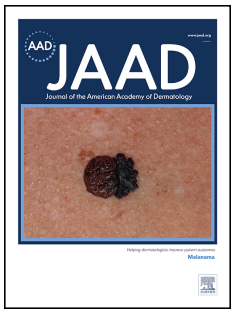

The clinical spectrum of COVID-19-associated cutaneous manifestations: an Italian multicentre study of 200 adult patients

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ABSTRACT

Background: COVID-19 is associated with a wide range of skin manifestations.

Objective: To describe the clinical characteristics of COVID-19-associated skin manifestations, and explore the relationships between the six main cutaneous phenotypes and systemic findings.

Methods: Twenty-one Italian Dermatology Units were asked to collect the demographic, clinical and histopathological data of 200 patients with COVID-19-associated skin manifestations. The severity of COVID-19 was classified as asymptomatic, mild, moderate, or severe.

Results: A chilblain-like acral pattern significantly associated with a younger age ($p<0.0001$) and, after adjusting for age, significantly associated with less severe COVID-19 ($p=0.0009$). However, the median duration of chilblain-like lesions was significantly longer than that of the other cutaneous manifestations taken together ($p <0.0001$). Patients with moderate/severe COVID-19 were more represented than those with asymptomatic/mild COVID-19 among the patients with cutaneous manifestations other than chilblain-like lesions, but only the confluent erythematous/maculo-papular/morbilliform phenotype significantly associated with more severe COVID-19 ($p=0.015$), and this significance disappeared after adjusting for age.

Limitations: Laboratory confirmation of COVID-19 was not possible in all cases.

Conclusions: After adjusting for age, there was no clear-cut spectrum of COVID-19 severity in patients with COVID-19-related skin manifestations although chilblain-like acral lesions were more frequent in younger patients with asymptomatic/paucisymptomatic COVID-19.

CAPSULE SUMMARY

- There are six main COVID-19-related cutaneous phenotypes, but only the chilblain-like acral pattern significantly associated with younger age.
- After adjusting for patient age, there was no spectrum of COVID-19 severity in relation to cutaneous phenotypes, although the longer-lasting chilblain-like acral pattern significantly associated with milder disease.

INTRODUCTION

Coronavirus disease 19 (COVID-19) is an infectious illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that may affect multiple organs, including the skin (the prevalence of cutaneous involvement was 7.8% in one bi-national Chinese-Italian cohort of 678 hospitalised adults with laboratory-confirmed disease).[1]

A number of skin manifestations have been described in individual case reports and nationwide case series. Galván Casas *et al*. published the first large clinical study of 375 patients with various COVID-19-associated skin manifestations[2] and, on the basis of the available literature and direct clinical experience, three of the authors of this paper (A.V. Marzano, G. Genovese and C. Moltrasio) have identified six main phenotypes: i) urticarial rash; ii) confluent erythematous/maculo-papular/morbilliform rash; iii) papulovesicular exanthem; iv) a chilblain-like acral pattern; v) a livedo reticularis/racemosa-like pattern; and vi) a purpuric "vasculitic" pattern.[3] However, there have been reports of a miscellany of other cutaneous presentations that cannot be included in this classification, including erythema multiforme-like[4], pityriasis rosea-like[5], and Grover's disease-like manifestations.[6] Galván Casas *et al*. found maculopapular eruptions accounted for almost half of the cutaneous manifestations in their study,[2] but the majority of published studies have focused on chilblain-like acral lesions,[7-10] which are generally associated with a benign clinical course and more frequently reported in children.[11-13]

The aim of this nationwide multicentre study was to provide clinical data concerning COVID-19-associated skin manifestations in order to improve the clinical and demographic characterisation of the cutaneous phenotypes that have previously been defined only on the basis of previously published preliminary data.[3] The main study objective was to explore the possible associations between these phenotypes, extra-cutaneous symptoms, and the severity of COVID-19.

