

SYSTEMATIC REVIEW

Are the chilblain-like lesions observed during the COVID-19 pandemic due to severe acute respiratory syndrome coronavirus 2? Systematic review and meta-analysis

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Abstract

The expansion of the COVID-19 pandemic has been accompanied by numerous reports of chilblain-like lesions (CLL) in different countries; however, the pathogenesis of these lesions is still unclear. This systematic review and meta-analysis aimed to assess the prevalence of COVID-19 (diagnosed using PCR and/or serology) in patients with CLL. We undertook a literature search in PubMed, Embase, and Scopus (to 15 March 2021), including studies that reported on the number of patients with CLL with positive PCR and/or serology for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or with a clinical suspicion of COVID-19. Regardless of data heterogeneity, a random-effects model was used to pool prevalence estimates. The meta-analysis included 63 original studies, involving 2919 cases of CLL. A subgroup of these patients underwent diagnostic tests for COVID-19 (PCR: $n = 1154$, 39.5%; serology: $n = 943$, 32.3%). The pooled prevalence of COVID-19 in the overall sample and in the subgroup who were tested for COVID-19 was, respectively: (i) positive PCR: 2.6% [95% confidence interval (CI) 1.9% to 3.4%] and 5.5% (95% CI, 3.7–7.7%); (ii) positive serology for SARS-CoV-2: 7.2% (95% CI, 4.7–10.2%) and 11.8% (95% CI, 7.9–16.3%); and (iii) positive PCR and/or serology, 15.2% (95% CI, 10.4–20.7%) and 7.5% (95% CI, 5.1–10.3%). Altogether, a small proportion of diagnostic tests for SARS-CoV-2, both PCR and serologies, show positive results in patients with CLL.

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Conflict of interest

The authors declare no conflicts of interests.

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Introduction

The new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causal agent of COVID-19, has been spreading globally since it first emerged in Wuhan (China) in December 2019.¹ As the pandemic has expanded its reach, numerous cutaneous manifestations associated with COVID-19 have been reported,² encompassing a diverse range of clinical presentations, from skin rashes and chilblain-like lesions (CLL) to purpish lesions and skin necrosis.³

Since the pandemic began, there has been an uptick in reports of cases of acral, chilblain-like lesions. Different

studies have suggested or investigated a potential association between these lesions and infection from the SARS-CoV-2 virus. However, their pathophysiology remains unclear and widely debated, because despite the temporal association between the outbreak of CLL and the COVID-19 pandemic, only a fraction of patients with CLL have tested positive for SARS-CoV-2.

The primary objective of this systematic review and meta-analysis is to assess the prevalence of SARS-CoV-2 infection (as diagnosed by PCR and/or serological antibody testing) in patients with CLL. These results can inform an evaluation of whether these CLL⁴ or COVID toes are truly associated with COVID-19.

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Material and methods

Protocol and registration

We conducted a systematic review of the literature using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).⁵ The review was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021240721).

Information sources and search strategy

This systematic review was performed in accordance with PRISMA guidelines. A systematized search strategy was designed to search for articles in the MEDLINE (PubMed), Embase, and Scopus databases. The last search was undertaken on 15 March 2021.

The search terms were chosen in accordance with MEDLINE Medical Subject Headings (MeSH), using a combination of key terms extracted from the research question. The first two authors ran independent searches and managed the retrieved records using the Mendeley (Elsevier) bibliographic software.

The search strategy employed in the PubMed and Scopus databases was: ("Coronavirus disease 2019" OR "2019 Novel Coronavirus" OR "SARS-CoV-2" OR "2019-nCoV" OR "COVID-19") AND ("chilblain-like" OR "pernio" OR "chilblain" OR "chilblains" OR "acral" OR "toes" OR "achro ischemic").

The search strategy for Embase was: ('coronavirus disease 2019'/exp OR 'coronavirus disease 2019' OR '2019 novel coronavirus'/exp OR '2019 novel coronavirus' OR 'sars-cov-2'/exp OR 'sars-cov-2' OR '2019-ncov'/exp OR '2019-ncov' OR 'covid-19'/exp OR 'covid-19') AND ('chilblain-like' OR 'pernio'/exp OR 'pernio' OR 'chilblain'/exp OR 'chilblain' OR 'chilblains'/exp OR 'chilblains' OR 'acral' OR 'toes'/exp OR 'toes' OR 'achro ischemic').

Inclusion criteria

Studies that were published or forthcoming and written in English, Spanish, or Italian were selected based on the following (PICOS) criteria:

- Population: children and adults with CLL diagnosed since December 2019.
- Intervention: diagnostic tests for COVID-19 (PCR and/or serology) and study of the epidemiological characteristics in patients with CLL.
- Comparator: not applicable.
- Outcomes: percentage of patients with CLL who were diagnosed or presented symptoms consistent with infection by SARS-CoV-2; positivity rate of PCRs and serologies in patients with CLL.
- Study design. Observational studies involving at least five patients diagnosed with CLL and specified how many participants presented positive diagnostic tests for COVID-19 (PCR and/or serology) or had a clinical suspicion of SARS-CoV-2 infection.

Study selection

No date restrictions were applied. Following the PRISMA procedure,⁵ duplicate articles were excluded. Two review authors (V.S.G. and R.H.Q.) independently screened the title and abstract of records yielded by the search to classify the reference as potentially relevant or irrelevant. After retrieving the full text of all potentially relevant papers, the two authors independently checked them against the review's inclusion criteria. Disagreements were resolved by consensus.

Data extraction and collection

Two review authors (V.S.G. and R.H.Q.) independently extracted and summarized data for each included article on an Excel spreadsheet, and a third author (J.M.R.R.) checked them. For each included record, the following information was collected: first author, journal of publication, date of publication, country of study, language of publication, study design, sample size, proportion of men and women, patient age (mean/median and range), number of patients considered close contacts of people diagnosed or suspected of having COVID-19, total PCRs performed, total positive and negative PCRs, total serologies performed, total positive and negative serologies, total patients diagnosed with COVID-19, case definition (patients with compatible clinical signs and patients diagnosed with COVID-19), and patients with symptoms compatible with infection by SARS-CoV-2.

Risk of bias of included studies

Two review authors independently assessed the methodological quality of the studies included in the meta-analysis, using Quality Assessment Tool for Case Series Studies of National Heart, Lung and Blood Institute (NHLBI) according to the study design.⁶ Disputes were resolved by consensus. The seven domains assessed were: bias due to confounding, bias in selection of participants into the study, bias in measurement of interventions, bias due to departures from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported result.

