Cutaneous manifestations of COVID-19: a systematic review and analysis of individual patient-level data

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Abstract

Distinctive patterns in the cutaneous manifestations of COVID-19 have been recently reported. We conducted a systematic review to identify case reports and case series characterizing cutaneous manifestations of confirmed COVID-19. Key demographic and clinical data from each case were extracted and analyzed. The primary outcome measure was risk factor analysis of skin related outcomes for severe COVID-19 disease. Seventy-one case reports and series comprising 144 cases of cutaneous involvement in COVID-19 were included. The most frequently occurring morphologies were: morbilliform (30.6%), varicelliform (18.8%), urticarial (13.2%), chilblains-like (12.5%), and acro-ischemic (9%). The median age of patients was 51 years (mean: 45.9, range: 0 to 91). Patients with chilblains-like eruptions had lower frequencies of extracutaneous COVID-19 symptoms (5/18, 27.8%, P<0.05) and were less likely to have severe COVID-19 disease (2/18, 11%, 95% CI 1.4% to 34.7%, P=0.02). Patients with livedoid and acro-ischemic morphologies had severe COVID-19 more frequently than those with other morphologies (17/21, 81%, 95% CI 58.0% to 94.5%, P<0.0001). The most frequently observed cutaneous manifestations of COVID-19 (morbilliform, varicella-form, and urticarial) are well-described patterns of viral exanthems. However, chilblains-like, livedoid, and acro-ischemic morphologies are not traditionally associated with viral infections and were significantly associated with severity of COVID-19 disease.

Keywords: cutaneous manifestation, SARS-CoV-2

Introduction

In December 2019, reports from Wuhan, China described new clusters of patients with severe pneumonia linked to a novel coronavirus strain, now referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), [1]. Coronavirus disease 2019 (COVID-19) has since reached pandemic proportions, with over 12·7 million cases worldwide, 566,000 deaths, and 188 countries affected at the time of this article's submission [2]. Primarily a respiratory disease, COVID-19 is now known to have a wide spectrum of clinical phenotypes, ranging from asymptomatic carriage to multi-system organ failure.

The first report of cutaneous involvement in COVID-19 was in February 2020, when Guan et al. listed rash as a sign of infection in two of 1099 patients with laboratory-confirmed COVID-19 in China [3]. Multiple subsequent case reports and series have described COVID-19 with cutaneous involvement. It is now understood that coagulopathy and thrombotic events can be observed in more severe cases of COVID-19 infection [4,5]. This trend has also been recently reflected in a large-scale registry-based case series in which livedo racemosa, retiform purpura, and acral ischemia were exclusively observed in critically ill patients [6]. We conducted a systematic review of the literature to characterize the cutaneous manifestations of COVID-19 and analysis of individual patient-level data to identify potential associations between skin presentation and severity of COVID-19 infection.

Methods

Eligibility criteria

All case reports and case series that provided patient-level data and characterized cutaneous manifestations of COVID-19 were included in this systematic review. The search was conducted from October 1, 2019 to May 21, 2020. There were no language, publication status, or publication year limits. Papers published in Chinese and Spanish were initially translated with the Google Translate tool, then proofread by a Chinese- or Spanish-speaking medical professional.

Information sources

PubMed, Embase, Cochrane databases, and Google Scholar were searched. The following trial registries were also searched: Cochrane Central Register of Controlled Trials, the World Health Organization International Clinical Trials Registry Platform. Elsevier and Wiley websites were also searched separately. Moreover, medRxiv and Research Square as pre-print databases were searched and only one eligible study was identified.

Search strategy

The search strategy (**Appendix 1**) was developed by author FG. Detailed search strategy for all databases is provided in **Appendix 1**. We performed the entire search on May 21, 2020.