MATERIALS AND METHODS

Patients

With the support of the Italian Society of Dermatology and Sexually Transmitted Diseases (SIDeMaST), 21 Italian Dermatology Units contributed to collecting the clinical data of patients with COVID-19-associated skin manifestations who were examined between 1 and 18 March 2020. The data included sex, age at the time of onset of COVID-19, the presence/absence of co-morbidities, cutaneous patterns, the presence/absence of mucosal lesions, the duration of skin manifestations, skin-related symptoms, systemic symptoms, the duration of systemic symptoms, the latency between the cutaneous manifestations and systemic symptoms, death, and the severity of COVID-19. Each participating centre was asked to provide data on the basis of the following patient inclusion criteria: i) an age of ≥18 years; ii) probable or laboratory-confirmed COVID-19; and iii) the presence of COVID-19-related skin manifestations confirmed by an expert dermatologist. A COVID-19 diagnosis was considered to be laboratory-confirmed in the case of a nasopharyngeal swab positive for SARS-CoV-2 RNA or positive serology for anti-SARS-CoV-2 IgG/IgM antibodies. COVID-19 was considered probable in any patient meeting the clinical criteria (dry cough, fever, dyspnea, the sudden onset of hyposmia or hypogeusia) who had been in close contact with someone with confirmed COVID-19 in the 14 days before symptom onset. A history of new medications in the 15 days before the onset of the skin manifestations was considered an exclusion criterion.

Clinical assessment

Systemic symptoms were taken from the charts of hospitalised patients or reported by outpatients, and assessed by a physician (pulmonologist, or a specialist in internal/emergency medicine or infectious diseases). The duration of the skin manifestations was directly evaluated by a dermatologist in the case of hospitalised patients, or reported by outpatients. Each patient was examined at least twice (during the period of skin manifestations and after their resolution).

The severity of COVID-19 was classified as asymptomatic, mild (in the presence of fever, cough and/or gastrointestinal symptoms with no imaging sign of pneumonia), moderate (in the presence of

dyspnea and/or radiological findings of pneumonia) or severe (a need for invasive assisted ventilation, the occurrence of thromboembolic events, or death),[14] and was assessed by considering the worst systemic symptoms over the entire course of the disease as shown in hospital records or self-reported by outpatients.

Statistical analysis

Continuous variables are expressed as median values and interquartile ranges (IQR), and dichotomous variables as absolute numbers and percentages. Quantitative variables (disease severity, symptoms, cutaneous phenotypes) were compared between groups using the non-parametric Wilcoxon-Mann-Whitney test.

Logistic regression analysis was used to assess the role of the six predefined skin phenotypes as risk factors for extra-cutaneous symptoms (fever, cough, dyspnea, pneumonia, gastrointestinal symptoms, hyposmia/hypogeusia) and the severity of COVID-19 (dichotomised as asymptomatic or mild *vs* moderate or severe). Univariate logistic regression models of each cutaneous phenotype were fitted by considering the severity of COVID-19 and the six extra-cutaneous symptoms as dependent variables (seven separate models); the phenotype was considered an independent variable. In addition, age-adjusted logistic regression analyses were made because of the possible confounding effect of age on symptoms and the severity of COVID-19. Odds ratios (ORs) and their 95% confidence intervals (CI) were obtained from the estimates of the logistic model parameters. Differences in the prevalence of symptoms between phenotypes were assessed using chi-square tests. Given the small number of patients with a livedo reticularis-like/racemosa-like pattern, only five phenotypes were considered (the purpuric and reticularis/racemosa-like patterns were merged). Patients with more than one cutaneous phenotype were not included in the statistical analyses, which were made using SAS statistical software (release 9.4, SAS Institute, Inc., Cary, North Carolina). A two-sided P value of <0.05 was considered statistically significant

Ethical approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and the full protocol was approved by the Institutional Review Board of the Ethics Committee of the Principal Investigator's centre (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; Protocol No. 464_2020). All of the subjects enrolled in the study gave their written informed consent.

RESULTS

Patients and cutaneous manifestations

The demographic and clinical features of the 200 patients are summarised in Table 1. The patients were predominantly males (n=108; 54%), and their median age at the time of the diagnosis of COVID-19 was 57 years (IQR 40.25-72.25). Eighty-six of the 195 patients with available data (43%) had experienced at least one co-morbidity.

