold exposure. Vasculitis, Raynaud's phenomenon, acrocyanosis, and cryoglobulinemia are the main differential diagnoses.² During the pandemic, there has been an increase in cases of pernio-like lesions, which raises the hypothesis of an association with COVID-19. Furthermore, several reports have hypothesized that pernio-like lesions are a late manifestation of COVID-19.³ However, this theory is still purely speculative, with heterogeneous clinical, laboratory, and histopathological reports in the scientific literature.

The purpose of this meta-analysis was to evaluate and summarize the clinical, laboratory, and histopathological characteristics of COVID-19-related pernio-like lesions. For this purpose, we evaluated case reports and observational studies with different statistical methods to obtain greater descriptive and inferential depth from articles published in the scientific literature.

2 | METHODS

This meta-analysis was conducted following the recommendations of the Preferred Reporting Items for Systematic Reviews

and Meta-Analyses (PRISMA). A review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) with ID CRD42020225055. Ethical board approval was not necessary because the study was a literature review.

2.1 | Data sources and search strategy

Searches were carried out on PubMed, SciELO, and ScienceDirect for articles published between January 1, 2020 and November 30, 2020. The following search strategy was used: (acral OR pernio OR pernio-like OR perniosis OR chilblain OR chilblain-like) AND ("COVID-19" OR "coronavirus" OR "SARS-CoV-2"). There was no language restriction.

Study selection, data extraction, assessment of risk of bias, and data synthesis are detailed in Appendix A.

3 | RESULTS

The article selection process is detailed in Figure 1.

