Skin manifestations of COVID-19: A worldwide review

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Objective: Because of the increasing emergence of skin manifestations of COVID-19 worldwide, we investigated the published reports of these lesions.

Methods: We conducted a literature search for original and review articles published from November 11, 2019 to September 30, 2020.

Results: We identified 5 skin lesions common in patients with COVID-19: pseudo-chilblains, rashes containing macules and papules, and urticarial, vesicular, and vaso-occlusive lesions. These lesions manifested at various times in relation to the COVID-19 symptoms, which may indicate whether the lesions are virus-induced or are delayed immunological responses to the infection. Skin lesions were more prevalent among Europeans and United States residents than among Asians, as was pseudo-chilblain, and the morphology of the skin lesions varied among continents. Pseudo-chilblains were the most common COVID-19 skin manifestation in Europe and the United States, but there was only 1 reported case from Asian populations. Additionally, patients with vaso-occlusive lesions were more likely than those with pseudo-chilblains to be admitted to the intensive care unit and to die.

Conclusion: Different cutaneous manifestations in patients with COVID-19 could reflect a wide spectrum of viral interactions with the skin, though reporting bias may play a role as well. (JAAD Int 2021;2:119-33.)

Key words: acral ischemia; coagulopathy; COVID-19; pseudo-chilblains; rash containing macules and papules; skin manifestations; urticaria; vesicle.

INTRODUCTION

As COVID-19 continues to spread globally, the clinical spectrum of the disease remains incompletely known. The most common clinical features at the onset of illness are fever (85.6%), cough (68.7%), and fatigue (39.7%).[1] The spectrum of manifestations of symptomatic infection ranges from mild to critical. An increasing number of reports worldwide concern the cutaneous manifestations of COVID-19 that precede common acute respiratory symptoms. The most commonly described cutaneous manifestation that precedes other COVID-19 symptoms is vesicular lesions, but they are not well characterized.[2] For this literature review, we examined the published reports of the cutaneous manifestations of COVID-19, and we described these manifestations in relation to clinical practice. We report the geographical differences in the morphology of rashes, the onset of the rash eruption with reference to the illness progression, and the relationship of the rash to disease severity.

METHODS

We searched PubMed, OVID, EMBASE, MEDLINE, and Google Scholar for original and review articles written in English and published from November 11, 2019, to September 30, 2020. We used the keywords "cutaneous," "skin," "rash," and "dermatology" in combination with "COVID-19," "2019-nCOV" (2019 novel coronavirus), and "SARS-CoV-2" (severe acute

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respiratory syndrome coronavirus 2). We limited the number of articles by eliminating those that lacked direct relevance to cutaneous manifestations (Fig 1). We extracted the following data from the included studies: author, region, age, sex, the morphology of the rash, the location of the skin manifestations, the time of the cutaneous eruption in relation to the other COVID-19 symptoms, and the clinical outcomes of the patients.

CAPSULE SUMMARY

- There are geographical differences in the morphology and prevalence of reported COVID-19–associated skin manifestations.
- While genetic differences may play a role in the development of cutaneous manifestations and different types of lesions may be predictive of outcomes, reporting bias may be responsible for the observed regional variation.

RESULTS

We summarized the findings of 51 articles in this review, of which 27 were case series and 24 were case reports. A total of 1211 patients were described in these articles. The median age of the patients was 41.9 years (range: 15 days to 91 years); the ages of 451 patients were not reported. Of the patients, 336 (27.8%) were male and 424 (35.1%) were female; the gender of 451 patients (37.1%) was not reported. COVID-19 was confirmed in 627 patients (51.8%) and suspected in 584 (48.2%). Tables I and II detail these findings.[3-53]

We found demographic differences in the prevalence and the morphology of the skin manifestations in COVID-19. Of the 1211 patients with COVID-19–associated skin manifestations, 39 (3.1%) patients were from Asian populations and 1172 (96.9%) patients were from Europe and the United States (Tables I and II). Pseudo-chilblains were the most common COVID-19–related skin manifestations among Europeans and United States residents, but there was only 1 reported case from Asia.

We classified cutaneous manifestations in patients with COVID-19 into 5 major classes according to the order of severity (Table III). In nearly all patients, the lesions could be classified into one of these groups:

1. Vaso-occlusive lesions, which included fixed livedo racemosa (netlike violaceous skin lesions composed of irregularly broken macules with an annular pattern), retiform purpura (stellate purpuric skin lesions), and acral ischemia (ischemic lesions on the digits or toes). Vaso-occlusive lesions were the least common but were associated with the lowest survival rate of 78.9% (Table III).
2. Vesicular lesions, which tended to affect the trunk and whose configuration varied. Herpetiform, varicella-zoster–like, and monomorphic vesicle formation had been described previously in the literature on COVID-19. Vesicular lesions were reported as usually occurring at the onset of COVID-19 symptoms (Table IV). Among patients with COVID-19 and vesicular lesions, the survival rate was 96.1% (Table III).
3. Erythematous rash containing macules and papules, predominantly involving the trunk. More than half of the affected patients were female, and itchiness was the major symptom. Among patients with COVID-19 and rash containing macules and papules, the survival rate was 98.2% (Table III).
4. Urticarial lesions, which were transient edematous papules and plaques that disappeared within 24 h. More than half of the affected patients were middle-aged women. Urticarial lesions were associated with a survival rate of 97.5% (Table III).
5. Pseudo-chilblains presented as erythematous or violaceous papules on acral surfaces. Vesicles and pustules with purpuric areas have also been described. This condition was termed "pseudo-chilblains" because of the similar appearance of these lesions to chilblains, but there was no documented exposure to cold or other risk factors for chilblains. Pseudo-chilblains were more common in young adults compared with elderly patients and were associated with a survival rate of 98.7% (Table III).

