

## Review

**Skin manifestations in COVID-19 patients, state of the art. A systematic review**

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**Introduction**

SARS-CoV-2 became a pandemic in March 2020.<sup>1</sup> Many efforts were conducted by the researcher to clarify and classify the clinical manifestation of COVID-19 disease.<sup>2,3</sup> The commonest symptoms of COVID-19 are fever, cough, anosmia, and lymphocytopenia.<sup>3,4</sup> However, other less common clinical symptoms have been described.<sup>3</sup> Recently, clinicians have focused their attention on other signs of COVID-19. Skin manifestations are not uncommon in viral infections (viral exanthemas).<sup>5-7</sup>

**Abstract**

**Introduction** Since COVID-19 has become a pandemic, extensive literature has been produced. The commonest symptoms of COVID-19 disease are fever, cough, anosmia, and lymphocytopenia. However, other apparently less common clinical symptoms have been described, including skin lesions. We conducted a systematic review to evaluate skin involvement in COVID-19.

**Methods** The authors performed a systematic review of literature, in accordance with the Preferred Reporting Items for Systematic and Meta-Analysis (PRISMA). The search was reiterated until May 06, 2020.

**Results** Overall, 1593 patients (M/F ratio: 1 : 9) with suspect of COVID-19 were examined. The mean age was 37.8 (range 0–91) years. Among the analyzed patients, 84 (5.3%) were pediatrics (<18 years). Chilblains are very common among skin lesions and represent almost half of all skin lesions reported (46%); in 75% of patients with cutaneous manifestation, the latter presented before other typical clinical manifestation of COVID-19. Vasculitis or thrombosis was identified in almost 70% of patients who suffered from skin manifestations.

**Conclusion** The present study highlights the importance of skin involvement in COVID-19. Limbs should be examined to eventually foresee the onset of further typical symptoms. Chilblains can be considered typical features. Studies with higher scientific evidence are required.

Hence, variable clinical skin manifestations were described in COVID-19.<sup>5-47</sup> Different kinds of rash, chilblains, livedo reticularis, urticaria, purpura, and vasculitis were observed in COVID-19-positive patients.<sup>5-47</sup>

The role of skin manifestations, where present, in the clinical history of COVID-19 is still unclear.<sup>5,6,8,13,20,25,32,33,36,41,46</sup>

The aim of the present study was to review the available literature data on skin manifestations related to COVID-19 and evaluate their epidemiology, possible clinical correlation, and prognostic factors.

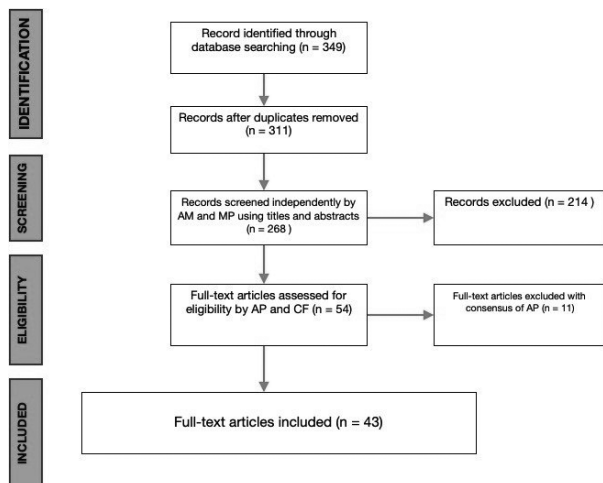


Figure 1 Study flow chart

## Material and methods

### Study setting and design

The present study is a systematic literature review reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1).<sup>48</sup>

### Review questions

The review questions were formulated following the PICO scheme (population, intervention, comparison, and outcome) as follows:

- Did patients suffering from COVID-19 (P) report worse clinical outcomes (C) in terms of comorbidity and mortality (O) when cutaneous manifestation occurred (I)?
- Were the clinical outcomes (O) influenced by the type of lesions' pattern (I)?
- Was the type of pattern (I) influenced by comorbidities (P)?

### Inclusion and exclusion criteria

In the present investigation, full-text articles were analyzed evaluating the correlation between the COVID-19 and the presence of skin lesions. Only articles written in English were included. No publication date limits were set. Exclusion criteria were: studies on animals, unpublished reports, cadaver or *in vitro* investigations, review of the literature, abstracts from scientific meetings, and book chapters.