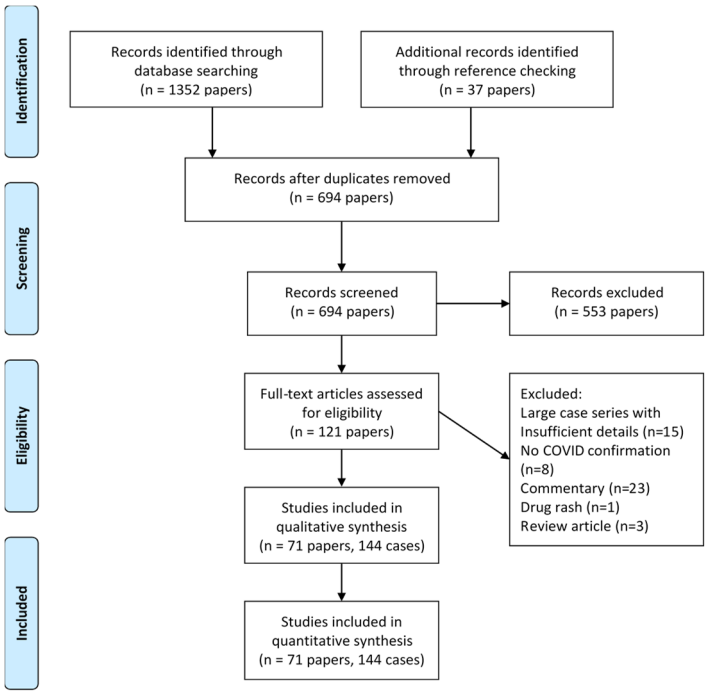

Figure 1. *Flow diagram of the study.*

Study selection

The search results were screened independently by two investigators. Duplicate publications were removed by FG. Two investigators (PM & FG) independently screened all the results of searches and selected the potentially eligible studies based on title and abstract.

Data collection process

All full texts were retrieved. DL & FG independently appraised and extracted data from the selected studies. Any differences between the data sets were discussed and a consensus reached. If case details were insufficient, corresponding authors were solicited for further details when their contact information was available. **Figure 1** demonstrates the flow diagram of the study.

Study aims

Our primary outcome measure was risk factor analysis of skin related outcomes for severe COVID-19 disease. A patient was defined as COVID-19 positive if having a positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2, IgG or IgM anti-SARS-CoV-2 serology testing by enzyme-linked immunosorbent assay (ELISA), or radiological features characteristic for COVID-19 on computed tomography or chest X-ray. Severe COVID-19 disease was defined as infection that required intensive care unit (ICU) care or mechanical ventilation or infection that resulted in death.

Secondary outcomes included the frequency of different morphologies of cutaneous eruptions in COVID-19 patients. Other secondary outcomes included timing of cutaneous manifestations relative to other COVID-19 symptoms and presence of drug administration prior to rash onset.

Cutaneous morphology characterization

When clinical images of cutaneous manifestations were available, the images were independently evaluated by three board-certified dermatologists and assigned one or more primary cutaneous morphologies and/or secondary descriptors (**Table 1**). Of note, cases of retiform purpura were classified as livedoid morphology owing to their overlapping pathophysiology. Targetoid morphology included

typical and atypical targetoid lesions similar to those seen in erythema multiforme. Assigned morphologies and descriptors were included in the final assessment if consensus on a given variable was reached by two or more dermatologists. When clinical images were unavailable, the morphology and/or descriptor were assigned based on the author's written description.

Country of affiliation, demography (age, gender), anatomical site of skin involvement, non-cutaneous COVID-19 symptoms (**Figure 2**), duration of skin eruption, latency between other COVID-19 symptoms and rash onset, and medication exposures relative to rash onset were extracted from the studies.

Statistical methods

Details of statistical methods are described in **Appendix 1**.

We performed analyses using Python (Python software foundation, version 3·7) and SPSS (IBM Corp., Armonk, N.Y., USA), version 26. The proportion of patients with severe COVID-19 disease as the main outcome measure was reported with binomial 95% confidence intervals (CIs). Kolmogorov-Smirnov analysis was used to test the normality of the quantitative variables. Regarding the primary outcome measure of risk factors for severe COVID-19 disease, we performed analyses using chi-square and Fisher exact test for dichotomous variables, and Mann-Whitney U test for continuous variables such as age owing to lack of normal distribution. Given their overlapping pathophysiology, livedo and acro-ischemic cutaneous morphologies were combined to form a new category of "Livedo/Acro-ischemia" prior to the primary outcome measure analysis. Multivariate binary logistic regression analysis was utilized to model the prognostic factors associated with severe COVID-19 disease. Odds ratios and relevant 95% confidence intervals (CIs) were reported accordingly. Violin plots, bar charts, and heatmaps were used to present the data.

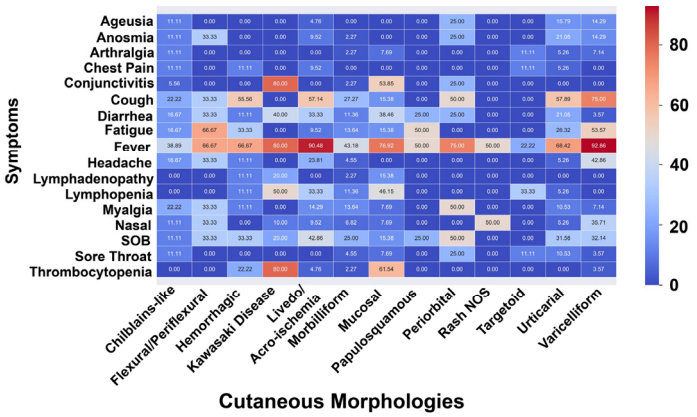

Figure 2. *Heatmap of cutaneous morphologies and other COVID-19 symptoms. The value within each cell is the percentage of occurrence of the corresponding COVID-19-related symptom within the corresponding cutaneous morphology. This figure is color-coded as a standard heatmap. NOS, not otherwise specified.*