Thirty-eight of 1211 patients (3%) showed other skin manifestations, such as petechiae, cutaneous mottling, eruptive cherry angioma, violaceous macules with "porcelain-appearance," non-necrotic or necrotic purpura, aphthous ulcers, purpuric exanthema, telogen effluvium, and relapsing livedo reticularis.[9,15,44,54]

DISCUSSION

We wished to characterize these manifestations for further diagnostic and prognostic value because cutaneous manifestations of COVID-19 have been increasingly reported worldwide.

In this review, we found that the reported prevalence of COVID-19–associated cutaneous manifestations differed globally, from 0.2% in China[55] to 7.25% in India[48] and 20.4% in Italy[13] The

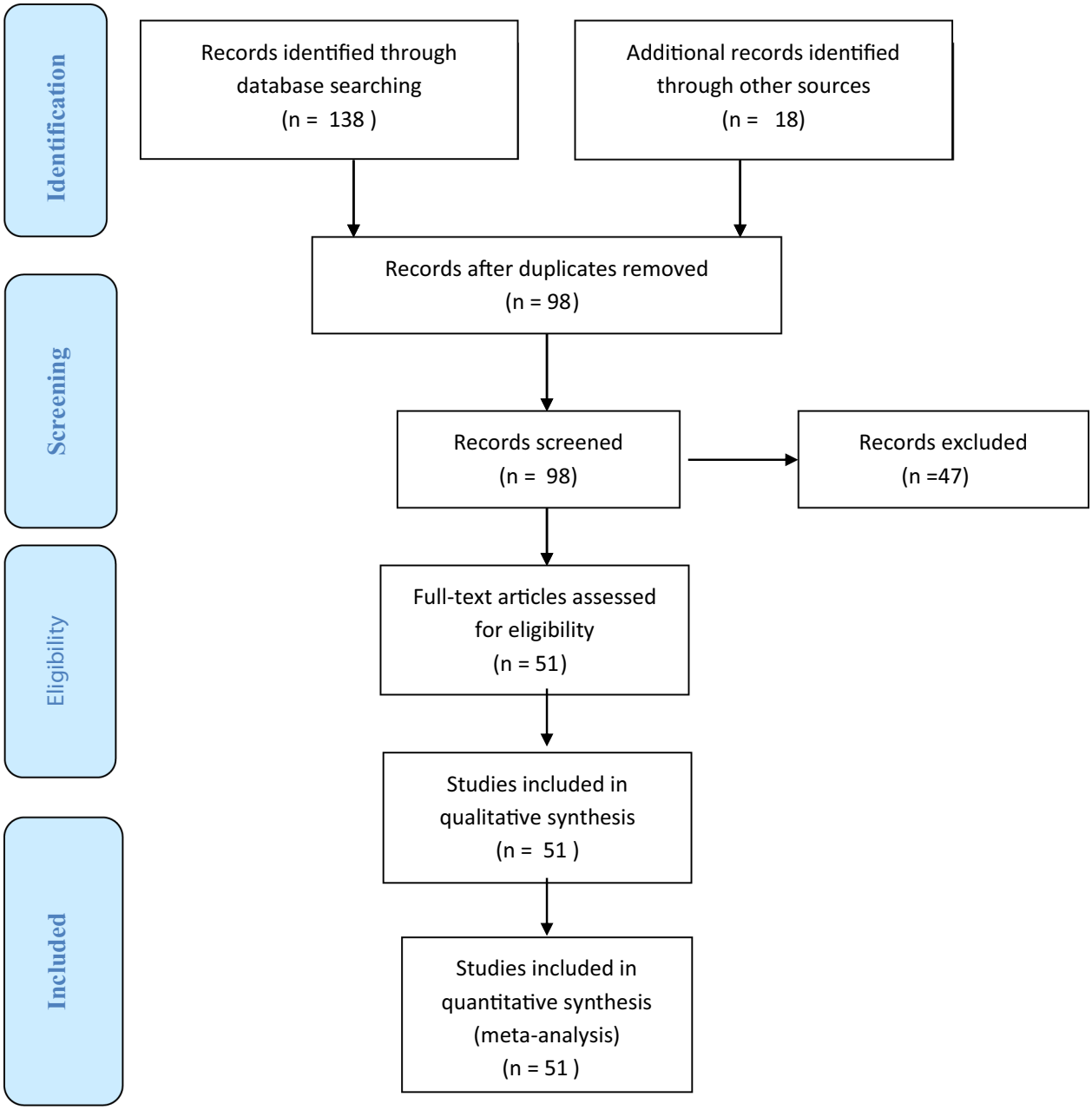

Fig 1. COVID-19: summary of systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

morphology of the skin manifestations in COVID-19 also differed geographically. Pseudo-chilblains were the most common COVID-19 skin manifestations in Europe and the United States, but there was only 1 reported case from Asia.