### Search strategy and study selection

MEDLINE via PubMed and Scopus were searched using the keywords: "SARS-CoV-2", "Covid 19", "Skin", "cutaneous", "dermatological", "rash", "dermatology", and their MeSH terms in any possible combination. The reference lists of relevant studies were forward searched to identify other studies of interest. The search was reiterated until May 06, 2020.

## Data extraction and analysis

Two independent reviewers (M.P. and A.M.) pulled out the data from the studies included. Any discordances were solved by consensus with a third author (A.P.). For each study, the following data were collected: demographic features, COVID-19 diagnosis, respiratory symptoms, type of skin lesions, treatment options, possible complications and outcomes, and follow-up. Numbers software (Apple Inc., Cupertino, CA, USA) was used to tabulate the collected data. Categorical variables are presented as frequency and percentages. Continuous variables are presented as means and standard deviation. Only one decimal digit was reported and was rounded up.

## Results (literature review)

### Study selection

After the screening of 298 articles by title and abstract, 57 studies were considered eligible for the full-text analysis. After exclusion of 14 studies, 43 studies that met inclusion criteria were included in the present review<sup>5-47</sup> (Fig. 1). Among the included studies, one had a level of evidence I, while 42 had a level of evidence IV.<sup>49</sup> Eleven of the included studies were conducted in Spain, 10 in Italy, eight in France, four in USA, three in China, two in Belgium, two in Iran, one in Germany, one in Kuwait, and one in Thailand.

### Patient characteristics

Overall, 1593 patients (M/F ratio: 1:9) with suspect of COVID-19 were examined. The mean age was 37.8 (range 0-91) years. Among analyzed patients, 84 (5.3%) were pediatrics (<18 years). Only 746 patients (46.8%) had a confirmed diagnosis of COVID-19. In 24 patients, comorbidities such as diabetes, hypertension, and obesity were described, while in two patients, previous skin disease was reported. In 1027 patients (64.4%), systemic symptoms were observed. Among these, 341 (30.7%) presented fever, seven (0.6%) systemic vasculitis or thrombosis, and 679 (68.7%) respiratory symptoms. We summarized demographic characteristics of the included studies in Table 1.

### Skin lesions

Among all patients examined, skin lesions were reported in only 957 (60.1%) cases. In 13 (1.3%) patients, a nonspecific rash was observed. In 120 (12.5%) patients, the presence of vesicular lesions was reported. In 86 (9%) patients, erythematous skin lesions and urticaria were documented. Livedo reticularis was observed in 35 (3.6%) cases. Maculopapular skin lesions were described in 218 (22.8%) patients. The prevalent skin lesion pattern reported was chilblain lesions, observed in 460 patients (48%). Concerning location of skin lesions, 456 (47.6%) patients presented hand (149) or feet (307) lesions, 370 (38.7%) patients had chest or back lesions, 314 (32.8%) patients had limb (lower and upper) lesions, and 20 (2.1%) patients had facial or neck lesions. Hand and feet lesions were prevalently