Results

A total of 1352 records were identified through database searching and reference screening (**Figure 1**). After exclusion of duplicate records and screening of articles for eligibility, 71 unique publications (**Appendix 2**) meeting inclusion criteria were included for qualitative assessment and data extraction. Large case series without detailed reporting of individual patient-level data were excluded from this study. Cases for which COVID-19 was not confirmed or skin findings were attributed to causes other than COVID-19 were also excluded.

Seventy-one case reports and case series from 16 countries were included in this review. Among included articles, 144 cases of cutaneous involvement in confirmed COVID-19 were identified. COVID-19 was confirmed with SARS-CoV-2 RT-PCR assay in 128 patients (88·9%), ELISA antibody testing in 12 patients (8·3%), and pulmonary radiologic studies consistent with COVID-19 in 34 patients (23·6%). Thirty cases (20·8%) were confirmed by multiple methods.

Among patients included in this study, 67 (46·5%) were female and 75 (52·1%) were male. The median age of included patients was 51 years (mean: 45·9, range: 0 to 91). Twenty-six patients (18·1%) were under 18 years of age, whereas 114 patients (79·2%) were 18 years of age or older. Age was not reported in the remaining four cases.

The five most frequently occurring primary cutaneous morphologies were: morbilliform (30·6%),

varicelliform (18·8%), urticarial (13·2%), chilblains-like (12·5%), and acro-ischemic (9%), (**Table 1**). The three most common secondary cutaneous descriptors were: mucosal (9%), hemorrhagic (6·3%), and periorbital (2·8%). In 35 cases (24·3%), multiple cutaneous morphologies and/or descriptors were assigned.

Morbilliform, urticarial, hemorrhagic, and targetoid morphologies were reported more frequently in females, whereas livedo/acro-ischemic, varicelliform, chilblains-like, and Kawasaki-like morphologies were reported more frequently in males (**Figure 3**). Female predominance among patients with morbilliform eruptions reached statistical significance (28/44 [63·6%], P=0·008).

In 106 patients (73·6%), skin manifestations appeared after other COVID-19 symptoms (**Table 1**). In 9 patients (6·3%), rash appeared prior to other COVID-19 symptoms and in 17 patients (11·8%) rash and other COVID-19 symptoms appeared concurrently. Seven patients (4·9%) presented with rash alone and no other COVID-19 symptoms. The temporal sequence of events was not reported in three cases. The mean latency between other COVID-19 symptoms and rash onset was 9·1 days (9·1±10·2) and the mean duration of rash was 8·8 days (8·8±6·9).

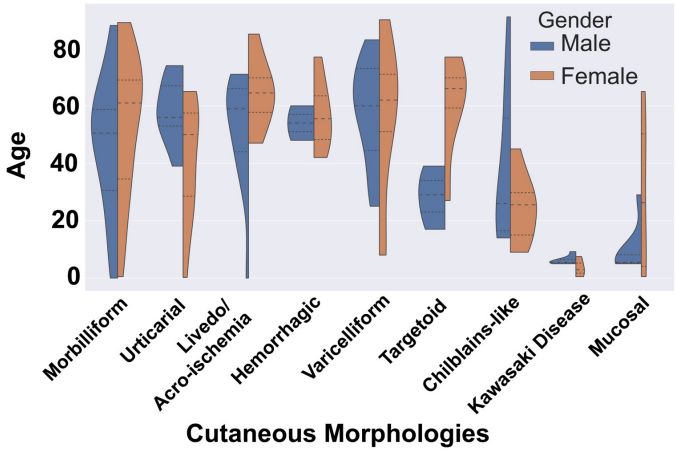

Figure 3. *Violin plot of cutaneous morphologies, age, and gender. As explained in the methods section, violin plots depict probability density and distribution pattern. To represent the actual data, the graphs were cut at the minimum and maximum values. The higher and lower small dotted lines represent 25th and 75th percentiles, and the middle large dotted line represents the median.*

Fever (118, 81·9%), followed by cough (70, 48·6%), shortness of breath (48, 33·3%), and fatigue (40, 27·8%) were the most frequently reported COVID-19 symptoms in patients with rash (**Figure 2**). Fever was present in ≥80 percent of cases of Kawasaki-like, livedo/acro-ischemic, and varicelliform morphologies. In contrast, patients with chilblains-like (P=0.16), morbilliform (P<0.0001), and targetoid (P=0.01) morphologies had lower frequencies of extracutaneous COVID-19 symptoms compared with other morphologies.