Pseudo-chilblains presented as erythematous or violaceous papules on acral surfaces, most commonly on the hands and feet. Vesicles and pustules with purpuric areas have also been described. Because of their similar appearance to chilblains, these lesions were termed "pseudo-chilblains" as there was no cold exposure prior to lesion eruption. On March 29, 2020, the first report of chilblain-like lesions appeared in Italy. A series of cases of chilblain-like lesions then began to emerge in Italy, France, Spain, and the United States. Pseudo-chilblains were suspected of being related to COVID-19 because the outbreak of these lesions during the early spring was concurrent with the COVID-19 pandemic. A few teledermatology groups were created in Italy, France, and Spain to collate the details of the patients and skin lesions. Our review

Table I. Characteristics of cutaneous manifestations of suspected and confirmed COVID-19 cases published in the literature in European and United States populations

Author; region/country	Type of study, number of specific rashes reported (n)/total number of rashes, Age, sex	Cutaneous signs	Clinical outcomes
Vaso-occlusive lesions			
Freeman; USA[3]	Case series, n = 11/716 Median age: 66 9 M: 2 F	Retiform purpura: 11 Vesicular: 18 Rash containing macules and papules: 61 Urticarial: 27 Pseudo-chilblain: 31	8 (72.7%) survival
Casas; Spain[2]	Case series, n = 21/375, Mean age: 63.1 11 M: 10 F	Acral ischemia: 21 Pseudo-chilblain: 71 Vesicular: 34 Urticarial 73 Rash containing macules and papules: 176	19 (90%) survival
Magro; New York, USA[4]	Case series, n = 3/3 Mean age: 46 1 M: 2 F	Retiform purpura: 1 Fixed livedoid rash: 2	3 (60%) survival
Suarez-Valle; Madrid, Spain[5]	Case series, n = 3/3 NR, NR	Acral ischemia	3 (100%) Survival
Young; Cleveland, USA[6]	Case series, n = 1/2, Age: 68 1 M	Case 1 (multiple morphologies on a single patient): Rash containing macules and papules on the abdomen, pseudo-chilblain on digits, retiform purpura on buttock Case 2: Urticaria	NR
De Masson; France[7]	Case series, n = 4/277 NR, NR	Pseudo-chilblain: 106 Rash containing macules and papules: 25 Vesicular lesion: 41 Vaso-occlusive: 4 Urticarial: 26	NR
Bosch-Amate; Spain[8]	Case report, n = 1 Age: 79 1 F	Painful retiform violaceous patches on both legs	1 (100%) survival
Vesicular lesions			
Freeman; USA[3]	Case series, n = 18/716 Median age: 55 8 M: 10 F	Vesicular: 18 Retiform purpura: 11 Rash containing macules and papules: 61 Urticarial: 27 Pseudo-chilblain: 31	18 (100%) survival
Askin; Turkey[9]	Case series, n = 3/76 NR, NR	Monomorphic vesicles unilateral at the upper trunk	NR
Marzano; Italy[10]	Case series, n = 22/22 Mean age: 60 16 M: 6 F	Varicella-like papulovesicular exanthema on trunk and limbs	19 (86.4%) survival
Tammaro; Spain[11]	Case series, n = 3/3 NR, NR	Herpetiform lesions on the back	NR

Continued

Table I. Cont'd

Author; region/country	Type of study, number of specific rashes reported (n)/total number of rashes, Age, sex	Cutaneous signs	Clinical outcomes
Casas; Spain[2]	Case series, n = 34/375, Mean age: 45.6 15 M: 19 F	Pseudo-chilblain: 71 Vesicular: 34 Urticarial 73 Rash containing macules and papules: 176 Acral ischemia: 21	34 (100%) survival
Matar; France[12]	Case series, N = 2/8 Mean age: 55.6 6 M: 2 F	Exanthema with macules and papules: 3 Digitate papulosquamous rash: 1 Herpes recurrence: 1 Papulovesicular rash: 1 Grover's disease: 1	NR
Recalcati; Lombardy, Italy[13]	Case series, n = 1/18 NR, NR	Vesicles: 1 Rash containing macules and papules: 14 Urticaria: 3	NR
De Masson; France[7]	Case series, n = 41/277 NR, NR	Pseudo-chilblain: 106 Rash containing macules and papules: 25 Vesicular lesion: 41 Vaso-occlusive: 4 Urticarial: 26	NR
Mahé; France[14]	Case series, n = 3/3 Mean age: 53.3 3 F	Vesicular rash on the trunk and upper limbs	3 (100%) survival
Bouaziz; France[15]	Case series, n = 2/14 NR, NR	Vesicles: 2 Exanthem: 4 Urticaria: 1 Pseudo-chilblains: 2 Others: 5	NR
Rash containing macules and papules			
Freeman; USA[3]	Case series, n = 78/716 Median age: 40.6 36 M: 42 F	Vesicular: 18 Retiform purpura: 11 Rash containing macules and papules: 78 Urticarial: 27 Pseudo-chilblain: 31	76 (97.4%) survival
Recalcati; Lombardy, Italy[13]	Case series, n = 3/18 NR, NR	Urticaria: 3 Rash containing macules and papules: 14 Vesicles: 1	NR
Casas; Spain[2]	Case series, n = 176/375 Mean age: 63.1 78 M: 98 F	Rash containing macules and papules: 176 Urticaria: 73 Pseudo-chilblain: 71 Vesicular: 34 Acral ischemia: 21	172 (98%) survival
Sachdeva; Milan, Italy[16]	Case series n = 3/3 Mean age: 73.3 3 F	Macules and papules	3 (100%) survival