Definition of variables

Confirmed cases of COVID-19 were defined based on a positive PCR for SARS-CoV-2 (nasopharyngeal or stool swab) and/or positive serology for SARS-CoV-2 antibodies. Suspected cases of COVID-19 were those in patients that did not undergo a COVID-19 diagnostic test or who presented a negative test but met European Centre for Disease Prevention and Control (ECDC) criteria for a possible COVID-19 infection.⁷

Participants were considered contacts of COVID-19 cases when they had been in contact with a patient who had tested positive for SARS-CoV-2 via nasopharyngeal or stool swab and/or had a positive serology for SARS-CoV-2 antibodies. People who had been in contact with suspected cases of COVID-19

(based on ECDC criteria⁷) were considered to be possible contacts of COVID-19 patients.

Analysis of outcomes

We used descriptive statistics to present the data, including counts, ranges, and percentages, along with a narrative synthesis summarizing results in text and tables. Prevalence estimates were calculated as the proportion of patients with CLL and positive diagnostic tests for COVID-19, over both the total sample of patients with CLL and the subgroup of patients with CLL who underwent PCR and/or serology. The prevalence meta-analysis was performed using Statsdirect statistical software v. 3.3.5 (Merseyside, UK). Forest plots were constructed to graphically represent the pooled prevalence for positive PCRs and serological tests for COVID-19 in patients with CLL, with respect to the total number of diagnostic tests performed, and prevalence was expressed as a percentage with 95% confidence intervals (CIs). The Stuart-Ord method (inverse double arcsine square root) was used to calculate the 95% coefficient intervals and create effect diagrams.

The heterogeneity of included studies was assessed using the I^2 statistic (95% CI) and the Q statistic. I^2 values over 50% indicate heterogeneous data. The random-effects model was applied regardless of heterogeneity because of the substantial heterogeneity expected between studies. Risks of reporting bias or small study effects were analysed graphically using funnel plots and statistically using Egger's regression. P values of <0.10 on Egger's test were considered to indicate statistically significant reporting bias.

Results

Search results

The searches in the three bibliographic databases (PubMed, Embase, and Scopus) yielded a total of 875 articles. Following deduplication and screening of titles and abstracts, 165 full-text records were retrieved and assessed against eligibility criteria. The final meta-analysis included 63 records that met all inclusion criteria; 52 other studies were excluded from the meta-analysis due to a sample size of fewer than five patients (see PRISMA flow chart in Fig. 1).

Characteristics of included studies

Table 1 presents the characteristics of included studies. Most (84.1%) were case reports in patients with CLL. Seven other studies (11.1%) used a retrospective study design, while the remaining three (4.8%) were prospective. Studies took place in Spain ($n = 23$, 36.5%), Italy ($n = 19$, 30.2%), France ($n = 12$, 19.1%), the USA ($n = 7$, 11.1%), Belgium ($n = 1$, 1.6%), and Australia ($n = 1$, 1.6%).

The number of included participants ranged from 5^{8–11} to 534.¹² For the meta-analysis, we extracted data on 2919 cases of

skin lesions classified on the clinical spectrum of CLL from December 2019 to March 2021. Participants included 1092 (37.4%) women and 1200 (41.1% men); five large studies involving 627 patients (21.5%) did not report participants' gender.^{12–16}

Participants' ages varied by study, with the age ranging from 0^{17–20} to 100 years²¹ among all participants. The mean age in studies reporting this variable ranged from 10.6 years²² to 62 years.⁹ Overall, the mean age for the sample was 20.9 years.

A total of 502 patients (17.2%) were considered close contacts of people with a confirmed diagnosis or high clinical suspicion of COVID-19 infection. Of the 2919 cases with CLL, 1154 (39.5%) underwent PCRs and 943 (32.3%) serology.

In quality assessment, 41 studies were ranked as having good quality, 19 studies ranked as having fair quality and three studies were ranked as having poor quality (Table S1).

Pooled prevalence of positive diagnostic tests for COVID-19

Table 2 shows the main findings of the meta-analysis for prevalence of positive COVID-19 diagnostic tests among the total patients with CLL and in the subgroup who underwent some diagnostic tests for COVID-19.

In the study of positive PCRs, five studies were excluded from the meta-analysis: two for not presenting any positive PCRs^{19,23} and three for not having performed any PCRs in the sample.^{9,24,25} The pooled prevalence of COVID-19-positive PCRs among all patients with CLL was 2.6% (95% CI, 1.9–3.4%; Fig. 2), with low heterogeneity and no asymmetry apparent in the funnel plot, corroborated by Egger's test (Fig. S1). The pooled prevalence of positive PCRs in patients with CLL who underwent PCR testing for COVID-19 was 5.5% (95% CI, 3.7–7.7%), with moderate heterogeneity and asymmetry in the funnel plot.

In the meta-analysis for prevalence of positive serology, 15 studies were excluded for not having performed serological testing in their participants.^{10,18–20,22,23,26–34} The pooled prevalence of positive serologies for SARS-CoV-2 antibodies in all patients with CLL was 7.2% (95% CI, 4.7–10.2%; Fig. 3). Data showed high heterogeneity and asymmetry in the funnel plot (Fig. S2). The pooled prevalence for positive serological tests in patients with CLL who underwent serological testing was 11.8% (95% CI, 7.9–16.3%), with high heterogeneity and asymmetry in the funnel plot.

In the meta-analysis pooling prevalence estimates for any positive COVID-19 diagnostic test in patients with CLL, four studies were excluded: two for not specifying the number of patients with CLL who were diagnosed with COVID-19 (by PCR and/or serology),^{12,35} and two for not performing either test or not specifying how many tests were done.^{19,23} The pooled prevalence of patients with CLL who were diagnosed with a SARS-CoV-2 infection by PCR and/or serology was