Forty patients (27·8%) were on long-term medications prior to rash onset and 34 patients (23·6%) were started on new medications prior to rash onset during their course of COVID-19 (**Table 1**). Among primary cutaneous morphologies, targetoid (6/9, 66%, P=0.03), followed by morbilliform (19/44, 43·2%, P=0.003) morphologies had the highest frequencies of new medications administered prior to rash onset.

Nineteen patients (13·2%) received anticoagulation at some point during their course of COVID-19. Five of these 19 patients were newly anticoagulated prior to rash onset. Anticoagulation occurred more frequently in patients with hemorrhagic eruptions, with four of 9 patients with hemorrhagic eruptions receiving anticoagulation at some point during their clinical course and two of 9 patients anticoagulated prior to their skin eruption. When compared with the incidents of anticoagulation among non-hemorrhagic cases, both findings were statistically significant by Fisher exact test (P=0.03, and P=0.04, respectively).

Thirty-eight patients (38/125, 30·4%, 95% CI 22·4%-39·2%) had severe COVID-19 disease (**Table 1**, **Figure 4**). The median age of patients with severe COVID-19 was 62 years (N=38), compared with a median age of 43 years for patients without severe disease (N=87).

Patients with livedoid and acro-ischemic morphologies had severe COVID-19 more frequently than those with other morphologies (17/21, 81%, 95% CI 58·0% to 94·5%, P<0·0001). Conversely, patients with chilblains-like eruptions were less likely to have severe disease (2/18, 11%, 95% CI 1·4% to

34·7%, P=0·02). These correlates were supported by multivariate binary logistic regression analysis (**Table 2**).

Table 2. *Multivariate binary logistic regression analysis for binary outcome of severe COVID disease.*

Risk Factor	Odds ratio	Range of 95% CI	P value
Livedo/Acro-ischemia	31.94	6.28-162.31	<0.0001
Shortness of Breath	6.11	2.17-17.16	0.001
Chilblains-like eruption	0.04	0.003-0.68	0.02
Nasal/sinus symptoms	0.08	0.007-0.95	0.04

CI, confidence interval.

Discussion

As the rapidly emerging pandemic of COVID-19 infection has swept the world, the medical community has moved just as quickly to share clinical observations of the disease and develop best practices. Initially, it seemed that cutaneous manifestations of COVID-19 were absent or minimal. However, this was likely related to underreporting early in the pandemic, as we are now seeing increasing reports highlighting various skin findings. Characterizations of these skin findings have contributed to our understanding of this emergent viral illness.

Recent publications have proposed varying frameworks for the classification of cutaneous manifestations of COVID-19. One approach is to classify by pathophysiology, as some cutaneous presentations of COVID-19 appear to be directly virally mediated whereas others appear to be secondary to a robust host response to infection [7]. Alternatively, cutaneous manifestations can be classified by morphologic and/or anatomic distribution [8]. Beyond classification, another important consideration is whether one can identify any important patterns or potentially predictive information from the aggregate of reported cases thus far. In this systematic review, we evaluated a number of demographic and cutaneous characteristics as well as associated clinical findings and outcomes to determine whether there were significant associations or trends among recently published cases. One advantage of our approach to this review was that all available clinical case images were independently evaluated by three board-certified dermatologists prior to inclusion in statistical analyses.

In this review, we found that cutaneous findings were reported more frequently in men than in women (51·4% versus 46·5%) and in adults than in children (114/144 ≥18 years; 26/144 <18 years). These findings are consistent with the overall reported demographic characteristics of COVID-19 infection; lower infection rates have been noted in children and higher infection rates and disease severity have been reported in men [9,10].

The three most frequently reported primary cutaneous morphologies of morbilliform, varicelliform, and urticarial are features common to viral infections. The less frequent morphologies of chilblains-like and acro-ischemic, however, are not typical manifestations of viral infections and may represent secondary vascular and or autoimmune phenomena. Morbilliform rashes were seen significantly more frequently in women (63·6%, 28/44, P=0·008) whereas livedoid/acro-ischemic presentations were seen more commonly in men. Interestingly, these morphologies mirrored disease severity with morbilliform morphology associated with less severe COVID-19 and livedoid/acro-ischemic findings associated with more severe disease. The emerging "androgen hypothesis" has proposed that androgens and the androgen receptor may play an important role in the infectivity of the COVID-19 virus and could help explain both the observed gender bias and the lower infection rates in children [11-14]. It is unclear whether androgens also play a role in the manifestations or severity of cutaneous findings.