Thirteen patients (6.5%) presented with more than one cutaneous phenotype. Of the 187 patients with only one phenotype, 19 (10.2%) developed urticarial rash; 48 (25.7%) confluent erythematous/maculo-papular/morbilliform rash; 29 (15.5%) papulovesicular exanthem; 46 (24.6%) a chilblain-like acral pattern; 4 (2.1%) a livedo reticularis/racemosa-like pattern; and 13 (6.9%) a purpuric "vasculitic" pattern (Supplemental Fig. 1). Cutaneous manifestations other than those included in the classification mentioned above[3] were observed in 28 patients (15.0%): pityriasis rosea-like lesions in 10; erythema multiforme-like lesions in eight; erythema nodosum-like lesions in four; panniculitis in four; and angioedema in two. No mucosal lesions were recorded. The most frequent skin-related symptom was pruritus (n=81; 40.5%), followed by pain/burning (n=22; 11%).

Among the 168 patients for whom data were available, the median duration of the skin manifestations was 12 days (IQR 8-20). However, the median duration of chilblain-like acral lesions was significantly longer than that of the other cutaneous manifestations taken together (21.5 [15-31] *vs* 10 [7-15] days; p <0.0001). The median latency between the cutaneous manifestations and systemic symptoms was 14 days (IQR 4-27) in the 155 patients for whom the data were available. The median duration of the individual skin manifestations and the latency between these and systemic symptoms are detailed in Table 1.

Interestingly, the median age of the patients with a chilblain-like acral pattern was significantly lower than that of the patients with all of the other cutaneous phenotypes taken together (38.5 [23-55] *vs* 60 [50-75] years; p<0.0001). The median age of the patients with purpuric and livedo reticularis-like/racemosa-like patterns was significantly higher than that of the patients with the other

manifestations taken together (66 [58-84] *vs* 55 [39-71] years; p=0.0022), and the median age of the patients with confluent erythematous/maculo-papular/morbilliform rash was also significantly higher than that of the patients with the other manifestations taken together (61 [51.5-78] *vs* 55 [36-71] years; p=0.029). There was no statistically significant association with age in the case of the papulovesicular and urticarial phenotypes.

The median age of the patients with moderate/severe COVID-19 was significantly higher than that of those with asymptomatic/mild COVID-19 (64 [54.5-78] *vs* 40 [27-57] years; p<0.0001). It was also significantly higher in the patients with fever than in those without (59 [50-75] vs 38 [26-61] years; p<0.0001), in those with cough than in those without (58.5 [50-74] vs 52 [30-71] years; p=0.0077), in those with dyspnea than in those without (65 [55-78] vs 49 [30.5-63] years; p<0.0001), and in those with pneumonia than in those without (65 [55-80] vs 41.5 [28-57] years; p<0.0001). There was no statistically significant difference in median age in the case of gastrointestinal symptoms or hypogeusia/hyposmia.

Clinical features of COVID-19

As shown in Table 2, COVID-19 was laboratory-confirmed in 124 patients, and regarded as probable in the remaining 73. Thirty-one patients (15.5%) were asymptomatic; 51 (25.5%) had mild disease; 95 (47.5%) had moderate disease; and 23 (11.5% had severe disease. Among the 124 patients for whom the data were available, the median duration of systemic symptoms was 23 days (IQR: 12-31).

Skin signs pre-dated systemic symptoms in 11 patients; among the remaining 189, they followed (n=186) or were concomitant with systemic symptoms (n=3). Fever was the most frequent systemic symptom (n=146; 73%), followed by cough (n=108; 54%), pneumonia (n=106; 53%), dyspnea (n=77; 38.5%), gastrointestinal symptoms (n=46; 23%), and hypogeusia/hyposmia (n=44; 22%). Thromboembolic complications occurred in 11 patients (5.5%), and death in seven (3.5%).

The median duration of systemic symptoms by each cutaneous phenotype is detailed in Table 2.