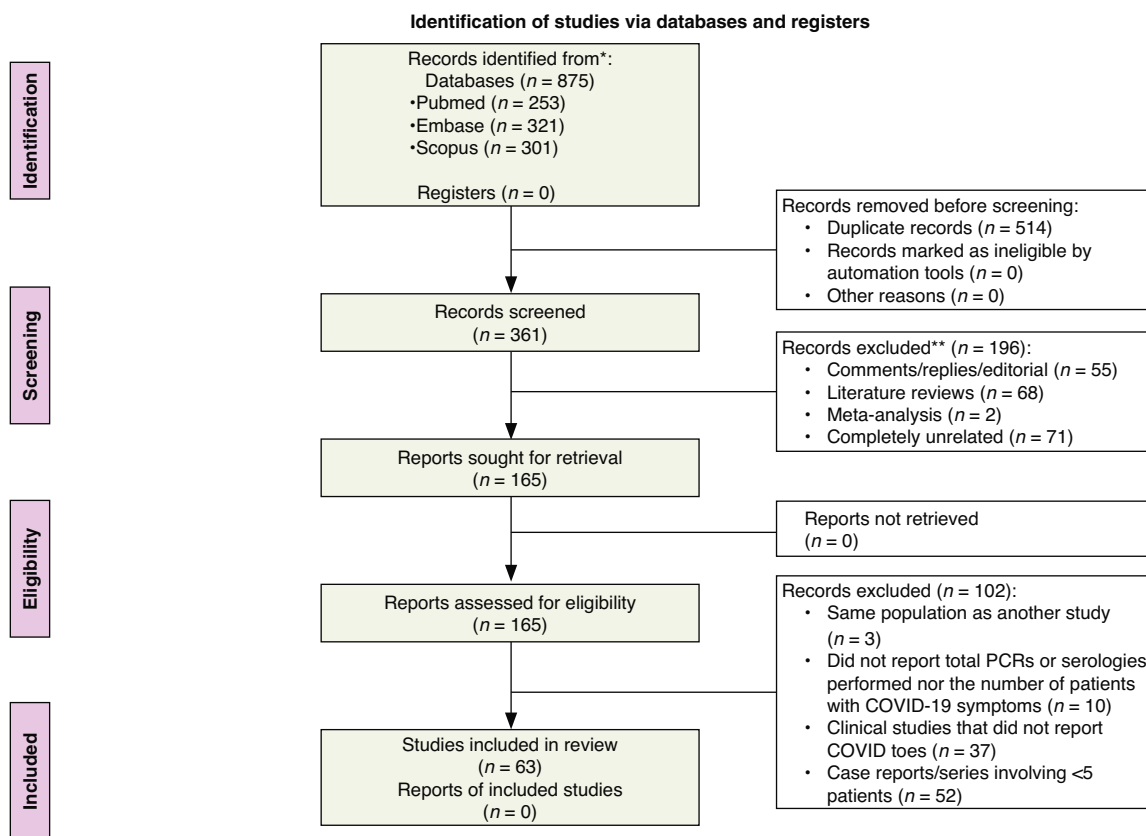


Figure 1 PRISMA flow chart for study selection.

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.⁷⁹

15.2% (95% CI, 10.4–20.7%; Fig. 4), with high heterogeneity and asymmetry in the funnel plot (Fig. S3). The pooled prevalence for positive PCRs and/or serologies in patients with CLL who underwent a diagnostic test for COVID-19 was 7.5% (95% CI, 5.1–10.3%), with high heterogeneity and asymmetry in the funnel plot.

Discussion

Our meta-analysis shows a low prevalence of positive PCRs among patients with CLL and only a slightly higher prevalence of positive serologies for SARS-CoV-2 antibodies. Altogether, the pooled prevalence of positive PCRs among patients with CLL was 2.6%, and of positive serologies, 7.2%. Although the results show that 502 patients were named contacts of people with suspected or confirmed COVID-19 infections, the number of people infected was much lower.

The CLL lesions appear relatively late in the course of COVID-19, often during the convalescent phase, from 1 to 5 weeks after onset of the first symptoms of infection.^{36,37} This

could explain the negative results of the PCRs; however, the prevalence estimates based on antibody testing—while showing slightly higher results—were still quite low.

Despite the temporal association between the increased cases of CLL and the COVID-19 pandemic, the low proportion of positive diagnostic tests for SARS-CoV-2 in these patients does not support the hypothesis that there is a relationship between the two pathologies. In 1996, Fredericks & Relman called for a reconsideration of Koch’s postulates for analysing the causal relationship between a microorganism and an infectious disease, with seven criteria that the patients with these acral lesions do not fulfil.³⁸

However, different theories have emerged to explain this discrepancy. One is that the low prevalence of positive diagnostic tests for COVID-19 in these patients could be due to the generation of IgA antibodies against the respiratory mucus, the site of the first contact with the virus.¹³ This would justify the lack of memory in the immune response (self-limiting disease) and explain why only a few cases present an IgG memory. This

Table 1 Characteristics of the included studies reporting chilblain-like lesions during the COVID-19 pandemic

Authors Country	Study design	Sample (N)	Age (years) Sex: number of patients (%)	N contacts with probable or confirmed COVID-19 cases (%)	N PCRs performed (%) / N positive (%)	N serologies performed (%) / N positive (%)	COVID cases*
Hubiche T, <i>et al.</i> ⁴⁸ France	Case series	40	Median age: 22 Range: (12–67) F: 21 (52.5%) M: 19 (47.5%)	24 (60%)	26 (65%)/0 (0%)	40 (100%)/12 (30%)	Confirmed: 12 Suspected: 7
Gómez-Fernández C <i>et al.</i> ⁴⁹ Spain	Prospective cohort study	54	Mean age: 14 Range: (8–66) F: 23 (42.6%) M: 31 (57.4%)	14 (25.9%)	34 (63%)/0 (0%)	53 (98.1%)/0 (0%)	Confirmed: 0 Suspected: 22
Giavedoni P <i>et al.</i> ⁵⁰ Spain	Retrospective analysis of a prospectively collected cohort	17	Median age: 29 Range: (24.8–47.4) F: 7 (41.2%) M: 10 (58.8%)	N/A	7 (41.2%)/3 (42.9%)	7 (41.2%)/4 (57.1%)	Confirmed: 7 Suspected: 10
Sohier P <i>et al.</i> ³¹ France	Case series	13	Median age: 32 Range: (22–36) F: 6 (46.2%) M: 7 (53.8%)	N/A	13 (100%)/0 (0%)	0 (0%)/0 (0%)	Confirmed: 0 Suspected: 9
Feito-Rodríguez M <i>et al.</i> ³⁵ Spain	Prospective cohort study	37	Mean age: 22.08 Median age: 14 F: 20 (54.1%) M: 17 (45.9%)	N/A	37 (100%)/3 (8.1%)	37 (100%)/3 (8.1%)	Confirmed: N/A Suspected: N/A
Fabbrocini G <i>et al.</i> ³² Italy	Case series	15	13 years ± 2.08 DS Range: (8–17) F: 6 (40%) M: 9 (60%)	3 (20%)	15 (100%)/0 (0%)	0 (0%)/0 (0%)	Confirmed: 0 Suspected: 6
Piccolo V <i>et al.</i> ⁵¹ Italy	Case series	10	Mean age: 13.2 Range: (11–20) Median age: 13 F: 3 (30%) M: 7 (70%)	N/A	1 (10%)/0 (0%)	2 (20%)/0 (0%)	Confirmed: 0 Suspected: 0
Fertitta L <i>et al.</i> ⁵² France	Case series	17	Mean age: 11.2 Range: (1.8–17.3) F: 7 (41.2%) M: 10 (58.8%)	14 (82.4%)	3 (17.6%)/0 (0%)	16 (94.1%)/1 (6.3%)	Confirmed: 1 Suspected: 10
Docampo-Simón A <i>et al.</i> ¹⁷ Spain	Prospective study	59	Median age: 14 Range: (0–50) F: 25 (42.4%) M: 34 (57.6%)	17 (29.9%)	37 (62.7%)/0 (0%)	25 (42.4%)/0 (0%)	Confirmed: 0 Suspected: 9
Gallizzi R <i>et al.</i> ⁵³ Italy	Case series	9	Mean age: 11.4 Range: (5–15) F: 5 (55.6%) M: 4 (44.4%)	2 (22.2%)	9 (100%)/0 (0%)	9 (100%)/0 (0%)	Confirmed: 0 Suspected: 6
Diociaiuti A <i>et al.</i> ⁵⁴ Italy	Case series	30	Mean age: 14.4 Range: (11–17) F: 9 (30%) M: 21 (70%)	10 (33.3%)	30 (100%)/1 (3.3%)	30 (100%)/18 (60%)	Confirmed: 18 Suspected: 1
Freeman EE <i>et al.</i> ¹² USA	Case series	534	N/A F: N/A M: N/A	N/A	157 (29.4%)/23 (14.6%)	78 (14.6%)/15 (19.2%)	Both confirmed and suspected: 534
Marchetti F <i>et al.</i> ⁵⁵ Italy	Case series	14	Mean age: 13.5 Range: (10–18) F: 9 (64.3%) M: 5 (35.7%)	6 (42.9%)	14 (100%)/0 (0%)	14 (100%)/0 (0%)	Confirmed: 0 Suspected: 9
Cuenca Saez MA <i>et al.</i> ¹³ Spain	Retrospective study	11	Range: (2–40) F: N/A M: N/A	N/A	2 (18.2%)/1 (50%)	11 (100%)/3 (27.3%)	Confirmed: 3 Suspected: N/A