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Table I. Cont'd

Author; region/country	Type of study, number of specific rashes reported (n)/total number of rashes, Age, sex	Cutaneous signs	Clinical outcomes
Askin; Turkey[9]	Case series, n = 12/34 NR, NR	Rash containing macules and papules: 12 Pseudo-chilblain: 1 Urticaria: 7	NR
De Masson; France[7]	Case series, n = 25/277 NR, NR	Pseudo-chilblain: 106 Rash containing macules and papules: 25 Vesicular lesion: 41 Vaso-occlusive: 4 Urticarial: 26	NR
Reymundo; Spain[17]	Case series, n = 7/7 Mean age: 66.6 2 M: 5 F	Erythematous macules and papules	7 (100%) survival
Young; Cleveland, USA[6]	Case series, n = 1/2, Age: 68 1 M	Case 1 (multiple morphologies on a single patient): Rash containing macules and papules, pseudo-chilblain, and retiform purpura Case 2: Urticaria	1 (100%) survival
Matar; France[12]	Case series, n = 2/8 Mean age: 55.6 6 M: 2F	Exanthem with macules and papules: 3 Digitate papulosquamous rash: 1 Herpes recurrence: 1 Papulovesicular rash: 1 Grover's disease: 1	NR
Bouaziz; France[15]	Case series, n = 4/14 NR, NR	Exanthem: 4 Vesicles: 2 Urticaria: 1 Pseudo-chilblains: 2 Others: 5	NR
Hunt; New York, USA[18]	Case report, n = 1 Age: 20 1 M	Generalized, morbilliform rash containing macules and papules	NR
Jimenez-Cauhe; Madrid, Spain[19]	Case report, n = 1 Age: 84 1 F	Erythematous-purpuric, millimetric, coalescing macules at flexural areas	NR
Mahé; Colmar, France[20]	Case report, n = 1 Age: 64 1 F	Erythematous rash on both antecubital fossae, then to the trunk and axillary folds	1 (100%) survival
Ahouach; France[21]	Case report, n = 1 Age: 57 1 F	Diffuse rash containing macules and papules on limbs and trunk	NR
Najarian; New Jersey, USA[22]	Case report, n = 1 Age: 58 1 M	Morbilliform exanthem on the trunk, upper limbs, and lower limbs	1 (100%) survival
Maniaci; Catania, Italy[23]	Case report, n = 1 Age: 15 1 M	Erythematous rash on lower limbs	1 (100%) survival
Boix-Vilanova; Spain[24]	Case report, n = 1 Age: 59 1 M	Pruriginous papulovesicular eruption on the trunk	1 (100%) survival

Continued

Table I. Cont'd

Author; region/country	Type of study, number of specific rashes reported (n)/total number of rashes, Age, sex	Cutaneous signs	Clinical outcomes
Iancu; Sibiu, Romania[25]	Case report, n = 1 Age: 41 1 F	The rash containing macules and papules started on the trunk and spread centrifugally	1 (100%) survival
Paolino; Milan, Italy[26]	Case report, n = 1 Age: 37 1 F	Cranio-caudal progression of the rash containing macules and papules	1 (100%) survival
Moreno; Madrid, Spain[27]	Case report, n = 1 Age: 32 1 F	Cranio-caudal progression of the rash containing macules and papules	1 (100%) survival
Urticarial lesions			
Freeman; USA[3]	Case series, n = 27/716 Median age: 42 years 6 M: 21 F	Vesicular: 18 Retiform purpura: 11 Rash containing macules and papules: 61 Urticaria: 27 Pseudo-chilblain: 31	26 (96.3%) survival
Casas; Spain[2]	Case series, n = 73/375 Mean age: 45.6 years 26 M: 47 F	Urticaria: 73 Pseudo-chilblain: 71 Vesicular: 34 Rash containing macules and papules: 176 Acral ischemia: 21	100% survival
Recalcati; Lombardy, Italy[13]	Case series, n = 3/18 NR, NR	Urticaria: 3 Rash containing macules and papules: 14 Vesicular: 1	NR
Cepeda-Valdes; Mexico[28]	Case series, n = 2/2 Mean age: 35 years 2 F	Disseminated urticarial rash	2 (100%) survival
Askin; Turkey[9]	Case series n = 7/34 NR, NR	Urticaria: 7 Rash containing macules and papules: 12 Pseudo-chilblain: 1	NR
De Masson; France[7]	Case series, n = 26/277 NR, NR	Pseudo-chilblain: 106 Rash containing macules and papules: 25 Vesicular: 41 Vaso-occlusive: 4 Urticaria: 26	NR
Bouaziz; France[15]	Case series, n = 1/14 NR, NR	Urticaria: 1 Vesicular: 2 Exanthem: 4 Pseudo-chilblain: 2 Other: 5	NR
Morey-Olivé; Barcelona, Spain[29]	Case series, n = 2 Mean age: 3 years 1M: 1F	Urticaria	2 (100%) survival
Young; Cleveland, USA[6]	Case series, n = 1/2, Age: 39 years 1 F	Case 1: multiple morphologies on a single patient Case 2: Urticarial rash on the trunk, thigh	1 (100%) survival