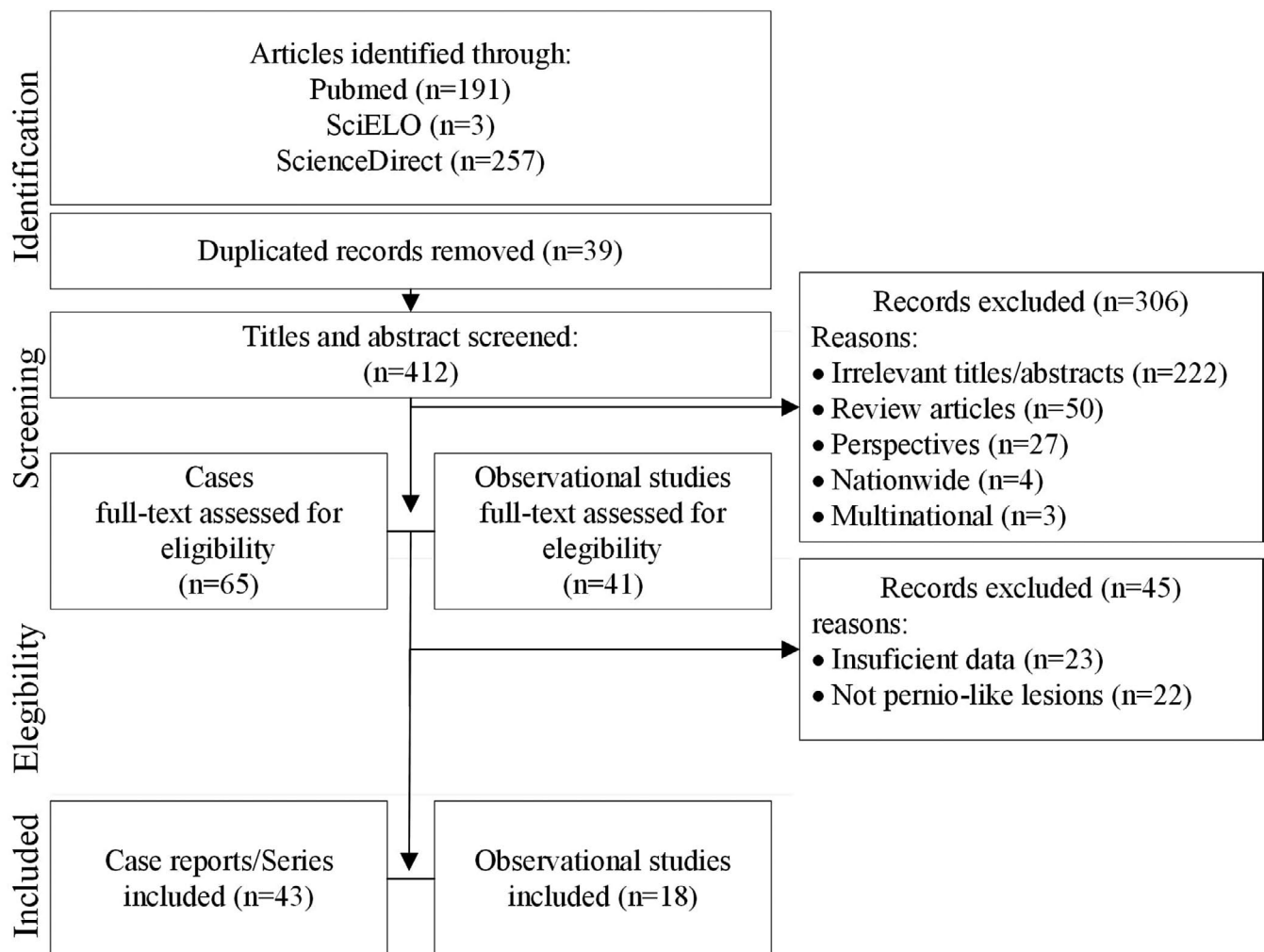


FIGURE 1 PRISMA diagram describing the article selection process. SciELO, Scientific Electronic Library Online

3.1 | Evaluations from observational studies

The observational studies included patients from four countries: Spain (68.8%), France (15.9%), Italy (10.9%), and Belgium (4.3%). Overall, the mean age of patients was 16.6 years (95% CI [14.5, 18.8]). Regarding the location of lesions, the feet and hands had an estimated prevalence of 91.4% and 17.9%, respectively. These studies showed significant heterogeneity and publication bias ($P < .001$) in the feet and hand proportions. The statistical results from observational studies are presented in Table 1. The morphology, color, secondary characteristics, and treatments were not included in the observational studies.

3.2 | Evaluations from case and series reports

The case reports included patients from nine countries: Italy (47.6%), Spain (15.5%), United Kingdom (13.9%), USA (10.7%),

France (5.9%), Austria (3.7%), Canada (1.1%), Kuwait (1.1%), and Germany (0.5%).

Overall, the median age of patients was 15 years (range 12–28): 15 years (range 12.5–25) for males and 15 years (range 11–30) for females. The age data did not show a symmetrical distribution ($P < .001$; Figure 2), with 125 (66.8%) cases younger than 20 years and 62 (33.2%) cases 20 years or older. There was no significant age difference between the sexes ($P = .838$).

Hand and foot involvement was evaluated in 187 cases. The frequency of foot involvement was significantly associated with male sex ($P = .037$), with 90.7% of males and 80.0% of females presenting with foot involvement. Hand involvement was significantly associated with females (30.0%) compared with males (17.5%) ($P = .045$). Foot involvement was significantly associated with patients under 20 years of age ($P < .001$; 92.0%) versus 72.6% in patients 20 years and older, whereas hand involvement was significantly associated with patients aged 20 years and older (32.3%) compared with those older than 20 years of age (19.2%) ($P = .048$).

TABLE 1 Pooled mean and prevalence, confidence interval, and Egger's test of clinical and laboratorial aspects found in observational studies with COVID-19-associated pernio