Table 1 Continued

Authors Country	Study design	Sample (N)	Age (years) Sex: number of patients (%)	N contacts with probable or confirmed COVID-19 cases (%)	N PCRs performed (%) / N positive (%)	N serologies performed (%) / N positive (%)	COVID cases*
Rosés-Gibert P <i>et al.</i> ⁵⁶ Spain	Retrospective study	36	Mean age: 11.1 Range: (3–13) F: 13 (36.1%) M: 23 (63.9%)	15 (41.7%)	7 (19.4%)/0 (0%)	1 (2.8%)/0 (0%)	Confirmed: 0 Suspected: 11
Recalcati S <i>et al.</i> ⁵⁷ Italy	Case series	32	Mean age: 16.3 Range: (3–39) F: 15 (46.9%) M: 17 (53.1%)	N/A	11 (34.4%)/2 (18.2%)	22 (68.8%)/3 (13.6%)	Confirmed: 5 Suspected: 10
Baeck M <i>et al.</i> ¹⁴ Belgium	Case series	54	N/A F: N/A M: N/A	N/A	47 (87%)/1 (2.1%)	54 (100%)/2 (3.7%)	Confirmed: 3 Suspected: N/A
Daneshjou R <i>et al.</i> ⁵⁸ USA	Case series	7	Mean age: 33 Range: (25–44) F: 3 (42.9%) M: 4 (57.1%)	4 (57.1%)	5 (71.4%)/0 (0%)	6 (85.7%)/1 (16.7%)	Confirmed: 1 Suspected: 3
Stavert R <i>et al.</i> ⁵⁹ USA	Case series	24	Mean age: 32.1 Range: (11–64) F: 12 (50%) M: 12 (50%)	N/A	21 (87.5%)/1 (4.8%)	24 (100%)/4 (16.7%)	Confirmed: 5 Suspected: 12
Neri I <i>et al.</i> ⁶⁰ Italy	Case series	5	Mean age: 3 Range: (1–4) F: 4 (80%) M: 1 (20%)	N/A	5 (100%)/0 (0%)	5 (100%)/0 (0%)	Confirmed: 0 Suspected: 2
Denina M <i>et al.</i> ⁶¹ Italy	Case series	35	Mean age: 13 Range: (6–17) F: 24 (68.6%) M: 12 (34.3%)	9 (25.7%)	21 (60%)/1 (4.8%)	24 (68.6%)/4 (16.7%)	Confirmed: 4 Suspected: N/A
Ko CJ <i>et al.</i> ⁹ USA	Case series	5	Mean age: 62 Range: (31–82) F: 4 (80%) M: 1 (20%)	0 (0%)	0 (0%) / 0 (0%)	3 (60%)/0 (0%)	Confirmed: 0 Suspected: 0
Hébert V <i>et al.</i> ⁶² France	Case series	33	Mean ± standard deviation age: 23.4 ± 8.7 F: 14 (42.4%) M: 19 (57.6%)	0 (0%)	3 (9.1%)/0 (0%)	33 (100%)/1 (3%)	Confirmed: 1 Suspected: 10
Le Cleach L <i>et al.</i> ³⁷ France	Case series	311	Mean age: 25.7 Range: (18–39) F: 182 (58.5%) M: 129 (41.5%)	N/A	121 (38.9%)/7 (5.8%)	75 (24.1%)/5 (6.7%)	Confirmed: 10 Suspected: 163
Battesti G <i>et al.</i> ⁶³ France	Case series	7	Mean age: 42 F: 4 (57.1%) M: 3 (42.9%)	4 (57.1%)	7 (100%)/0 (0%)	7 (100%)/1 (14.3%)	Confirmed: 1 Suspected: 4
Caselli D <i>et al.</i> ⁴⁶ Italy	Case series	38	Median age: 13.5 Range: (7–18) F: 16 (42.1%) M: 22 (57.9%)	N/A	38 (100%)/0 (0%)	38 (100%)/0 (0%)	Confirmed: 0 Suspected: 8
Rizzoli L <i>et al.</i> ⁶⁴ Italy	Case series	12	Mean age: 13.5 Range: (9–19) F: 8 (66.7%) M: 4 (33.3%)	9 (75%)	12 (100%)/0 (0%)	12 (100%)/1 (8.3%)	Confirmed: 1 Suspected: N/A
Lesort C <i>et al.</i> ⁶⁵ France	Case series	45	Mean age: 30.1 F: 19 (42.2%) M: 26 (57.8%)	15 (33.3%)	17 (37.8%)/0 (0%)	17 (37.8%)/0 (0%)	Confirmed: 0 Suspected: 12
Rouanet J <i>et al.</i> ⁶⁶ France	Case series	10	Mean age: 34 Median age: 33 Range: (11–57) F: 5 (50%) M: 5 (50%)	0 (0%)	10 (100%)/0 (0%)	9 (90%)/0 (0%)	Confirmed: 0 Suspected: 5