Of the cases reviewed, the majority (72·6%) had onset of skin manifestations after other COVID-19 symptoms with a mean latency of 9·1 days (9·1±10·2). Only a minority (4·9%) were reported to have a rash with no other COVID-19-related symptoms. Considering that these reports are from early in the

pandemic, the data may be subject to bias such as less frequent involvement of dermatologists or a bias toward reporting cutaneous manifestations in more ill patients admitted to the hospital. As further data emerges on cutaneous manifestations, it remains to be seen whether this pattern of relatively late onset of cutaneous symptoms persists. Interestingly, patients with chilblains-like eruptions were more likely to present without any other COVID-19 symptoms compared to those with other morphologies (5/18 versus 2/126, P=0·0003). It is unclear whether this observation relates to the relatively younger age of patients with this cutaneous morphology or to a protective attribute of the individual's inflammatory response to the virus.

Among cases included in this study, fever, cough, shortness of breath, and fatigue were the most frequently reported non-cutaneous COVID-19 symptoms, mirroring the most commonly reported symptoms in large-scale reports of COVID-19 [3,15].

Overall, 23·6% of cases had a new medication administered prior to the onset of a rash, with targetoid and morbilliform morphologies being the most likely to have an antecedent new drug prescription (6/9, 66%, P=0.03 and 19/44, 43·2%, P=0.003 respectively). Although no specific medications were significantly associated with these two morphologies, targetoid and morbilliform are well-described patterns of drug eruptions. Thus, it is possible that a portion of cases presented as cutaneous manifestations of COVID-19 may actually represent incidental drug eruptions. However, since most cases we present had no reported drug-associations, it is reasonable to conclude that COVID-19 infection does have distinctive cutaneous manifestations.

Anticoagulants were prescribed in 19 patients (13·2%) and although the numbers were small, anticoagulants were prescribed in a significantly higher number of patients with hemorrhagic eruptions than in those with other morphologies. It has been suggested that vascular dysfunction may be a specific feature of COVID-19 infection [16]. The virus may predispose patients to thrombotic disease, both in venous and arterial circulations, owing to excessive inflammation, platelet activation, endothelial dysfunction, and/or stasis [17]. Complement-mediated cutaneous microvascular injury has also been identified in patients with severe lung disease and vascular/hemorrhagic cutaneous changes [18]. However, based on our review, it is possible that some of these cutaneous vascular changes may have been prompted or exacerbated by anticoagulant medications. Future publications in this area should include detailed medication information to further determine the impact of medications on COVID-19.

Severe COVID-19 disease was noted in 38 (26·4%) of reviewed cases. As expected, the median age for the patients with severe disease was higher than in those without severe disease (62 versus 43 years).

Our multivariate logistic regression analysis identified livedoid and acro-ischemic morphologies as a poor prognostic factor (OR=31·94) associated with severe COVID-19 infection and chilblains-like eruption as a favorable prognostic factor (OR=0.04, **Table 2**) and less likely to be associated with severe infection. These correlations corroborate those recently reported by Freeman et al. in their international registry-based case series of laboratory-confirmed COVID-19 cases with cutaneous manifestations [6].

Livedoid, retiform purpuric, and acro-ischemic skin findings have been associated with morbidity even before the emergence of COVID-19 [19]. Thus, it is not surprising that patients with these morphologies were more likely to have severe disease than those with other morphologies. As previously mentioned, it is possible that in more severe COVID-19 infection, vasculopathic and/or pro-thrombotic processes are activated by the virus itself or by the host immune response, leading to these skin changes.

Chilblains-like eruptions have been reported in mostly healthy patients and the vast majority of chilblains-like eruptions reported have not been confirmed to be COVID-19-related [8,20-28]. It has been suggested that this may be related to a robust interferon-related response that prevents severe infection [29]. Some patients with chilblains-like lesions have been nasopharyngeal PCR negative but have had confirmed SARS-CoV-2 on immunohistochemical analysis of skin biopsy

specimens [30,31]. More detailed studies of the immune response in these patients and other pauci-symptomatic or asymptomatic patients may reveal key insight into the complexities of the immune reaction to this virus.