Variable (n participants)	Pooled mean (95% CI)	I ² (%)	Eggers (p)
Age (years, n = 715)	16.6 (14.5; 18.8)	96.1 (94.9; 97.0)	0.203
Time from pernio onset to consultation (days, n = 352)	17.3 (12.6; 23.7)	96.3 (94.6; 97.5)	-
Pooled prevalence (95% CI) (%)			
Sex			
Female (n = 715)	46.8 (43.1; 49.5)	<0.1% (0; 40.9)	0.333
Male (n = 715)	54.2 (50.5; 57.9)	<0.1% (0; 40.9)	0.333
Topography			
Feet (n = 698)	91.4 (87.0; 94.4)	53.9% (20.2; 73.4)	<0.001
Toes (n = 196)	92.1 (73.2; 98.0)	79.7 (55.9; 90.7)	-
Heels (n = 163)	27.2 (16.2; 41.8)	63.4 (3.4; 86.1)	-
Hands (n = 698)	17.9 (13.1; 23.9)	63 (37.6; 78.0)	<0.001
Feet and hands (n = 634)	11.7 (8.2; 16.5)	53 (11.7; 74.4)	0.059
Focal symptoms			
Pruritus (n = 395)	35.8 (29.0; 43.4)	52 (0; 77.5)	-
Pain (n = 362)	24.8 (20.3; 29.9)	8 (0; 70.2)	-
Asymptomatic (n = 330)	35.7 (21.9; 52.3)	84.7 (70.3; 92.1)	-
General symptoms			
Fever (n = 387)	11.6 (6.4; 20.1)	72.0 (46.8; 85.2)	<0.001
Respiratory (cough, sore throat, rhinorrhea) (n = 354)	28.6 (19.3; 40.1)	76.2 (54.4; 87.6)	-
Gastrointestinal (n = 387)	12.9 (9.6; 17.0)	8.2 (0; 65.5)	0.034
Myalgia (n = 180)	6.5 (3.6; 11.4)	<0.1 (0; 46.0)	-
Headache (n = 144)	9.6 (5.1; 17.3)	16.2 (0; 87.2)	-
Close contact with COVID-19 suspect patients (n = 580)	32.0 (21.5; 44.7)	84.5 (74.9; 90.4)	0.219
Rt-PCR positive (n = 289)	7.9 (4.4; 13.8)	22.7 (0; 57.5)	0.006
Serology positive (n = 190)	12.3 (4.5; 29.2)	69.4 (36.1; 85.3)	-

Abbreviation: Rt-PCR, reverse transcription-Polymerase Chain Reaction.

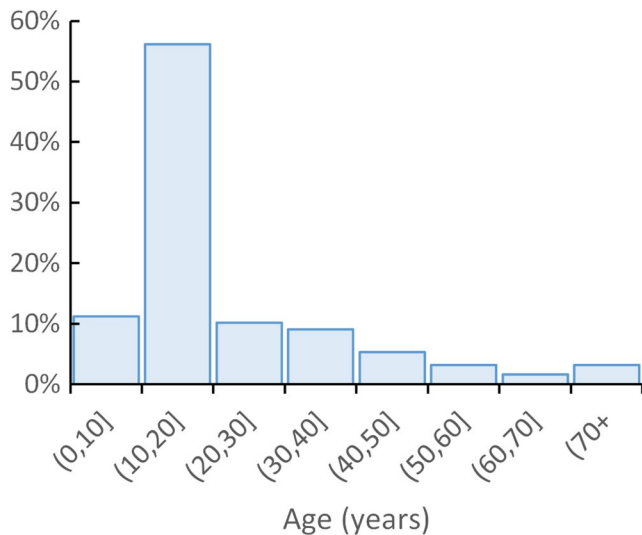


FIGURE 2 Frequency distribution of age (y) for case reports

Morphology and color were reported for 151 (80.7%) cases. Macules and patches were the most prevalent morphology (71.5%). Neither morphology (macules and patches or papules and plaques) nor color (red violaceous or purplish) was associated with sex. Macules and patches were associated with patients aged under 20 years (79.1%) compared with older patients ($P < .001$; 51.2%), while papules and plaques were seen in 43.9% of those 20 years or older compared with 23.6% of younger patients ($P = .015$). The time from lesion onset to remission was reported for 63 (33.7%) cases, with a median of 21 days (range 10-27).

Focal symptoms were reported in 111 (59.4%) cases and grouped into two strata: pain or tenderness; or pruritus, tingling, or burning. The frequency of focal symptoms was not associated with sex.