Continued

Table I. Cont'd

Author; region/country	Type of study, number of specific rashes reported (n)/total number of rashes, Age, sex	Cutaneous signs	Clinical outcomes
Henry; Orleans, France[30]	Case report, n = 1 Age: 27 years 1 F	Disseminated erythematous urticarial plaque eruption	1 (100%) survival
Sousa Gonçalves; Portugal[31]	Case report n = 1 Age: 57 years 1 F	Urticarial rash on elbow and abdomen	1 (100%) survival
Fernandez-Nieto; Spain[32]	Case report, n = 1 Age: 32 years 1 F	Urticaria	1 (100%) survival
van Damme; Belgium[33]	Case report, n = 1 Age: 71 years 1 M	Urticaria	0 (0%) survival
Pseudo-chilblain lesions			
Freeman; USA, Canada, France, UK, Italy, Mexico, Netherlands, Iran[34]	Case series, n = 31/716 Mean age: 32 15 M: 16 F	Pseudo-chilblain: 31 Macular erythema: 23 Urticaria: 27 Morbilliform: 38 Vesicular: 18 Papulosquamous: 17 Retiform purpura: 11	29 (93.5%) survival
Casas; Spain[2]	Case series, n = 71/375, Mean age: 45.6 26 M: 47 F	Urticaria: 73 Pseudo-chilblain: 71 Vesicular: 34 Rash containing macules and papules: 176 Acral ischemia: 21	71 (100%) survival
Fernandez-Nieto; Spain[35]	Case series, n = 95/132 Mean age: 23.4 years 49 M: 46 F	Pseudo-chilblain: 95 Erythema multiform-like: 37	NR
De Masson; France[7]	Case series, n = 106/277 NR, NR	Pseudo-chilblain: 106 Rash containing macules and papules: 25 Vesicular: 41 Vaso-occlusive: 4 Urticaria: 26	NR
Duong; France[36]	Prospective; crowd-sourced social media n = 146/295 NR, NR	Pseudo-chilblain: 146 Other: 149	NR
Askin; Turkey[9]	Case series, n = 1/34 NR, NR	Pseudo-chilblain: 1 Rash containing macules and papules: 12 Urticaria: 7	1 (100%) survival
Landa; Spain[37]	Case series, n = 6/6 Mean age: 35.3 3 M: 3 F	Pseudo-chilblains on toes, fingers	6 (100%) survival
Colonna; Italy[38]	Case series, n = 30 Mean age: 11 17 M: 13 F	Pseudo-chilblains	30 (100%) survival
Tosti; Italy[39]	Case series, n = 4 Mean age: 38 2 M: 2 F	Pseudo-chilblains at heels and extensor surfaces of toes	4 (100%) survival

Continued

Table I. Cont'd

Author; region/country	Type of study, number of specific rashes reported (n)/total number of rashes, Age, sex	Cutaneous signs	Clinical outcomes
Bouaziz; France[15]	Case series, n = 2/14 NR, NR	Pseudo-chilblains: 2 Exanthem: 4 Vesicles: 2 Urticaria: 1 Others: 5	NR
Young; Cleveland, USA[6]	Case series, n = 1/2, Age: 68 1 M	Case 1 (multiple morphologies on a single patient): Maculopapular rash on abdomen, pseudo-chilblain on digits, retiform purpura on buttock Case 2: urticaria	NR
Mazzotta; Italy[40]	Case report, n = 1 Age: 13 1 M	Erythematous-violet rounded lesions onplantar surfaces of 1st right toe and dorsal surface of 2nd toe on both feet	1 (100%) survival
Estébanez; Spain[41]	Case report, n = 1 Age: 28 1 F	Pruritic, confluent erythematous-yellowish papules on both heels	1 (100%) survival
Other lesions			
Fernandez-Nieto; Spain[35]	Case series, n = 37/132 Mean age: 12.2 22 M: 15 F	Pseudo-chilblain: 95 Erythema multiforme-like: 37	NR
Askin; Turkey[9]	Case series, n = 12/34	Petechiae (n = 4); aphthous stomatitis (n = 3); Necrosis of maxillary region/ sacrum (n = 4); pruritus (n = 1)	
Jimenez-Cauhe; Spain[42]	Case series, n = 4/4	Erythema multiforme-like eruptions	NR
Manalo; Atlanta, Georgia, USA[43]	Case series, n = 2/2 Mean age: 57 1 M: 1 F	Livedo reticularis: 2	NR
Bouaziz; France[15]	Case series, n = 5/14 NR, NR	Macules with "porcelain-like" appearance: 1 Livedo reticularis: 1 Non-necrotic purpura: 1 Necrotic purpura: 1 Eruptive cherry angioma: 1 Exanthem: 4 Vesicles: 2 Urticaria: 1	NR
Verheyden; Brussel[44]	Case report, n = 1 Age: 57 1 M	Relapsing livedo reticularis	NR
Kamali Aghdam; Iran[45]	Case report, n = 1 Age: 15 days old 1 M	Cutaneous mottling	NR