Relationships between cutaneous phenotypes and the severity of COVID-19/extra-cutaneous features

It is worth noting that, after adjusting for age, chilblain-like acral lesions were associated with a decreased risk of experiencing more severe COVID-19 (OR = 0.23, 95% CI 0.09-0.55; p=0.0009). On the other hand, confluent erythematous/maculopapular/morbilliform rash was associated with more severe COVID-19 before (OR = 2.49, 95% CI 1.19-5.18; p=0.015) but not after adjusting for age (OR = 1.9, 95% CI 0.83-4.37; p=0.1307).

Although patients with moderate/severe COVID-19 were more represented than those with asymptomatic/mild COVID-19 among the patients with cutaneous phenotypes other than chilblain-like lesions, there was no statistically significant association with the severity of COVID-19.

After adjusting for age, confluent erythematous/maculo-papular/morbilliform rash was identified as a significant risk factor for cough (OR = 2.25, 95% CI 1.1-4.63; p=0.0269); the urticarial pattern as a significant risk factor for gastrointestinal symptoms (OR = 6.10, 95% CI 2.25-16.59; p= 0.0004); and the livedo-like/vasculitic pattern as a significant risk factor for dyspnea (OR =4.17, 95% CI 1.05-16.5; p= 0.042).

DISCUSSION

With the exponential increase in the number of COVID-19 patients worldwide, the clinical features of the disease are being better defined and a number of reports have documented the occurrence of various cutaneous manifestations. In our nationwide cohort, the patients mainly presented with the six cutaneous phenotypes previously identified by our group.[3]

The most frequent cutaneous phenotypes were confluent erythematous/maculo-papular/morbilliform rash and a chilblain-like acral pattern, which affected respectively 25.7% and 24.6% of the 187 patients included in the statistical analysis, whereas the least frequent was a livedo reticularis-like/racemosa-like pattern (2.1%). The median latency between the onset of the cutaneous manifestations and systemic symptoms was 14 days (varying from four days in the case of papulovesicular exanthem to 24.5 days in the case of a livedo reticularis-like/racemosa-like pattern). The median duration of the cutaneous manifestations was 12 days (ranging from eight days in the case of urticarial rash to 22 days in the case of a chilblain-like acral pattern).

Pityriasis rosea-like and erythema multiforme-like patterns were the most frequently reported skin manifestations falling outside our classification, but it is still debated whether the former is directly mediated by SARS-CoV-2 or caused by COVID-19-related immune system dysfunction leading to human herpes virus(HHV)-6/HHV-7 reactivation,[5,15,18] and whether the latter is triggered by SARS-CoV-2 or other viruses.[4]

In line with previous observations, none of our patients experienced mucosal membrane lesions.[16] Although the angiotensin-converting enzyme 2 (ACE2) receptor of the spike protein of SARS-CoV-2 has been described as being not only expressed on keratinocytes[17] but also in the oral cavity,[18] mucosal membrane lesions have very rarely been reported in patients with COVID-19[16].

The main strength of this study is our exploration of the relationships between cutaneous phenotypes and the severity of COVID-19. Two studies of large cohorts of patients with COVID-19-related skin manifestations have found a gradient of increasingly severe systemic symptoms going from chilblain-like lesions to a livedo/necrotic pattern.[3,19] However, unlike these studies, our study

adjusted for patient age and failed to confirm this spectrum. Only the chilblain-like acral phenotype significantly associated with less severe COVID-19 and, although patients with severe disease were prevalent in each of the other five phenotypic categories, none of them significantly associated with an increased risk of more severe COVID-19.

Moreover, in line with the findings of other studies,[7] the chilblain-like acral phenotype was associated with a younger age at the time of COVID-19 diagnosis, whereas the livedo-like/vasculitic and maculo-papular phenotypes were associated with an older age at the time COVID-19 diagnosis. The pathological mechanisms underlying these relationships remain unclear but, in line with the acknowledged correlation between age and COVID-19 severity,[20] we found that patients with more severe disease, fever or respiratory symptoms (cough, dyspnea and pneumonia) had a higher median age, thus confirming the need for careful observation and an early intervention in order to prevent the development of severe COVID-19 in the elderly.