**Table 1** Literature review

Study	Country	Level of evidence	Number of patients analyzed	Number of patients with skin lesion	Skin lesions (the number of cases are reported in brackets)
Galván Casas 2020 <sup>33</sup>	Spain	I	429	375	Maculopapular (176), Urticaria (73), Chilblain (71), Vesicular (34), Livedo (21)
Morey-Olivé 2020 <sup>18</sup>	Spain	IV	2	2	Maculopapular (1), Urticaria (1)
Fernandez-Nieto 2020 <sup>34</sup>	Spain	IV	1	1	Urticaria (1)
Bouaziz 2020 <sup>41</sup>	France	IV	54	44	Chilblain (36), Erythematous (4), Vesicular (2), Livedo (2), Vasculitis (2), Urticaria (1)
Tammaro 2020 <sup>11</sup>	Italy/Spain	IV	130	3	Vesicular (2)
Avellana Moreno 2020 <sup>42</sup>	Spain	IV	1	1	Maculopapular (1)
Amatore 2020 <sup>43</sup>	France	IV	1	1	Maculopapular (1)
Piccolo 2020 <sup>16</sup>	Italy	IV	63	63	Chilblain (63), Vesicular (21)
Recalcati 2020 <sup>13</sup>	Italy	IV	14	14	Erythematous (14), Maculopapular (14)
Van Damme 2020 <sup>9</sup>	Belgium	IV	2	2	Urticaria (2)
Landa 2020 <sup>24</sup>	Spain	IV	6	6	Nonspecific Rash (5), Maculopapular (1)
Duong 2020 <sup>38</sup>	France	IV	295	219	Chilblain (219)
Genovese 2020 <sup>32</sup>	Italy	IV	1	1	Vesicular (1)
Gianotti 2020 <sup>31</sup>	Italy	IV	3	3	Erythematous (2), Maculopapular (3)
Najarian 2020 <sup>5</sup>	USA	IV	1	1	Erythematous (1)
Hedou 2020 <sup>30</sup>	France	IV	104	2	Nonspecific Rash (2), Urticaria (2)
Marzano 2020 <sup>19</sup>	Italy	IV	22	22	Vesicular (12), Maculopapular (10)
Alramthan 2020 <sup>44</sup>	Kuwait	IV	2	2	Erythematous (1), Maculopapular (1)
Magro 2020 <sup>7</sup>	USA	IV	5	5	Purpura (5)
Ackerman 2020 <sup>29</sup>	France	IV	1	1	Urticaria (1)
Estebanez 2020 <sup>36</sup>	France	IV	1	1	Maculopapular (1)
Fernandez-Nieto 2020 <sup>35</sup>	Spain	IV	132	132	Chilblain (95), Vesicular (37)
Mahé 2020 <sup>21</sup>	France	IV	1	1	Erythematous (1)
Jimenez-Cahue 2020 <sup>46</sup>	Spain	IV	1	1	Erythematous (1)
Manalo 2020 <sup>20</sup>	USA	IV	2	2	Livedo (2)
Hunt 2020 <sup>28</sup>	USA	IV	1	1	Maculopapular (1)
Kamali Aghdam 2020 <sup>26</sup>	Iran	IV	3	3	Nonspecific Rash (3)
Recalcati 2020 <sup>14</sup>	Italy	IV	88	18	Erythematous (14), Urticaria (3), Vesicular (1)
Zhang 2020 <sup>8</sup>	China	IV	7	7	Vesicular (7), Livedo (7)
Joob 2020 <sup>27</sup>	Thailand	IV	48	1	Urticaria (1)
Lu 2020 <sup>22</sup>	China	IV	1	1	Dengue (1)
Lopez-Robles 2020 <sup>23</sup>	Spain	IV	41	41	Chilblain (41)
Kolivras 2020 <sup>25</sup>	Belgium	IV	1	1	Chilblain (1)
Ehsani 2020 <sup>37</sup>	Iran	IV	1	1	Maculopapular (1)
Tosti 2020 <sup>10</sup>	Italy	IV	4	4	Erythematous (4)
Paolino 2020 <sup>17</sup>	Italy	IV	1	1	Erythematous (1)
Zengarini 2020 <sup>6</sup>	Italy	IV	1	1	Erythematous (1)
Ahouach 2020 <sup>45</sup>	France	IV	1	1	Erythematous (1)
Diaz-Guimaraens 2020 <sup>39</sup>	Spain	IV	1	1	Erythematous (1)
Sanchez 2020 <sup>12</sup>	France	IV	1	1	Maculopapular (1)
Quintana-Castanedo 2020 <sup>15</sup>	Spain	IV	1	1	Urticaria (1)
Hoehl 2020 <sup>47</sup>	Germany	IV	114	1	Nonspecific Rash (2)
Chen 2020 <sup>40</sup>	China	IV	4	2	Nonspecific Rash (1)

chilblain lesions (98%). Two hundred and sixty-one patients (27.3%) had itchy skin lesions, while 76 (7.9%) patients had painful skin lesions. In 846 (88.4%) patients, presentation time of lesions was reported. Among these patients, skin lesions appeared before other clinical manifestation of COVID-19 in 613 (72.5%) patients, while in 233 (27.5%) patients, skin manifestation started together with the typical symptoms. Only a few authors (11 studies of 44 included) reported the histological

pattern of the observed lesion. We summarized the histological findings in Table 2.