This systematic review only includes case reports and case series of confirmed COVID-19-positive patients. Many reports included incomplete patient-level information, so our analysis was performed with limited data based on factors reported in disparate manuscripts; this introduces possible reporting bias and selective outcome reporting bias. Missing information could skew conclusions, leading to truncation bias. By only analyzing cases with confirmed COVID-19 tests, this analysis may skew toward more severe or earlier findings related to the limitations of availability and sensitivity of widespread testing at the onset of this epidemic. The lack of consistent reporting of patient-level data, including other symptoms, timing of rash, methods of testing, medications, hospitalization status, and outcomes in existing case series, limits the ability to generalize.

Conclusion

As our understanding of the cutaneous manifestations of COVID-19 infection continues to evolve, it is becoming clear that there is a wide array of morphologic presentations. Having a dermatologist involved in the care of COVID-19 patients can help with prompt and accurate identification of cutaneous disease, may impact treatment, and may help inform disease prognosis. Detailed patient-level reporting of cutaneous findings, including photographs, drug information, and other relevant outcomes such as markers of disease severity, will help with future efforts to aggregate data and study this emergent disease. Further developments including use of antibody testing and appropriate controls may also further our understanding of the pathophysiologic mechanisms of cutaneous disease.

Potential conflicts of interest

The authors declare no conflicts of interests.

Acknowledgements

We would like to thank Eve O. Melton and Quincy D. McCrary for their assistance in running part of search and retrieving full texts of the potentially eligible studies. There are no funding resources or conflict of interest associated to this work. FG developed the search strategy and developed the protocol. PM, and FG screened the potentially eligible publications. DSL and FG extracted the data from included studies. DSL, PEM, and PM evaluated the clinical photos. FG additionally rechecked some of the clinical photos. FG, and MM performed the data analysis, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. DSL drafted the manuscript, and all other authors read and edited the manuscript.

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Table 1. *General characteristics of patients with cutaneous manifestations of COVID-19.*

	Frequency, n (%)	M:F ratio	Age, Median (min, max)	Severe COVID-19,* n (%)	Duration of rash, Median (min, max)	Duration between other symptoms and rash, Median (min, max)	New medication prior to rash
Primary morphologies							
Chilblains-like	18 (12.5%)	10/8 (1.3)	**25.5 (9.0, 91.0)**	**2/18 (11.1%)**	**14.0 (2.0,44.0)**	5.0 (2.0, 24.0)	2 (11.1%)
Acro-ischemia	13 (9%)	9/4 (2.3)	**65.0 (40.0,85.0)**	**11/13 (84.5%)**	**14.0 (14.0,14.0)**	**19.0 (17.0, 59.0)**	2 (15.4%)
Livedo-Retiform purpura	8 (5.6%)	6/2 (3)	47.5 (0,67)	**6/8 (84.6%)**	3.5 (0.1,17.0)	11.0 (0.0, 20.0)	1 (12.5%)
Varicelliform	27 (18.8%)	18/9 (2)	**61.0 (8.0, 90.0)**	3/8 (37.5%)	8.0 (4.0, 15.0)	**3.0 (0.0, 12.0)**	2 (7.4%)
Kawasaki disease	10 (6.9%)	7/3 (2.3)	**5.5 (0.5, 9.2)**	3/10 (30%)	5.5 (5.0,6.0)	3.5 (0.0, 3.5)	1 (10.0%)
Urticarial	19 (13.2%)	7/11 (0.6)	55.0 (0.2,74.0)	3/19 (15.8%)	**5.0 (1.0,7.0)**	**2.0 (0.0, 12.0)**	5 (26.3%)
Papulosquamous	4 (2.8%)	2/2 (1)	27.0 (18.0,42.0)	1/4 (25.0%)	5.0 (3.0, 7.0)	4.5 (3.0, 6.0)	1 (25.0%)
Rash NOS	2 (1.4%)	1/1 (1)	48.0 (34.0,62.0)	1/1 (50.0%)			1 (50.0%)
Morbilliform	44 (30.6%)	**16/28 (0.6)**	57.5 (0.0, 89.0)	9/44 (20.5%)	7.0 (2.0,31.0)	8.5 (0.0, 33.0)	**19 (43.2%)**
Targetoid	9 (6.3%)	3/6 (0.3)	58.0 (17.0,77.0)	1/9 (11.1%)	**18.0 (7.0,18.0)**	15.5 (0.0,24.0)	**6 (66.7%)**
Secondary descriptors							
Hemorrhagic	9 (6.3%)	2/6 (0.3)	55.5 (42.0,77.0)	2/9 (22.2%)	5.0 (3.0, 9.0)	3.0 (0.0,8.0)	2 (22.2%)
Mucosal	13 (9%)	7/6 (1.2)	**7.0 (0.5,65.0)**	3/13 (23.1%)	5.0 (3.0,10.0)	3.5 (0.0,24.0)	4 (30.8%)
Flexural/Periflexural	3 (2.1%)	0/3 (0)	64.0 (55.0,84.0)	0/3 (0%)		4.0 (2.0,11.0)	1 (33.3%)
Periorbital	4 (2.8%)	2/2 (1)	36.5 (2.0,50.0)	0/4 (0%)	**3.0 (1.0,5.0)**	2.0 (0.0,11.0)	0 (0%)

Min, minimum; max, maximum; n, number; NOS, not otherwise specified; SD, standard deviation; Variables in bold show statistically significant differences from the average age of other cutaneous morphologies.