The close association between the urticarial phenotype and gastrointestinal symptoms found in our study is intriguing, and suggests that this phenotype is predictive of COVID-19-related gastrointestinal involvement. The pathophysiological link between skin and digestive manifestations needs further investigation, but it is likely that SARS-CoV-2 is a triggering factor for both.

The main limitation of this study is the absence of laboratory confirmation of COVID-19 in 73 patients (36.5%), which was mainly due to the fact that asymptomatic and paucisymptomatic patients did not undergo SARS-CoV-2 testing during the first wave of COVID-19 in Italy for economic reasons.

Selection bias due to the fact that the study only included patients whose COVID-19-related skin lesions had been evaluated by an expert dermatologist may be considered another limitation, but we believe that this is actually a strength insofar as it avoided the misdiagnoses that may have been made by non-specialists.

In conclusion, this study further defines the demographic and clinical features of the six main clinical phenotypes of COVID-19-associated skin manifestations by assessing the relationship between them and the extra-cutaneous symptoms and severity of COVID-19. The only correlation between the

289 cutaneous phenotype and the severity of COVID-19 was observed in the case of chilblain-like acral
290 lesions, a phenotype that is generally associated with the benign/sub-clinical course of COVID-19.

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REFERENCES

1. De Giorgi V, Recalcati S, Jia Z, et al. Cutaneous manifestations related to coronavirus disease 2019 (COVID-19): A prospective study from China and Italy. J Am Acad Dermatol 2020; 83:674-675. doi: 10.1016/j.jaad.2020.05.073.
2. Galván Casas C, Català A, Carretero Hernández G, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol. 2020; 183:71-77. doi: 10.1111/bjd.19163.
3. Marzano AV, Cassano N, Genovese G, et al. Cutaneous manifestations in patients with COVID-19: A preliminary review of an emerging issue. Br J Dermatol 2020; 183:431-442. doi:10.1111/bjd.19264
4. Torrelo A, Andina D, Santonja C, et al. Erythema multiforme-like lesions in children and COVID-19. Pediatr Dermatol 2020; 37:442-446. doi: 10.1111/pde.14246.
5. Ehsani AH, Nasimi M, Bigdelo Z. Pityriasis rosea as a cutaneous manifestation of COVID-19 infection [published online ahead of print, 2020 May 2]. J Eur Acad Dermatol Venereol. 2020;10.1111/jdv.16579. doi:10.1111/jdv.16579
6. Gianotti R, Veraldi S, Recalcati S, et al. Cutaneous Clinico-Pathological Findings in three COVID-19-Positive Patients Observed in the Metropolitan Area of Milan, Italy. Acta Derm Venereol. 2020;100:adv00124. doi: 10.2340/00015555-3490.
7. Freeman EE, McMahon DE, Lipoff JB, et al. Pernio-like skin lesions associated with COVID-19: a case series of 318 patients from 8 countries. J Am Acad Dermatol 2020; 83:486-492. doi: 10.1016/j.jaad.2020.05.109.