F, Female; *M*, male; *n*, number; *NR*, not reported; *USA*, United States.

Table II. Characteristics of cutaneous manifestations of suspected and confirmed COVID-19 cases published in the literature in Asian populations

Author; Region/country	Type of study, number of specific rashes reported (n)/total number of rashes, Mean age, sex	Cutaneous signs	Clinical outcomes
Vaso-occlusive lesions			
Zhang; China[46]	Case series, n = 7/7 Mean age: 59.8 4 M: 3 F	Vaso-occlusive	2 (28.6%) survival
Alramthan; Middle East/Qatar[47]	Case series, n = 2/2 Mean age: 31 years 2 F	Cases 1, 2: Vaso-occlusive	2 (100%) survival
Pangti; India[48]	Case series, n = 2/10 Mean age: 29.5 years 2 M	Vaso-occlusive: 2 Rash containing macules and papules: 2 Urticaria: 3 Pseudo-chilblain: 1 Other: 2 (desquamation, aphthous ulcer)	1 (50%) survival
Rashes containing macules and papules			
Dalal; North India[49]	Case series, n = 3/13 NR, NR	Rash containing macules and papules: 3 Urticaria: 2 Pruritus: 8	NR
Pangti; India[48]	Case series, n = 2/10 Mean age: 35 2 M	Vaso-occlusive: 2 Rash containing macules and papules: 2 Urticaria: 3 Pseudo-chilblains: 1 Others: 2 (desquamation, aphthous ulcer)	2 (100%) survival
Ho; Singapore[50]	Case series, n = 2 Mean age: 59 1 M: 1 F	Rash containing macules and papules: 2	2 (100%) survival
Urticarial lesions			
Pangti; India[48]	Case series, n = 3/10 Mean age: 55.5 1 M: 2 F	Vaso-occlusive: 2 Rash containing macules and papules: 2 Urticaria: 3 Pseudo-chilblains: 1 Others: 2 (desquamation, aphthous ulcer)	3 (100%) survival
Lu; China[51]	Case report n = 1 NR, NR	Urticaria	1 (100%) survival
Abasaeed; Abu Dhabi, United Arab Emirates[52]	Case report, n = 1 Age: 40 1 M	Urticaria with angioedema (negative demographism)	1 (100%) survival
Shanshal; Baghdad, Iraq[53]	Case report, n = 1 Age: 35 1 F	Multiple morphologies in a single patient Urticarial lesions on the trunk, upper and lower extremities, anagen effluvium	1 (100%) survival
Pseudo-chilblain lesions			
Pangti, India[48]	Case series, n = 1/10 Age: 50 years 1 F	Vaso-occlusive: 2 Rash containing macules and papules: 2 Urticaria: 3 Pseudo-chilblain: 1 Other: 2 (desquamation, aphthous ulcer)	1 (100%) survival
Other lesions			
Pangti, India[48]	Case series, n = 2/10 Age: 26 years 2 M	Desquamation: 1 Aphthous ulcer: 1	2 (100%) survival

F, Female; *M*, male; *n*, number; *NR*, not reported.

Table III. A summary of worldwide cutaneous manifestations of COVID-19 and survival Data

Characteristics	Vaso-occlusive lesions	Vesicular lesions	Urticarial lesions	Rashes containing macules and papules	Pseudo-chilblains
Number of patients	56	129	153	339	496
Median age	63	54.3	43.7	55.5	27.2
Sex	28 M: 21 F 7 not reported	39 M: 38 F 52 not reported	36 M: 77 F 40 not reported	124 M: 155 F 60 not reported	111 M: 130 F 255 not reported
Region/Country	USA 14 Spain 25 France 4 China 7 Kuwait 2 India 2	USA 18 Spain 37 Italy 23 France 48 Turkey 3	USA 28 Mexico 2 Spain 76 Italy 3 France 28 Belgium 1 Portugal 1 Turkey 7 China 1 India 5 United Arab Emirates 1	USA 81 Spain 186 Italy 19 France 33 Romania 1 Turkey 12 India 4 Singapore 2	USA 32 Spain 173 Turkey 1 Italy 35 France 254 India 1
Survival	41 (78.9%); 4 not reported	74 (96.1%); 52 not reported	112 (98.2%); 39 not reported	270 (97.5%); 62 not reported	145 (98.7%); 349 not reported

F, Female; *M*, male; *USA*, United States.