### Treatment and outcomes

In 10 studies, the skin lesions were treated with pharmacological therapies. In seven patients, systemic antihistamines were administered until cutaneous manifestations disappeared, while in three cases topical steroids were prescribed. In the other

**Table 2** Skin biopsy and histologic patterns

Study	Histological presentation of skin lesions
Amatore 2020 <sup>43</sup>	Perivascular infiltrate of lymphocytes. Mild lymphocyte exocytosis, lichenoid and vacuolar interface dermatitis with occasional dyskeratotic keratinocytes in the basal layer.
Recalcati 2020 <sup>13</sup> Gianotti 2020 <sup>31</sup>	Lymphoid infiltrate, perivascular pattern, and signs of endothelial activation. <ul style="list-style-type: none"> <li>• Superficial perivascular dermatitis, lymphocytic exocytosis. Swollen thrombosed vessels with neutrophils, eosinophils, and nuclear debris in the dermis.</li> <li>• Superficial and deep perivascular dermatitis, lymphocytes surrounding blood vessels in a vasculitic pattern. Extravasated red blood cells from damaged vessels.</li> <li>• Acantholytic suprabasal clefts, dyskeratotic and ballooning herpes-like keratinocytes. Lymphocytic satellitosis, dense lymphocyte infiltration, eosinophils, Langerhans cells.</li> </ul>
Zengarini 2020 <sup>6</sup> Marzano 2020 <sup>19</sup> Sanchez 2020 <sup>12</sup> Magro 2020 <sup>7</sup>	Perivascular lymphocytic infiltrate, extremely dilated vessel in dermis. Atrophic epidermis and vacuolar degeneration of the basal layer. Dyskeratotic cells. Vacuolar alteration. Spongiosis with focal parakeratosis in the epidermis. Aggregates of lymphocytes and Langerhans cells. <ul style="list-style-type: none"> <li>• Significant vascular deposits of C5b-9 within dermal capillaries.</li> <li>• Thrombogenic vasculopathy, extensive necrosis of the epidermis and adnexal structures, perivascular neutrophilia, deposition of C5b-9.</li> <li>• Vascular ectasia, vascular deposits of C5b-9, C3d, and C4d, occluded artery.</li> <li>• Perivascular lymphocytic, deeper seated small thrombi, significant vascular deposits of C5b-9 and C4d.</li> </ul>
Fernandez-Nieto 2020 <sup>34</sup> Kolivras 2020 <sup>25</sup>	Perivascular infiltrate of lymphocytes, some eosinophils and upper dermal edema Lichenoid, perivascular, and perieccrine infiltrate of lymphocytes. The basement membrane zone was smudged, and there was papillary dermal fibrin confined near the ulcer edge. The infiltrate was dense and lichenoid in the papillary and superficial reticular dermis. The venules surrounded by the lymphoplasmacytic infiltrate had plump endothelial cells. No intraluminal fibrin thrombi.
Ahouach 2020 <sup>45</sup> Diaz-Guimaraens 2020 <sup>39</sup>	Light spongiosis, basal cell vacuolation, and mild perivascular lymphocytic infiltrate. Perivascular lymphocytic infiltrate with abundant red cell extravasation, focal papillary edema, focal parakeratosis, and isolated dyskeratotic cells. No intraluminal fibrin thrombi.

studies, no specific treatments were performed, and skin lesions healed spontaneously. Only in 442 cases, the fate of skin lesions was reported. In 422 patients, there was a complete recovery without sequelae; in eight, a partial recovery was observed, while 12 patients died before the skin lesions healed. The mean duration of cutaneous symptoms was  $7.5 \pm 3.6$  days.

### Review questions

This review showed that the clinical outcome of COVID-19 would not seem to be influenced by the presence of the skin lesions. However, Zang *et al.*<sup>8</sup> and Hunt *et al.*<sup>28</sup> observed skin lesions in critical patients with poor overall outcomes; therefore, these represented insignificant data. Regarding lesion patterns and the general health condition of patients, Maehè *et al.*,<sup>21</sup> Manalo *et al.*,<sup>20</sup> and Jimenez-Cahue *et al.*<sup>46</sup> argued that it could be a correlation between patients' comorbidities and type of skin lesions, caused by a mechanism of immunity downregulation.