An asymptomatic presentation was reported in 32.6% of patients aged younger than 20 years versus 9.8% of older patients ($P = .005$; $n = 130$). Pain and tenderness were associated with patients aged 20 years and older 56.1% ($P = .003$, $n = 130$) versus 29.2% in those under 20 years.

Edema was reported in 31.8% of patients younger than 20 years of age ($P = .015$; $n = 151$) versus 12.2% of older patients and there was no association with other focal or previous symptoms. Edema was most frequently associated with foot involvement (30.5%) versus hand involvement (4.3%) ($P = .009$; $n = 151$). Pruritus was equally distributed ($P = .193$) between patients younger than 20 years of age and older. Neither foot nor hand involvement was associated with the frequency of focal symptoms.

Cold exposure and close contact with potential COVID-19-infected people were reported in 13 (7.0%) and 94 (50.2%) cases, respectively. General symptoms and clinical history, which are described in Table 2, were not associated with sex. An absence of previous clinical history was associated with an age younger than 20 years (68.8%) versus 48.4% in older patients ($P = .007$; $n = 187$). In 187 patients, cough (19.4%; $P = .023$) and respiratory symptoms (29.0%; $P = .004$) were associated with patients aged 20 years and

TABLE 2 Frequency distribution of clinical and laboratory variables reported in clinical cases of COVID-19-associated perniois

Variable	n/N	(%)
Sex		
Female	90/187	48.1
Male	97/187	51.9
Topography		
Feet	160/187	85.6
Toes	112/145 ^a	77.2
Toe dorsum	63/83 ^b	75.9
Toe digits	13/83 ^b	15.7
Heels	22/145 ^a	15.2
Soles	24/145 ^a	16.6
Lesion in toe 1	34/42 ^c	81.0
Lesion in toe 2	34/42 ^c	81.0
Lesion in toe 3	35/42 ^c	83.3
Lesion in toe 4	28/42 ^c	66.7
Lesion in toe 5	24/42 ^c	57.1
Hands	44/187	23.5
Fingers	26/145 ^a	17.9
Finger dorsum	11/83 ^c	13.3
Finger digits	10/83 ^c	12.0
Palms	6/145 ^a	4.1
Lesion in finger 1	6/17 ^c	35.3
Lesion in finger 2	11/17 ^c	64.7
Lesion in finger 3	10/17 ^c	58.8
Lesion in finger 4	8/17 ^c	47.1
Lesion in finger 5	6/17 ^c	35.3
Feet and hands	17/187	9.1
Morphology		
Macular/patches	108/151 ^d	71.5
Papular/plaques	44/151 ^d	29.1
Petechial	2/151 ^d	1.3
Vesicular	9/151 ^d	6.0
Scale	9/151 ^d	6.0
Color		
Erythematous/red violaceous	113/151 ^d	74.8
Purplish	34/151 ^d	22.5
Cyanosis	2/151 ^d	1.3
Characteristic		
Edematous	40/151 ^d	26.5
Necrotic	3/151 ^d	2.0
Focal symptoms		
Pain or tenderness	49/130 ^d	37.7
Pruritus, tingling, or burning	62/130 ^d	47.7

(Continues)

TABLE 2 (Continued)

Variable	n/N	(%)
Not reported	57/187	30.5
Clinical history		
Patient has been exposed to cold		
Yes	1/13 ^e	7.7
Not reported	174/187 ^e	93.0
Close contact to possible COVID-19 contaminant		
Yes	55/94 ^e	58.5
Not reported	93/187 ^e	49.7
Previous symptoms history		
Fever	34/187	18.2
Cough	22/187	11.8
Headache	13/187	7.0
Respiratory (rhinorrhea, sore throat, or dyspnea)	33/187	17.6
Ageusia, dysgeusia, or anosmia	2/187	1.1
Gastrointestinal (diarrhea, nausea, abdominal pain, or poor appetite)	10/187	5.3
No history	116/187	62.0
Rt-PCR and serology findings		
Rt-PCR positive	15/113 ^e	13.3
IgA+	2/27 ^e	7.4
IgM+	1/65 ^e	1.5
IgG+	11/87 ^e	12.6
Laboratory findings		
Lymphopenia	1/61 ^f	1.6
Abnormal coagulation profile	2/61 ^f	3.3
Abnormal D-dimer	9/61 ^f	14.8
High ferritin	1/61 ^f	1.6
High C-reactive protein	2/61 ^f	3.3
Antinuclear antibody positive	7/61 ^f	11.5