Table IV. Prevalence of 5 common skin manifestations in 1211 patients with COVID-19 and the timing of the skin eruption in relation to the COVID-19 symptoms

	Eruption of lesions before the COVID-19 symptoms	Eruption of lesions together with the COVID-19 symptoms	Eruption of lesions after the COVID-19 symptoms	Eruption of lesions not documented
1. Pseudo-chilblain lesions (n = 496, 40.9%)	36 (7.3%)	71 (14.3%)	177 (35.8%)	41 (8.2%) not documented; 171 (34.4%) patients did not have other COVID-19 symptoms
2. Rashes containing macules and papules (n = 339, 27.9%)	17 (4.7%)	188 (55.8%)	109 (32%)	25 (7.5%)
3. Urticarial lesions (n = 153, 12.5%)	8 (4.6%)	79 (51.7%)	51 (33.1%)	15 (10.6%)
4. Vesicular lesions (n = 129, 10.7%)	11 (8.5%)	49 (38%)	62 (48.1%)	7 (5.4%)
5. Vaso-occlusive lesions (n = 56, 4.4%)	3 (3.75%)	36 (68%)	14 (24.5%)	3 (3.75%)
6. Others (n = 38, 3.1%)	0	0	18 (47.4%)	20 (52.6%)

showed that pseudo-chilblains appeared in the later stage of the disease and are associated with indolent disease progression. There are multiple postulated pathophysiologic mechanisms of pseudo-chilblains in COVID-19. Kolivras et al[56] from Belgium demonstrated histopathologic similarities between pseudo-chilblains and chilblain lupus. Interferon 1 plays an essential role in immune stimulation in both acute viral infections and cutaneous lupus erythematosus. It is hypothesized that a robust antiviral type 1 interferon response may truncate the clinical course and induce microangiopathic changes, producing chilblain-like lesions.[56] There is an interethnic discrepancy in the prevalence of pseudo-chilblain lesions. A multicentric case series by Freeman et al[34] collated a total of 318 patients with pseudo-chilblains; 89% of patients were white and only 0.7% were black or African American. Pseudo-chilblains were the most common COVID-19 skin manifestations in Europe and the United States, but no cases were reported in China. Interferon-induced helicase C domain-containing protein 1 (IFIH1) is an immune receptor that senses coronavirus RNA and initiates the cascade of antiviral responses, including

induction of type 1 interferons and proinflammatory cytokines. The role of the *IFIH1* polymorphism, rs1990760 (C>T; aaA946T) is well studied in viral infection, and individuals with the minor allele T have enhanced interferon production.[57] The minor allele frequency (Tmaf) is more common in white populations compared with Chinese and African populations.[57] This could explain why pseudo-chilblains were more frequently seen in white populations compared with other races. However, another possible explanation for the discrepancy is underreporting of skin manifestations in skin-of-color populations.

Vaso-occlusive lesions included fixed livedo racemosa, retiform purpura, and acral ischemia. Vaso-occlusive lesions were the least common skin manifestations of COVID-19, but they were associated with poorer outcomes. Because they erupted on acral surfaces, vaso-occlusive lesions should be distinguished from pseudo-chilblains. In contrast to pseudo-chilblains, which were more prevalent in young people,[37] vaso-occlusive lesions tended to affect elderly patients.[2] In comparison with patients who had other cutaneous manifestations, patients with vaso-occlusive lesions were at a higher risk of severe pneumonia requiring intensive care, which was associated with higher mortality rates.[2] Vaso-occlusive lesions were linked to markedly elevated levels of D-dimer and disseminated intravascular coagulation.[4,46] Histopathologic examination of vaso-occlusive lesions by Magro et al[4] demonstrated that thrombogenic vasculopathy with deposition of C5b9 and C4d vaso-occlusive lesions is a pauci-inflammatory thrombotic event. They also found a striking similarity between lung autopsy and skin histology results in 2 patients who succumbed to COVID-19. This suggested that complement system activation led to systematic microvascular injury. Cutaneous microvascular injury that manifests as vaso-occlusive lesions could be a potential marker of severe COVID-19 infection.