Table 1 Continued

Authors Country	Study design	Sample (N)	Age (years) Sex: number of patients (%)	N contacts with probable or confirmed COVID-19 cases (%)	N PCRs performed (%) / N positive (%)	N serologies performed (%) / N positive (%)	COVID cases*
Colmenero I <i>et al.</i> ³³ Spain	Case series	7	Mean age: 14.3 F: 3 (42.9%) M: 4 (57.1%)	4 (57.1%)	6 (85.7%)/0 (0%)	0 (0%)/0 (0%)	Confirmed: 0 Suspected: 5
Colonna C <i>et al.</i> ³⁴ Italy	Case series	30	Mean age: 10.9 Range: (2–17) F: 13 (43.3%) M: 17 (56.7%)	13 (43.3%)	6 (20%)/0 (0%)	0 (0%)/0 (0%)	Confirmed: 0 Suspected: 13
Neri I <i>et al.</i> ⁸ Italy	Case series	8	Range: (11–15) F: 5 (62.5%) M: 3 (37.5%)	0 (0%)	8 (100%)/0 (0%)	8 (100%)/0 (0%)	Confirmed: 0 Suspected: 0
Kanitakis J <i>et al.</i> ⁶⁷ France	Case series	17	Mean age: 32 Range: (15–63) F: 6 (35.3%) M: 11 (64.7%)	6 (35.3%)	17 (100%)/0 (0%)	17 (100%)/0 (0%)	Confirmed: 0 Suspected: 5
Freeman EE <i>et al.</i> ⁶⁸ USA	Case series	318	Median age: 25 Range: (17–38) F: 155 (48.7%) M: 163 (51.3%)	86 (27%)	60 (18.9%)/14 (23.3%)	20 (6.3%)/6 (30%)	Confirmed: 23 Suspected: 229
El Hachem M <i>et al.</i> ³⁹ Italy	Case series	19	Mean age: 14 Range: (11–17) F: 5 (26.3%) M: 14 (73.7%)	9 (47.4%)	19 (100%)/0 (0%)	19 (100%)/10 (52.6%)	Confirmed: 10 Suspected: 3
Docampo-Simón A <i>et al.</i> ¹⁸ Spain	Case series	58	Median age: 14 Range: (3 months–85 years) F: 29 (50%) M: 29 (50%)	19/55 (34.5%)	39 (67.2%)/1 (2.6%)	0 (0%)/0 (0%)	Confirmed: 1/39 Suspected: N/A
Ruggiero G <i>et al.</i> ¹⁹ Italy	Case series	33	Mean age: 12.8 Range: (0–54) F: 11 (33.3%) M: 22 (66.7%)	N/A	0 (0%)/0 (0%)	0 (0%)/0 (0%)	Confirmed: 0 Suspected: 3
Cordoro KM <i>et al.</i> ⁶⁹ USA	Case series	6	Range: (12–17) F: 1 (16.7%) M: 5 (83.3%)	6 (100%)	6 (100%)/0 (0%)	6 (100%)/0 (0%)	Confirmed: 0 Suspected: 2
Andina D <i>et al.</i> ²⁶ Spain	Retrospective study	22	Median age: 12 Range: (6–17) F: 9 (40.9%) M: 13 (59.1%)	13 (59.1%)	19 (86.4%)/1 (5.3%)	0 (0%)/0 (0%)	Confirmed: 1 Suspected: 9
García-Lara G <i>et al.</i> ⁷⁰ Spain	Retrospective, cross-sectional study	27	Mean age: 14.4 F: 9 (33.3%) M: 18 (66.7%)	7 (25.9%)	2 (7.4%)/0 (0%)	9 (33.3%)/0 (0%)	Confirmed: 0 Suspected: 1
López-Robles J <i>et al.</i> ²⁷ Spain	Case series	41	Mean age: 16 Range: (1–74) F: 19 (46.3%) M: 22 (53.7%)	6 (14.6%)	19 (46.3%)/0 (0%)	0 (0%)/0 (0%)	Confirmed: 0 Suspected: 6
Fernandez-Nieto D <i>et al.</i> ²⁸ Spain	Retrospective study	132	Mean age: 19.9 Range: (1–56) F: 61 (46.2%) M: 71 (53.8%)	82 (62.1%)	11 (8.3%)/2 (18.2%)	0 (0%)/0 (0%)	Confirmed: 2 Suspected: N/A
Piccolo V <i>et al.</i> ⁷¹ Italy	Case series	63	Median age: 14 Range: (12–16) F: 34 (54%) M: 29 (46%)	10 (15.9%)	11 (17.5%)/2 (18.2%)	6 (9.5%)/2 (33.3%)	Confirmed: 2 Suspected: N/A
Landa N <i>et al.</i> ⁷² Spain	Case series	6	Mean age: 35.3 Range: (15–91) F: 3 (50%) M: 3 (50%)	2 (33.3%)	3 (50%)/2 (66.7%)	1 (16.7%)/0 (0%)	Confirmed: 2 Suspected: 3

Table 1 Continued

Authors Country	Study design	Sample (N)	Age (years) Sex: number of patients (%)	N contacts with probable or confirmed COVID-19 cases (%)	N PCR performed (%) / N positive (%)	N serologies performed (%) / N positive (%)	COVID cases*
Mahieu R. <i>et al.</i> ¹⁵ France	Case series	10	Median age: 27 F: N/A M: N/A	N/A	10 (100%)/0 (0%)	10 (100%)/0 (0%)	Confirmed: 0 Suspected: 2
Rubio-Muniz C.A. <i>et al.</i> ²⁹ Spain	Case series	10	Median age: 39 Range: (17–62) F: 5 (50%) M: 5 (50%)	N/A	10 (100%)/2 (20%)	0 (0%)/0 (0%)	Confirmed: 2 Suspected: 6
Ruggiero G. <i>et al.</i> ²⁰ Italy	Case series	100	Mean age: 12.9 Range: (3 months–17 years) F: 36 (36%) M: 64 (64%)	N/A	11 (11%)/1 (9.1%)	0 (0%)/0 (0%)	Confirmed: 1 Suspected: 15
Mastrolonardo M. <i>et al.</i> ²² Italy	Case series	38	Mean age: 10.6 F: 13 (34.2%) M: 25 (65.8%)	N/A	38 (100%)/0 (0%)	0 (0%)/0 (0%)	Confirmed: 0 Suspected: N/A
Romani J. <i>et al.</i> ⁷³ Spain	Case series	12	Mean age: 18.5 Range: (7–46) F: 6 (50%) M: 6 (50%)	N/A	12 (100%)/0 (0%)	5 (41.7%)/0 (0%)	Confirmed: 0 Suspected: 0
Galván Casas C. <i>et al.</i> ²³ Spain	Case series	71	Mean age: 32.5 F: 48 (67.6%) M: 23 (32.4%)	N/A	N/A	N/A	Confirmed: 29 Suspected: 42
Recalcati S. <i>et al.</i> ³⁰ Italy	Case series	14	11 children (mean age 14.4 years) and three young adults (mean age 29 years) Range: (13–39) F: 8 (57.1%) M: 6 (42.9%)	0 (0%)	5 (35.7%)/0 (0%)	0 (0%)/0 (0%)	Confirmed: 0 Suspected: 3
García-Legaz Martínez M <i>et al.</i> ¹⁶ Spain	Case series	19	N/A F: N/A M: N/A	N/A	19 (100%)/0 (0%)	19 (100%)/3 (15.8%)	Confirmed: 3 Suspected: N/A
Hubiche T <i>et al.</i> ⁷⁴ France	Case series	103	Mean age: 11.1 Median age: 13 Range: (8–15) F: 48 (46.6%) M: 55 (53.4%)	66 (64.1%)	18 (17.5%)/0 (0%)	14 (13.6%)/2 (14.3%)	Confirmed: 2 Suspected: 100
Roca-Ginés J <i>et al.</i> ⁴⁵ Spain	Case series	20	Mean age: 12.3 Range: (1–18) F: 7 (35%) M: 13 (65%)	0 (0%)	20 (100%)/0 (0%)	20 (100%)/0 (0%)	Confirmed: 0 Suspected: 0
Ortega-Quijano D <i>et al.</i> ²⁴ Spain	Unicentre-matched case-control	45	Mean age: 30.7 Range: (9–61) F: 17 (37.8%) M: 28 (62.2%)	N/A	0 (0%)/0 (0%)	45 (100%)/17 (37.8%)	Confirmed: 17 Suspected: N/A
Freeman EE <i>et al.</i> ⁷⁵ USA	Case series	18	Median age: 22 F: 5 (27.8%) M: 13 (72.2%)	3 (16.7%)	18 (100%)/3 (16.7%)	18 (100%)/2 (11.1%)	Confirmed: 4 Suspected: 9
Kluckow E <i>et al.</i> ¹⁰ Australia	Case series	5	Mean age: 15.8 Range: (13–22) F: 4 (80%) M: 1 (20%)	N/A	2 (40%)/0 (0%)	0 (0%)/0 (0%)	Confirmed: 0 Suspected: 1
Jacquín-Porretaz C <i>et al.</i> ⁷⁶ France	Case series	19	Mean age: 35 Range: (15–95) F: 10 (52.6%) M: 9 (47.4%)	N/A	8 (42.1%)/1 (12.5%)	12 (63.2%)/3 (25%)	Confirmed: 3 Suspected: N/A