^aOnly cases which reported specific locations from lesion, excluded cases which reported only "feet" or "hands".

^bOnly cases which reported surface (toes/finger dorsum, lateral, digits).

^cOnly cases which reported affected toes/fingers number.

^dOnly cases which reported lesion characteristics.

^eOnly cases which explicitly informed this variable.

^fOnly cases which reported laboratorial findings.

older compared with 8.0% and 12.0%, respectively, in those younger than 20 years.

RT-PCR evaluation was reported in 113 (60.4%) cases (Table 2). RT-PCR ($P = .957$) and IgG ($P = .899$) positivity were not associated with sex. A positive RT-PCR result was reported in 44.4% of those 20 years and older versus 3.5% positivity in those under 20 years ($P < .001$). Histopathology was reported in 122 cases (Table 3).

TABLE 3 Frequency distribution of histopathological findings reported in cases of COVID-19-associated perniois

Variable	n	(%) ^a
Perivascular deep inflammation	113	92.6
Perivascular superficial inflammation	105	86.1
Periecrine inflammation	74	60.7
Dermal edema	65	53.3
Blood cell extravasation	63	51.6
Basal vacuolar changes	46	37.7
Dermal mucin	34	27.9
Necrotic keratinocytes	32	26.2
Endothelial cell swelling	32	26.2
Spongiosis	31	25.4
Lymphocytic infiltration of vessels	30	24.6
Thrombi in deep dermis	23	18.9
Parakeratosis	18	14.8
Exocytosis	17	13.9
Thrombi in superficial dermis	15	12.3
Lymphocytic panniculitis	7	5.7
Erosion or ulceration	2	1.6

^aTotal biopsy cases = 122.

Twenty-nine (15.5%) cases received some form of therapy. Five (2.6%) reported using no medications. Twenty-four (12.8%) reported the use of various medications: nonspecific topical corticosteroid,⁴ heparin gel,⁵ topical clobetasol,⁶ nitroglycerin gel,⁷ topical triamcinolone,⁶ topical clotrimazole,⁶ nonspecific topical antibiotic, azithromycin,^{8,9} hydroxychloroquine,^{8,9} oral antihistamine, nonspecific oral corticosteroid, aspirin,¹⁰ gabapentin,¹⁰ enoxaparin,⁷ heparin,¹¹ low-molecular-weight heparin,¹² and tocilizumab.⁸

4 | DISCUSSION

This paper highlights four main points to help clarify the mechanism behind COVID toes: (i) the pediatric population was mainly affected; (ii) age under 20 years was a determining factor for topography, morphology, signs, symptoms, and RT-PCR positivity; (iii) sex was not a determining factor; and (iv) the histopathological findings were nonspecific.

The age distribution of affected patients was one of the most striking aspects of this work. Pediatric patients were predominantly affected, but cases were reported across all age groups. A possible explanation for this phenomenon is based on robust type 1 interferon (IFN-1) production by the pediatric population. IFN-1 acts as a bridge between innate and adaptive immunity, and it plays direct roles in immunomodulation and the production of antiviral proteins. Higher production of IFN-1 in younger individuals is possibly associated with a better antiviral status, which may explain the lower rates of respiratory and systemic symptoms caused by SARS-CoV-2 in this population. Furthermore, disturbances in the downregulation

of interferon production are associated with autoimmune conditions and severe inflammation. Pernio-like lesions associated with COVID-19 are similar to those described in patients with interferonopathies, where there is defective regulation leading to excess of interferons production.¹³ Vascular lesions of the skin, such as pernio and livedo reticularis, are common characteristics of these conditions.