8. de Masson A, Bouaziz JD, Sulimovic L, et al. Chilblains is a common cutaneous finding during the COVID-19 pandemic: A retrospective nationwide study from France. J Am Acad Dermatol 2020; 83:667-670. doi:10.1016/j.jaad.2020.04.161
9. Fernandez-Nieto D, Jimenez-Cauhe J, Suarez-Valle A, et al. Characterization of acute acral skin lesions in nonhospitalized patients: A case series of 132 patients during the COVID-19 outbreak. J Am Acad Dermatol. 2020;83:e61-e63. doi:10.1016/j.jaad.2020.04.093.
10. Kanitakis J, Lesort C, Danset M, et al. Chilblain-like acral lesions during the COVID-19 pandemic ("COVID toes"): Histologic, immunofluorescence, and immunohistochemical study of 17 cases. J Am Acad Dermatol. 2020;83:870-875. doi: 10.1016/j.jaad.2020.05.145.
11. Colonna C, Genovese G, Monzani NA, et al. Outbreak of chilblain-like acral lesions in children in the metropolitan area of Milan, Italy, during the COVID-19 pandemic. J Am Acad Dermatol. 2020; 83:965-969. doi: 10.1016/j.jaad.2020.06.019.
12. El Hachem M, Diociaiuti A, Concato C, et al. A clinical, histopathological and laboratory study of 19 consecutive Italian paediatric patients with chilblain-like lesions: lights and shadows on the relationship with COVID-19 infection [published online ahead of print, 2020 May 31]. J Eur Acad Dermatol Venereol. 2020;10.1111/jdv.16682. doi:10.1111/jdv.16682.
13. Piccolo V, Neri I, Filippeschi C, et al. Chilblain-like lesions during COVID-19 epidemic: a preliminary study on 63 patients. J Eur Acad Dermatol Venereol. 2020 Apr 24:10.1111/jdv.16526. doi: 10.1111/jdv.16526. Epub ahead of print.
14. (Released by National Health Commission & National Administration of Traditional Chinese Medicine on March 3, 2020). Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7). Chin Med J (Engl) 2020;133:1087-1095. doi: 10.1097/CM9.0000000000000819.
15. Marzano AV, Genovese G. Response to "Reply to 'Varicella-like exanthem as a specific COVID-19-associated skin manifestation: multicenter case series of 22 patients': To consider varicella-like exanthem associated with COVID-19, virus varicella zoster and virus herpes simplex must be ruled out" J Am Acad Dermatol 2020; 83:e255-e256. doi: 10.1016/j.jaad.2020.05.072.
16. Zhou G, Chen S, Chen Z. Advances in COVID-19: the virus, the pathogenesis, and evidence-based control and therapeutic strategies. Front Med. 2020;14:117-125. doi: 10.1007/s11684-020-0773-x.
17. Xue X, Mi Z, Wang Z, Pang Z, Liu H, Zhang F. High Expression of ACE2 on Keratinocytes Reveals Skin as a Potential Target for SARS-CoV-2. J Invest Dermatol. 2020 May 23:S0022-202X(20)31602-X. doi: 10.1016/j.jid.2020.05.087.
18. Novak N, Peng W, Naegeli MC, Galvan C, Kolm-Djamei I, Brüggen C, Cabanillas B, Schmid-Grendelmeier P, Catala A. SARS-CoV-2, COVID-19, skin and immunology - What do we know so far? [published online ahead of print, 2020 Jul 13]. Allergy. 2020 Jul 13:10.1111/all.14498.