There were also differences in the reported prevalence of vaso-occlusive lesion among continents. The reported prevalence of vaso-occlusive lesions in Spain was 5.2%,[2] whereas the prevalence of vaso-occlusive lesions from a multicentric study from the United States was 6.4%.[3] However, the reported prevalence of vaso-occlusive lesions in India was 1.4%.[48] The findings raised the suspicion of the interplay of genetic thrombophilia-related factors within certain ethnic populations in vaso-occlusive lesions in COVID-19. Lipoprotein A (LpA) plays a major role in thrombo-occlusive vasculopathy.[58,59] Criado et al demonstrated thrombosis, fibrin, and LpA deposition on cutaneous blood vessels in a patient with livedoid vasculopathy. Convincing data has shown genetic variability in LpA levels between ethnic populations. Studies have consistently shown that black individuals have 2–3-fold higher LpA levels than white individuals. Although there are fewer studies in the Asian population, data showed that Chinese individuals had lower LpA levels compared with Caucasian individuals.[60] The interethnic difference in the prevalence of factor V Leiden mutations may also play a role. The mutation was most common among patients of Latino descent (2.21%), followed by patients of American descent (1.25%) and of African descent (1.23%), and least common in patients of Asian descent (0.45%).[61] These genetic differences correspond with the reported higher prevalence of vaso-occlusive lesions among US residents and Europeans than among Asians.[2,3,13,55,62]

Rash containing macules and papules was the second most common cutaneous manifestation of COVID-19. However, rashes containing macules and papules were not specific to COVID-19, and there were reports of misdiagnosed cases of COVID-19 as viral illness in patients with rash containing macules and papules.[18] Given the current pandemic, the presence of a rash containing macules and papules should prompt suspicion of COVID-19. This would help with early identification and containment of the disease. Approximately 55.8% of rashes containing macules and papules occurred during the active phase of the disease, which may correspond to the viremia phase (Table IV). Skin biopsy of the rash containing macules and papules showed a nest of Langerhans cells within the epidermis with mild perivascular lymphocytic infiltration in the papillary dermis.[63] Young and Fernandez[6] described the histopathology of a specimen from an elderly man with a rash containing macules and papules, which showed apoptotic keratinocytes in the epidermis. During the viremic phase, the virus spread in a hematogenous fashion, including to the endothelium of cutaneous vessels. Infected endothelial cells then attracted cytotoxic T cells, which caused rashes containing macules and papules.

Najarian[22] reported a 58-year-old Hispanic man who developed morbilliform exanthem on the trunk and limbs on day 2 of COVID-19 symptoms. However, this patient had also taken azithromycin and benzonatate for 2 days prior to the onset of rash. This highlighted another challenge in defining the etiological diagnosis of skin lesions in the COVID-19 pandemic. Some useful clues to differentiate between drug rashes and viral rashes are the

morphology and presence of enanthem pustular dusky lesions, which are suggestive of a drug etiology, whereas a petechial or vesicular pattern, involvement of the buttocks or acral sites, and presence of enanthem are suggestive of an infectious etiology, including a viral etiology.[64]

Joob and Wiwanitkit described a patient in Thailand who initially presented with fever and petechiae, which was misdiagnosed as dengue fever. The patient subsequently developed respiratory symptoms and tested positive for COVID-19 via reverse transcription polymerase chain reaction.[54] Thus, COVID-19–associated cutaneous manifestations could mimic other viral rashes. This is of importance in Southeast Asia, where dengue virus infection is endemic.

Urticaria was the third most common skin manifestation in patients with COVID-19. One of the postulated hypotheses about the pathogenesis of urticaria in COVID-19 was virus-induced mast cell degranulation, whereby SARS-CoV-2 enters vascular cells via angiotensin-converting enzyme-2. The deposition of antigen-antibody complexes leads to complement activation, mast cell degranulation, and bradykinin release.[65] This is supported by the demonstration of colocalization of SARS-CoV-2 glycoproteins with complement components in cutaneous blood.[4] However, Pathania reported that emotional stress related to COVID-19, rather than the infection itself, may trigger the urticaria.[66] Hassan described a patient with a history of atopic dermatitis who presented with urticaria as the prodromal cutaneous manifestation of COVID-19.[67]

Rashes reminiscent of symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) were described in 2 patients with COVID-19 from France and Spain. In both patients, SDRIFE-like skin manifestations developed on day 3 of the illness. The rashes were described as erythematous, millimetric, coalescing macules predominantly distributed at flexural areas.[20,68] Although SDRIFE is classically associated with drug reactions, the rashes reported in these 2 cases may have been associated with COVID-19, as no culprit drug was identified in either patient.

This literature review had a few limitations. First, many of the included studies were case reports and studies with small sample sizes. Second, not all the included subjects had COVID-19 confirmatory tests because of the limited resources in certain regions. The difference between the prevalence of cutaneous manifestations in Europeans and United States residents compared with Asians could be attributable to underreporting in Asian countries. However, in countries with a heterogeneous racial make-up, such as the United States, black and Latino populations have been disproportionately affected. The implication of genetic factors in polymorphous cutaneous reactions in COVID-19 remains to be explored.

The scientific understanding of cutaneous manifestations in patients with COVID-19 is still evolving. Polymorphous cutaneous manifestations in patients with COVID-19 infection could potentially reflect a full spectrum of viral interactions with the skin, characterized by direct viral action in infected cells, immune system hyperactivity, and hypercoagulability. Future studies with better scientific documentation would help elucidate the pathophysiologic features and the prognostic factors of the cutaneous manifestations in COVID-19.

Conflicts of interest

None disclosed.

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