### Discussion

The large amount of papers published on skin manifestations during COVID-19 underlines the growing interest of this topic in the literature.<sup>50</sup> Lesions on the limbs seem to be more frequent than trunk and face lesions. Chilblains are very common among skin lesions and represent almost half of all skin lesions

reported (46%). In 75% of patients with cutaneous manifestations, the skin lesions appeared before the other typical clinical manifestations of COVID-19. Hence, the main point is to not neglect skin medical history. The attention of the dermatologists on cutaneous manifestations of COVID-19 allows for a better characterization of the descriptions of lesions, the timing of onset, their duration, and localizations. However, the characteristics of the skin lesions during COVID-19 should be of interest to all physicians, especially those who take care of the limbs, such as orthopedists, physiatrists, and rheumatologists.

Vasculitis or thrombosis was suspected in almost 70% of patients who suffered from skin manifestations.<sup>7,31,34,39,51-54</sup> This suggests that a correlation between cutaneous manifestations and systemic vascular damage is possible in COVID-19. Magro *et al.* described five cases of microvascular injury and thrombosis in severe COVID-19, underlying the pathophysiological importance of complement cascade in COVID-19.<sup>7</sup> Perivascular infiltrate and microthrombosis were described in skin biopsies (Table 2).<sup>31,34,39</sup> These findings could play a determining role in the pathogenesis of COVID-19, shifting the attention from an organ disease to a systemic one; therefore, this topic should be further investigated.

COVID-19 seems to be less serious during childhood, even though recent cases of Kawasaki disease in children were increasingly reported, and SARS-CoV-2 was suspected to be responsible for this increase.<sup>51-54</sup> Being a systemic vasculitis,

Kawasaki disease may cause skin lesions and should be considered in further literature.<sup>51,53,54</sup> Additional investigations about skin vasculitis in SARS-CoV-2 are needed.<sup>51,53,54</sup>

Nevertheless, according to our results, low-quality evidence studies were produced in case reports and case series (level IV) with insufficient and/or unclear data. Therefore, it was not possible to answer the above-mentioned review questions. Higher-level evidence, such as prospective and multicentric studies, should be achieved.

The trend in recent literature regarding COVID-19 is to focus on the particular symptoms, often neglecting features of a more general nature.

However, the present article represents an evidence-based overview about cutaneous manifestations in COVID-19 and their epidemiological features, even though many biases can be identified. We hope that the following consideration can be useful for further publications.

It emerged from our research that M:F ratio was 1:9, although some studies did not report the sex of patients, and many of the examined studies did not report disaggregated data for sex. This represents a limitation in our study, and unfortunately it is in accordance with literature trends.<sup>55</sup> The same is true about general comorbidities; in fact, only a few studies clearly reported data about this issue. Comorbidity-reported data were frequently incomplete. Clinical images were reported only in a few articles, and only limited data regarding skin biopsy were presented.

We underline the need for more clear and factual data. In fact, the American Academy of Dermatology is also trying to collect data by registering online cases to the website: <https://www.aad.org/member/practice/coronavirus/registry>.<sup>50</sup>

To date, it is not possible to determine the true prevalence of skin lesions in COVID-19. Skin lesions were neglected for weeks after the COVID-19 outbreak.<sup>2-4,56,57</sup> Furthermore, not all patients who reported skin manifestations had a confirmed diagnosis of SARS-CoV-2. We want to underline that the authors excluded some articles according to the lack of a clear association between COVID-19 and skin involvement, and/or the presence of clear and irresolvable confounding factors (e.g., drug administration). According to Freeman et al., the bias in searching for the real prevalence of skin manifestations in COVID-19 remains even if all clinical findings are registered; however, this did not preclude the use of these helpful data.<sup>50</sup>

Because of the novelty of this disease, another problem that confronted the authors was the nonuniformity of data.<sup>58</sup> Hence, we have only included studies where a clear diagnosis of the skin lesions was possible.

## Conclusion

Although certain biases were found, this review highlights the importance of skin involvement in COVID-19. Limbs should be carefully examined to eventually foresee the onset of further

typical symptoms. Chilblains could be considered typical features of COVID-19. Studies with higher scientific evidence are required to validate our findings. Disaggregated data are welcome in order to improve knowledge.

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