Table 1 *Continued*

Authors Country	Study design	Sample (N)	Age (years) Sex: number of patients (%)	N contacts with probable or confirmed COVID-19 cases (%)	N PCRs performed (%)/N positive (%)	N serologies performed (%)/N positive (%)	COVID cases*
Alonso MN <i>et al.</i> ¹¹ Spain	Case series	5	Mean age: 44 F: 2 (40%) M: 3 (60%)	N/A	5 (100%)/3 (60%)	1 (20%)/0 (0%)	Confirmed: 3 Suspected: 2
Saenz Aguirre A <i>et al.</i> ²¹ Spain	Case series	74	Mean age: 19.7 Median age: 14.5 Range: (3–100) F: 32 (43.2%) M: 42 (56.8%)	18 (24.3%)	11 (14.9%)/1 (9.1%)	6 (8.1%)/0 (0%)	Confirmed: 1 Suspected: 20
Vázquez-Osorio I <i>et al.</i> ⁷⁷ Spain	Case series	14	Mean age: 13.3 Range: (7–20) F: 7 (50%) M: 7 (50%)	2 (14.3%)	14 (100%)/0 (0%)	14 (100%)/2 (14.3%)	Confirmed: 2 Suspected: 3
Recalcati S <i>et al.</i> ²⁵ Italy	Case series	7	Mean age: 15.3 F: 3 (42.9%) M: 4 (57.1%)	N/A	0 (0%)/0 (0%)	7 (100%)/0 (0%)	Confirmed: 0 Suspected: N/A
Oliva Rodríguez-Pastor S <i>et al.</i> ⁷⁸ Spain	Case series	34	Mean age: 11.4 F: 14 (41.2%) M: 20 (58.8%)	4 (11.8%)	17 (50%)/0 (0%)	34 (100%)/4 (11.8%)	Confirmed: 4 Suspected: N/A

Confirmed cases = patients with positive PCR and/or serology; Suspected cases = patients with clinical signs and symptoms compatible with COVID-19 according to ECDC criteria but with negative PCR/serology or no diagnostic test; N/A, not available.

Table 2 Pooled prevalence of COVID-19 in patients with chilblains-like lesions: summary of main findings

Pooled prevalence measures for COVID-19	Pooled proportion (random effects; 95% CI)	I ² (95% CI)	Egger bias (95% CI)
Total sample of patients with chilblains-like lesions			
Positive PCR	2.59% (1.86–3.43%)	22.2% (0–43.9%)	0.16 (–0.21 to 0.53) <i>P</i> = 0.392
Positive serology	7.22% (4.74–10.17%)	79.9% (73.9–84%)	1.03 (–0.45 to 1.61) <i>P</i> = 0.0008
Positive PCR and/or serology	15.20% (10.40–20.72%)	87.4% (83.7–89.9%)	2.43 (1.59 to 3.27) <i>P</i> < 0.0001
Subgroup of patients with chilblains-like lesions who underwent diagnostic tests for COVID-19			
Positive PCR	5.53 (3.7–7.7%)	46.8% (24–60.5%)	0.66 (–0.14 to 1.19) <i>P</i> = 0.01
Positive serology	11.77% (7.89–16.31%)	72.7% (63.1–78.9%)	1.41 (0.66 to 2.17) <i>P</i> = 0.0004
Positive PCR and/or serology	7.48% (5.08–10.31%)	75% (67.6–80%)	1.37 (0.81 to 1.92) <i>P</i> < 0.0001

CI, confidence interval.

theory opens the door to studying a possible role for neutralizing IgA antibodies in the resolution of the infection, especially in patients with mild symptoms.¹³ A few publications have reported IgA-positive serologies against SARS-CoV-2 in patients with CLL.^{39,40} However, these results must be interpreted with caution because the high sensitivity of these antibodies could cause some false positives.⁴¹

Other authors have considered CLL to be the cutaneous expression of a strong innate immune type 1 interferon (IFN-1) response. This would contribute to the clearance of the virus

prior to production of immunoglobulins, leading to failed serological detection.^{41–43} The up-regulation of the IFN-1 pathway would cause severe microangiopathy and trigger the generation of CLL in patients with a genetic predisposition.^{35,44} However, the absence of cutaneous or extra-cutaneous symptoms in other interferonopathies raises unanswered questions around this hypothesis.⁴¹

Specific T cells have been detected in serologically negative individuals with a history of asymptomatic or mildly symptomatic COVID-19, leading some authors to suggest that skin