19. Freeman EE, McMahon DE, Lipoff JB, et al. The spectrum of COVID-19-associated dermatologic manifestations: An international registry of 716 patients from 31 countries. J Am Acad Dermatol 2020; 83:1118-1129. doi: 10.1016/j.jaad.2020.06.1016.
20. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;146:110-118. doi: 10.1016/j.jaci.2020.04.006.

SUPPLEMENTARY MATERIAL

Supplemental Figure 1. Clinical features of COVID-19-associated skin manifestations. A) Urticarial rash on the lower limbs. B) Confluent erythematous rash on the chest and abdomen. C) Papulovesicular exanthem. D) Chilblain-like acral lesions on the feet. E) Palpable purpura on the outside of the thigh. F) Livedo reticularis-like lesions on the thighs. All photographs belong to the authors' own collections.

363 **TABLE 1. Demographic data and clinical features of 200 patients with COVID-19-associated cutaneous manifestations**

Median age at the time of the onset of COVID-19, years (IQR)		57 (40.25-72.25)
Males, n (%)		108 (54)
Females, n (%)		92 (46)
Median latency between cutaneous manifestations and systemic symptoms, days (IQR)*		14 (4-27)
Median duration of cutaneous manifestations, days (IQR)**		12 (8-20)
Cutaneous phenotypes	**Urticarial rash, n (%)[§]**	19 (10.2)
	Confluent erythematous/maculo-papular/morbilliform rash, n (%)[§]	48 (25.7)
	Papulovesicular exanthem, n (%)[§]	29 (15.5)
	Chilblain-like acral pattern, n (%)[§]	46 (24.6)
	Livedo reticularis-like/racemosa-like pattern, n (%)[§]	4 (2.1)
	Purpuric "vasculitic" pattern, n (%)[§]	13 (6.9)
	Other cutaneous phenotypes, n (%)[§]	28 (15)
	More than one phenotype, n (%)	13 (6.5)
Median duration of cutaneous manifestations, days (IQR)	**Urticarial rash**	8 (5-13)[1]
	Confluent erythematous/maculo-papular/morbilliform rash	10 (7-14.5)[2]
	Papulovesicular exanthem	10 (7-14)[3]
	Chilblain-like acral pattern	22 (15-32)[4]
	Livedo reticularis/racemosa-like pattern	14 (5-27)[5]
	Purpuric "vasculitic" pattern	11 (6.5-15.5)[6]
Median latency between cutaneous manifestations and systemic symptoms, days	**Urticarial rash**	12 (5-23)[7]
	Confluent erythematous/maculo-papular/morbilliform rash	21.5 (12-28.75)[8]

(IQR)	**Papulovesicular exanthem**	4 (1.25-8)[9]
	Chilblain-like acral pattern	16 (9-39)[10]
	Livedo reticularis/racemosa-like pattern	24.5 (4-48.25)[11]
	Purpuric "vasculitic" pattern	16 (3.5-34)[12]
Skin-related symptoms, n (%)	**Pruritus**	81 (40.5)
	Pain/burning	22 (11)

Data available for the following numbers of patients: *155, **171, [1] 19, [2] 49, [3] 21, [4] 43, [5] 5, [6] 17, [7] 24, [8] 44, [9] 28, [10] 23, [11] 6, and [12] 17.
§Percentages of 187 patients (excluding the 13 with more than one cutaneous phenotype)

366 **TABLE 2. The severity of COVID-19 and the clinical features of its systemic symptoms**

Patients with at least one co-morbidity, n (%)*		86 (43)
Median duration of systemic symptoms, days (IQR)**		23 (12-31)
Systemic symptoms, n (%)	**Fever**	146 (73)
	Cough	108 (54)
	Pneumonia	106 (53)
	Dyspnea	77 (38.5)
	Gastrointestinal symptoms	46 (23)
	Hypogeusia/hyposmia	44 (22)
Thromboembolic complications		11 (5.5)
Death		7 (3.5)
Disease severity, n (%)	**Asymptomatic**	31 (15.5)
	Mild	51 (25.5)
	Moderate	95 (47.5)
	Severe	23 (11.5)
Diagnosis of COVID-19, n (%)	**Suspected**	73 (36.5)
	Laboratory-confirmed	127 (63.5)
Median duration of systemic symptoms, days (IQR)	**Urticarial rash[1]**	21 (11-39.5)
	Confluent erythematous/maculo-papular/morbilliform rash[2]	28 (19-38)
	Papulovesicular exanthema[3]	19 (12-28.5)
	Chilblain-like acral pattern[4]	13 (7-21)
	Livedo reticularis/racemosa-like pattern[5]	26 (11.75-48.25)
	Purpuric "vasculitic" pattern[6]	22 (8.75-33.5)

367 *Data available for 195 patients; **Data available for 124 patients. Data available for the following numbers of patients: [1] 17, [2] 39, [3] 13, [4] 21, [5] 6, and [6] 12

TABLE 3. Age-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of COVID-19 severity and systemic symptoms by skin phenotype in patients with COVID-19-associated skin manifestations (n=187)*