Another important aspect of this work is the association of age with lesion topography and morphology. The observed topographic, sex, and age patterns may indicate a multifactorial influence on the development of pernio-like lesions. When specifically evaluating pediatric cases younger than 20 years of age, the frequencies of foot and hand involvement were not associated with sex. The same was true for cases aged 20 years or older. This indicates that the main topographic determinant of the lesions was age, not sex. This raises some hypotheses: (i) lesions have different pathophysiological conditions depending on age, characterizing different diseases; (ii) lesion pathophysiology depends on multifactorial aspects, which differ between the two age groups; or (iii) a type II error was present.

The multifactorial hypothesis integrates psychological, behavioral, nutritional, and environmental exposure aspects, which were all greatly affected by the uncertainties and social dynamics of the pandemic course in 2020. The general population experienced a decrease in physical activity and worsened nutritional quality. All of these conditions occurred in an environment of emotional distress and chronic stress. Such conditions can lead to neuroendocrine alterations, affecting metabolism, immune, and inflammatory modulation, which can contribute to the development of microvascular disorders.¹⁴

The histopathological findings are characterized by vascular damage with perivascular and perieccrine infiltrate. Endothelial damage can be caused directly by viral action, complement deposition, or the recruitment of immune-mediated cells.¹⁵ The histopathological findings are nonspecific to the main differential diagnoses. Therefore, performing a biopsy without the intention of immunohistochemical assessment will not be helpful for diagnosis and treatment.

Most pediatric individuals were not positive for SARS-CoV-2. However, the absence of antigen and antibody positivity does not necessarily rule out an association with COVID-19. The low positivity rate could be explained by the following hypotheses: (i) manifestation unrelated to COVID-19; (ii) antibody titers from mild manifestations do not reach the cut-off point for positive serological tests; (iii) mild or asymptomatic disease in the young population does not cause a robust adaptive immune response; or (iv) the antibodies have different epitopes from those evaluated by the tests used.⁶ The IgM peak occurs around 5-12 days postinfection, while the IgG peak occurs 20 days after infection.¹⁶ Most patients who underwent serological testing already had enough lesion time to detect IgM. However, most serological tests have critically ill patients with high antibody titers as the gold standard. Colmenero et al found positive immunohistochemistry staining of the SARS-CoV-2 spike protein in the acral lesions of patients with a negative RT-PCR result. The

positive predictive value of these tests is potentially lower in the pediatric population, especially for mildly symptomatic infections.

COVID-19-associated pernio-like lesions tend to be self-limited, regardless of the therapy adopted. Oral antihistamines can aid in pruritus relief.¹⁷ Reports about topical and oral corticosteroids are controversial and subjective, having various degrees of relief or no effect.^{6,18} We emphasize that individualized treatment and monitoring are even more important when there is a lack of therapeutic evidence.

4.1 | Limitations

This study has several limitations. Most of the studies were conducted on the European continent; therefore, care must be taken when generalizing these results. Race subgroups were not evaluated. Case reports have a low or very low evidence level, and many did not follow the methodological rigor of the Case Reports Guideline (CARE). Funnel plot evaluation showed substantial publication bias in some variables, indicated by asymmetry of the points. We acknowledge that some studies published in local non-indexed journals may not have been included in this study.

5 | CONCLUSION

In conclusion, COVID-19-associated pernio-like lesions mostly occur in the pediatric population. The topographic and morphological distribution tends to be different in pediatric and non-pediatric populations. Multifactorial aspects may be associated with the pathophysiology of these lesions. The histopathological patterns are nonspecific and may not help in diagnosis or therapeutic management. The absence of positivity in RT-PCR or serological tests does not rule out a possible association with COVID-19. There is no specific treatment for the lesions, which tend to be self-limited.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Zenodo at <http://doi.org/10.5281/zenodo.4657048>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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