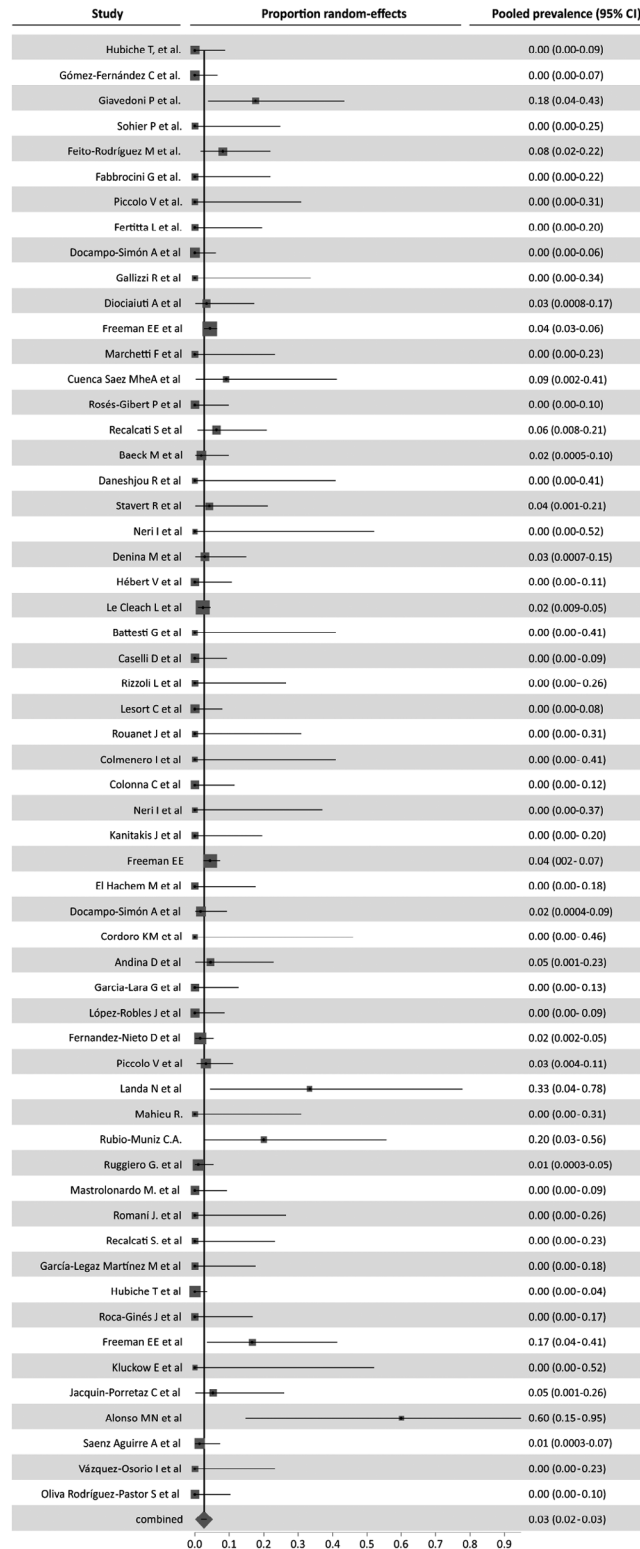


Figure 2 Pooled prevalence of positive PCRs for COVID-19 in patients with chilblains-like lesions, December 2019 to March 2021.

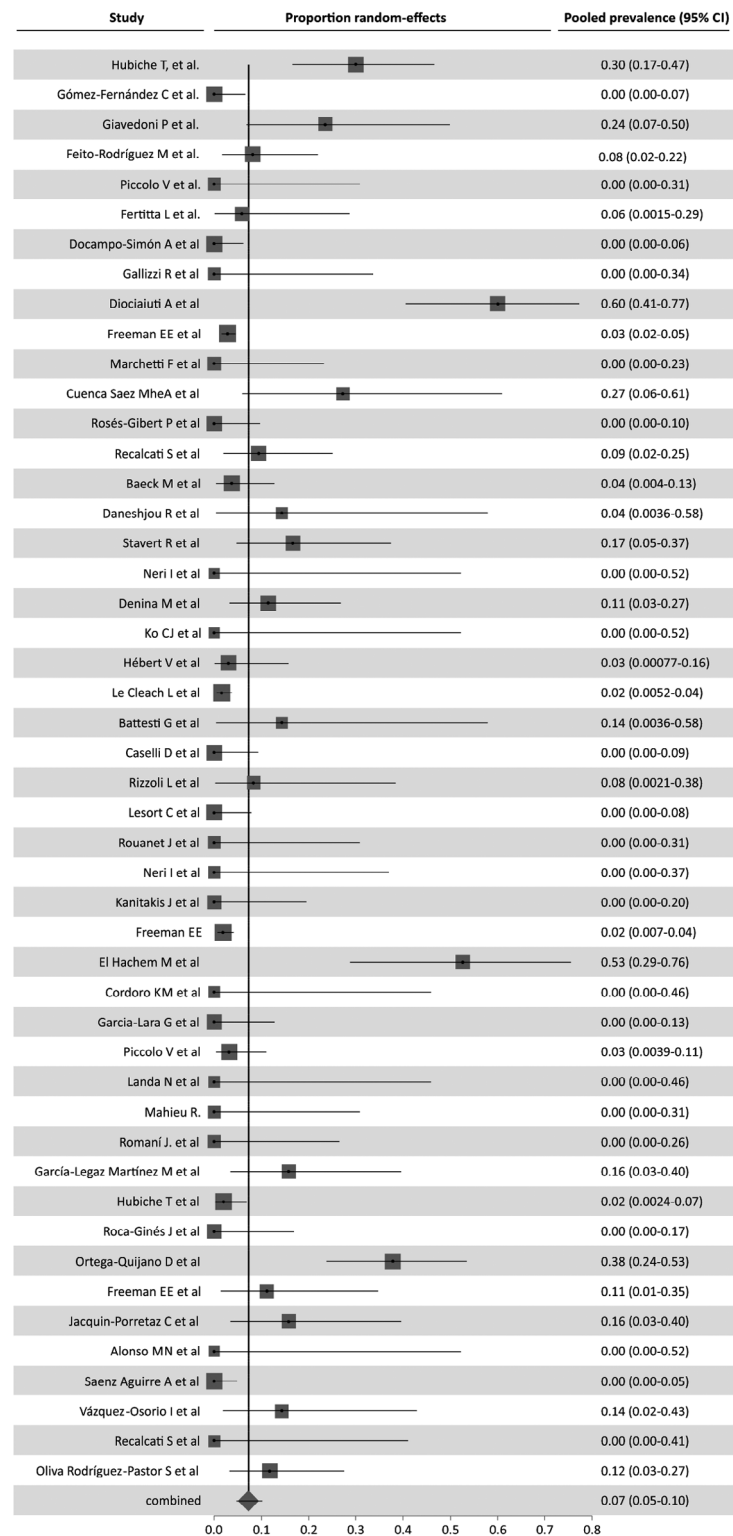


Figure 3 Pooled prevalence of positive serological results for SARS-CoV-2 antibodies in patients with chilblains-like lesions, December 2019 to March 2021