	Moderate/severe COVID-19		Fever		Cough		Dyspnea		Pneumonia		Hyposmia/hypogeusia		Gastrointestinal symptoms	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Urticarial rash	1.24 (0.43-3.62)	0.6938	2.69 (0.72-10.10)	0.1418	1.036 0.394 2.723	0.9433	1.78 (0.63- 5.02)	0.2781	1.351 0.467 3.906	0.579	2.23 (0.81- 6.12)	0.1196	6.10 (2.25-16.59)	0.0004
Confluent erythematous/maculo-papular/morbilliform rash	1.9 (0.83-4.37)	0.1307	0.83 (0.37-1.87)	0.6462	2.25 (1.1-4.63)	0.0269	2.05 (0.99- 4.24)	0.0519	1.5 (0.7- 3.3)	0.3121	0.67 (0.28- 1.59)	0.3632	0.82 (0.37-1.85)	0.6391
Papulovesicular exanthem	1.44 (0.55-3.79)	0.4565	2.44 (0.77-7.71)	0.1283	0.96 (0.42-2.16)	0.9185	0.71 (0.29-1.74)	0.4507	1.34 (0.53-3.41)	0.5387	1.83 (0.76-4.41)	0.1814	0.65 (0.23-1.82)	0.4154
Chilblain-like acral pattern	0.23 (0.09-0.55)	0.0009	0.21 (0.1- 0.46)	0.0001	0.28 (0.13-0.6)	0.001	0.2 (0.07- 0.56)	0.0024	0.29 (0.12-0.70)	0.0063	0.19 (0.06-0.61)	0.0054	0.51 (0.2- 1.30)	0.1579
Livedo reticularis/racemosa-like and purpuric "vasculitic" pattern	1.05 (0.25- 4.39)	0.9462	1.18 (0.24- 5.85)	0.8382	1.5 (0.43- 5.18)	0.5223	4.17 (1.05- 16.5)	0.0420	0.6 (0.17-2.16)	0.4302	1.19 (0.30- 4.64)	0.8054	0.25 (0.03-1.97)	0.1864

*Patients with more than one cutaneous phenotype were excluded from the statistical analysis

372 **TABLE 4. Comparison of the median age of patients with COVID-19-associated skin manifestations (n=187)***

			Median (IQR)	P-value
Cutaneous phenotypes	**Urticarial rash**	Yes (n=19)	54 (36-58)	0.1663
		No (n=168)	57.5 (41-74)	
	Confluent erythematous/maculo-papular/morbilliform rash	Yes (n=48)	61 (51.5-78)	0.029
		No (n=159)	55 (36-71)	
	Papulovesicular exanthem	Yes (n=29)	57 (44-75)	0.4863
		No (n=158)	57 (40-73)	
	Chilblain-like acral pattern	Yes (n=46)	38.5 (23-55)	<0.0001
		No (n=141)	60 (50-75)	
	Livedo reticularis/racemosa-like and purpuric "vasculitic" pattern	Yes (n=17)	66 (58-84)	0.0022
		No (n=170)	55 (39-71)	
Disease severity	**Asymptomatic status and mild COVID-19 (n=75)**		40 (27-57)	<0.0001
	Moderate and severe COVID-19 (n=112)		64 (54.5-78)	
Systemic symptoms	**Fever**	Yes (n=136)	59 (50-75)	<0.0001
		No (n=51)	38 (26-61)	
	Cough	Yes (n=102)	58.5 (50-74)	0.0077
		No (n=85)	52 (30-71)	
	Dyspnea	Yes (n=71)	65 (55-78)	<0.0001
		No (n=116)	49 (30.5-63)	
	Pneumonia	Yes (n=101)	65 (55-80)	<0.0001
		No (n=86)	41.5 (28-57)	
	Hyposmia/hypogeusia	Yes (n=41)	55 (44-65)	0.3337
		No (n=146)	57.5 (40-75)	
	Gastrointestinal symptoms	Yes (n=43)	55 (44-71)	0.9462
		No (n=144)	57 (38.5-73.5)	

373 *Patients with more than one cutaneous phenotype were excluded from the statistical analysis

CAPSULE SUMMARY

- There are six main COVID-19-related cutaneous phenotypes, but only the chilblain-like acral pattern significantly associated with younger age.
- After adjusting for patient age, there was no spectrum of COVID-19 severity in relation to cutaneous phenotypes, although the longer-lasting chilblain-like acral pattern significantly associated with milder disease.