**Severe COVID status is defined as ICU admission, needing assisted ventilation, or death.*

Gray highlighted cells lack sufficient data to report.

Appendix 1 (eMethods):

Search strategy
The following search strategies were used in this systematic review:

PubMed
("novel coronavirus"[All Fields] OR ("COVID-19"[All Fields] OR "COVID-2019"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019-nCoV"[All Fields] OR "SARS-CoV-2"[All Fields] OR "2019nCoV"[All Fields] OR (("Wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND (2019/12[PDAT] OR 2020[PDAT]))) OR COVID[All Fields] OR ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "sars cov 2"[All Fields])) AND ("vesicular"[All Fields] OR vesicular[All Fields] OR "vesicle"[All Fields] OR "livedo*"[All Fields] OR "maculopapule"[All Fields] OR "maculopapular"[All Fields] OR maculopapular[All Fields] OR "exanthem*"[All Fields] OR exanthematous[All Fields] OR ("exanthema"[MeSH Terms] OR "exanthema"[All Fields] OR "exanthem"[All Fields]) OR "dengue"[All Fields] OR "morbilliform"[All Fields] OR morbilliform[All Fields] OR "skin"[All Fields] OR "cutaneous"[All Fields] OR "urticaria*"[All Fields] OR "chilblain*"[All Fields] OR ("chilblains"[MeSH Terms] OR "chilblains"[All Fields]) OR ("chilblains"[MeSH Terms] OR "chilblains"[All Fields] OR "pernio"[All Fields]) OR "pernio"[All Fields] OR "rash"[All Fields] OR "dermatitis"[All Fields] OR "Raynaud"[All Fields] OR "cherry"[All Fields] OR "petechia*"[All Fields] OR "skin mottling"[All Fields] OR "retiform"[All Fields] OR "varicella"[All Fields] OR "chickenpox"[All Fields] OR "heel"[All Fields] OR "Erythema multiforme"[All Fields] OR "annular"[All Fields] OR "Grover"[All Fields] OR "acr*"[All Fields] OR "pityriasis rosea"[All Fields] OR "facial erythema"[All Fields] OR ("erythema"[MeSH Terms] OR "erythema"[All Fields]) OR "ulcer"[All Fields] OR "Kawasaki"[All Fields] OR “cutánea”[All Fields] OR “cutáneos”[All Fields] OR ("erythema"[MeSH Terms] OR "erythema"[All Fields])) NOT (("melanoma"[MeSH Terms] OR "melanoma"[All Fields]) OR ("achilles tendon"[MeSH Terms] OR ("achilles"[All Fields] AND "tendon"[All Fields]) OR "achilles tendon"[All Fields] OR "achilles"[All Fields]))

EMBASE
('covid 19'/exp OR 'covid 19' OR 'severe acute respiratory syndrome coronavirus 2'/exp OR 'severe acute respiratory syndrome coronavirus 2' OR 'sars-related coronavirus'/exp OR 'sars-related coronavirus' OR 'sars coronavirus'/exp OR 'sars coronavirus' OR 'sars cov 2' OR 2019ncov OR 'novel coronavirus' OR (novel AND ('coronavirus'/exp OR coronavirus))) AND ('skin disease'/exp OR 'skin disease' OR (('skin'/exp OR skin) AND ('disease'/exp OR disease)) OR cutaneous OR 'vesicular rash'/exp OR 'vesicular rash' OR 'livedoid vasculopathy'/exp OR 'livedoid vasculopathy' OR 'chilblains'/exp OR chilblains OR 'chilblain'/exp OR chilblain OR 'mucocutaneous lymph node syndrome'/exp OR 'mucocutaneous lymph node syndrome' OR 'maculopapular rash'/exp OR 'maculopapular rash' OR 'pityriasis rosea'/exp OR 'pityriasis rosea' OR 'rash'/exp OR rash OR 'urticaria'/exp OR urticaria OR 'transient acantholytic dermatosis'/exp OR 'transient acantholytic dermatosis' OR 'dengue'/exp OR dengue OR 'morbillivirus infection'/exp OR 'morbillivirus infection' OR 'raynaud phenomenon'/exp OR 'raynaud phenomenon' OR 'cherry red spot'/exp OR 'cherry red spot' OR 'petechia'/exp OR petechia OR 'skin mottling'/exp OR 'skin mottling' OR (('skin'/exp OR skin) AND mottling) OR 'retiform purpura'/exp OR 'retiform purpura' OR 'varicella zoster virus'/exp OR 'varicella zoster virus' OR 'heel'/exp OR heel OR 'erythema multiforme'/exp OR 'erythema multiforme') NOT (achilles OR 'melanoma'/exp OR melanoma OR 'achilles tendon'/exp OR 'achilles tendon') AND (2019:py OR 2020:py)