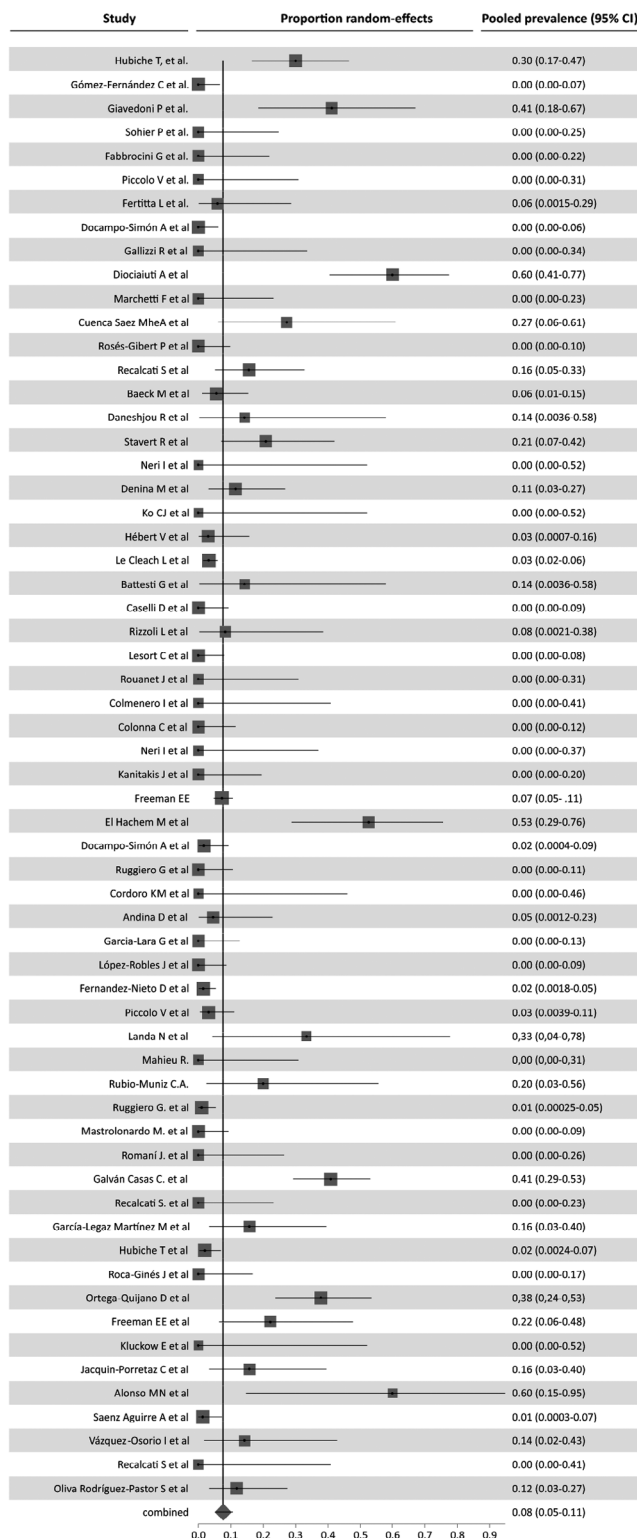


Figure 4 Pooled prevalence of positive SARS-CoV-2 diagnostic test in patients with chilblains-like lesions, December 2019 to March 2021.

manifestations could induce a weak response at a serological level but a robust one at the cellular level.²⁴ Unfortunately, there are no tests that measure the activation of T cells available in clinical practice.

Another possibility is that PCRs and serologies are negative when the viral inoculum is small. The patients would not develop symptoms, and the serological response would be of such low intensity as to be undetectable with the currently available tests. Some studies have reported that serological responses tend to be lower in young people; in such cases, the only manifestations of COVID-19 would be endothelitis and a propensity for thrombosis in the small distal veins of the extremities.⁴⁵ This theory is supported by the tendency for CLL to appear in young patients with few to no symptoms and who do not require hospitalization.³⁶ Our results provide further corroboration for this hypothesis, with our meta-analysis showing that the mean age of patients with CLL and COVID-19 is 20.9 years.

Another potential explanation that has been proposed is a more indirect relationship, provoked by behavioural changes brought on by lockdowns and quarantines, specifically, sedentary behaviours and the exposure of bare feet to cold interior environments. Children and adolescents were among the most affected populations by these restrictions, as they could not go to school and spent considerable time sitting in front of a television or computer. The lack of mobility could have reduced circulation and the subsequent appearance of chilblains.⁴² Improvements in CLL cases following thermal protection measures and the relaxation of confinement restrictions support this hypothesis.^{39,41,46} However, these lesions are not among the skin signs observed in paraplegic or wheelchair-bound patients.⁴²

Our meta-analysis has some limitations, the most important of which is the high between-study heterogeneity, evidenced by the I^2 values in the analyses. The patients were not all subjected to the same type of diagnostic tests for COVID-19, and most sample sizes were small. Generally, the funnel plots for each meta-analysis indicate reporting bias, backed up by significant results on Egger's test, suggesting that there have been small studies with negative results that have not been published. There may also be cases that have been reported in more than one series.⁴⁷ Furthermore, most studies did not systematically perform diagnostic tests for COVID-19 in all patients, but rather only collected tests that had already been undertaken. Thus, there is a risk of overestimation bias regarding the prevalence of COVID-19 in the total number of individuals tested, as in practice, PCRs or serologies are more likely to be performed in people with systemic symptoms that are compatible with COVID-19 or in those who are contacts of infected patients than in people without these characteristics.

By contrast, the main issue of the studies carried out is the low rate of patients fully investigated for COVID-19 status, due to the low rate of symptoms and the absence of the need for hospitalization in the most COVID-19

patients with CLL, as we have previously commented. So, we cannot be sure that, although this article shows a negative relationship between CLL and COVID-19, it can be excluded.

In sum, our meta-analysis does not definitively confirm the relationship between CLL and COVID-19. There is a need for further studies of high methodological quality that perform serological tests for COVID-19 that are sufficiently sensitive and specific as well as correctly timed in order to detect a possible seroconversion.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Funnel plot of studies on prevalence of positive PCRs for COVID-19 in patients with chilblains-like lesions, December 2019 to March 2021.

Figure S2. Funnel plot of studies on prevalence of positive serological results for SARS-CoV-2 antibodies in patients with chilblains-like lesions, December 2019 to March 2021.

Figure S3. Funnel plot of studies on prevalence of positive SARS-CoV-2 diagnostic test in patients with chilblains-like lesions, December 2019 to March 2021.

Table S1. Quality Assessment of Included Studies: Quality Assessment Tool for Case Series Studies of National Heart, Lung and Blood Institute (NHLBI).