Clinical Trials.gov
(skin OR cutaneous OR chilblains OR chilblains OR dengue OR erythema multiforme OR kawasaki OR chickenpox OR rash OR petechia OR retiform) | (novelcoronavirus OR covid-19 OR coronavirus OR SARS-COV-2)

Google Scholar
allintitle: (coronavirus OR "Covid 19" OR "Covid 2019" OR "SARS COV 2" OR "2019 nCoV" OR 2019nC0V OR Wuhan) AND (vesicular OR vesicular OR maculopapular OR skin OR cutaneous OR chilblain OR chilblains OR pernio OR rash OR dermatitis OR varicella OR rosea)

Cochrane Trials
("novel coronavirus" OR "COVID-19" OR "COVID-2019" OR "severe acute respiratory syndrome coronavirus 2" OR "severe acute respiratory syndrome coronavirus 2" OR "2019-nCoV" OR "SARS-CoV-2" OR "2019nCoV" OR ("Wuhan"AND "coronavirus" OR COVID) OR "severe acute respiratory syndrome coronavirus 2" OR "severe acute respiratory syndrome coronavirus 2" OR "sars cov 2") AND (vesicular OR vesicle OR livedo OR maculopapule OR maculopapular OR maculopapular OR exanthem OR exanthematous OR exanthema OR exanthem OR morbilliform OR morbilliform OR skin OR cutaneous OR urticaria OR chilblain OR chilblains OR pernio OR rash OR dermatitis OR Raynaud OR cherry OR petechia OR skin mottling OR retiform OR varicella OR chickenpox OR heel OR Erythema multiforme OR annular OR Grover OR acr OR pityriasis rosea OR facial erythema OR erythema OR ulcer OR Kawasaki OR erythema)"

WHO ICTRP database

"Skin" OR "cutaneous" OR "rash" in title.

medRxiv and Research Square were also searched using keywords (skin OR rash OR eruption) and COVID and found 1 eligible case report.

Additionally, Wiley and Elsevier websites were searched separately using the term "COVID" AND "Skin or Rash, or cutaneous or cutáneos OR cutánea."

Details of statistical methods
We performed analyses using Python (Python software foundation, version 3.7) and SPSS (IBM Corp., Armonk, N.Y., USA), version 26. The proportion of patients with severe COVID-19 disease as a main outcome measure was reported with binomial 95% confidence intervals (CIs). Kolmogorov-Smirnov test was used to test the normality of the quantitative variables. Regarding primary outcome measure of risk factors for severe COVID-19 disease, we performed analysis using chi-square and Fisher's exact test for dichotomous variables, and Mann-Whitney U test for continuous variables such as age due to lack of normal distribution. Additionally, we utilized multivariate binary logistic regression analysis as described below. Mann-Whitney U test was performed to compare the distribution of age among cutaneous morphologies and between patients with severe versus non-severe COVID-19 disease. A chi-square test or Fisher's exact test were used to compare other categorical variables when appropriate.

Given their overlapping pathophysiology, livedo and acro-ischemic cutaneous morphologies were combined to form a new category of "Livedo/Acro-ischemia" prior to the primary outcome measure analysis. Multivariate binary logistic regression analysis was utilized to model the prognostic factors associated with severe COVID-19 disease. Odds ratios and relevant 95% confidence intervals (CIs) were reported accordingly. Missing data were reported as is, and no computational analysis was performed. P values of 0.05 or less were considered significant. Frequencies were presented as n (%) and continuous variables were reported as median (minimum, maximum).

Violin plots, bar charts, and heatmaps were used to present the data.

Violin plots were utilized to illustrate the distribution and probability density of non-parametric data in a more detailed and intuitive manner. For heatmaps, a standard color-coding system was utilized, and the percentages of symptoms for each cutaneous morphology were reported in each cell to enhance the visual representation of the data.

Appendix 2 (eReferences)

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