Cutaneous Manifestations of COVID-19: A Systematic Review

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Systematic Review

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Abstract

Background: The COVID-19 pandemic has affected 4.5 million people and killed over 300,000 patients. Although this virus primarily causes respiratory symptoms, an increasing number of cutaneous manifestations associated with this disease have been reported.

Objective: The aim of this review was to collate and categorize the dermatologic findings reported in COVID-19 patients and identify specific lesions that may facilitate diagnosis and prognostication.

Methods: A systematic review of the PubMed database was conducted on May 14th, 2020 using the search terms “Covid-19 skin,” “Covid-19 rash,” “Covid-19 exanthem,” and “Covid-19 chilblains.” Peer-reviewed publications containing original COVID-19 patient cases and a discussion of the associated cutaneous findings were included in the analysis.

Results: The literature search identified 115 records, of which 34 publications describing 996 dermatologic patients were included. Case reports (*n*=15), case series (*n*=10) and observational studies (*n*=7) were the most common publication types. Pseudo-chilblains (PC) was the most frequent lesion identified (40.4% of cases), appearing in young adults (mean age, MA, 23.2 years) after the onset of extracutaneous COVID-19 symptoms (55/100 patients). Erythematous maculopapular rashes (EMR) affected 21.3% of patients, most frequently impacting middle-aged adults (MA 53.2 years) and occurring at the same time as non-cutaneous symptoms (110/187 patients). Vesicular rashes (VR) affected 13.0% of patients, appearing in middle-aged adults (MA 48.3 years) after the onset of other symptoms (52/84 patients). Urticarial rashes (UR) affected 10.9% of patients, appearing in adults (MA 38.3 years) and occurring at the same time as non-cutaneous symptoms (46/78 patients). Vascular rashes resembling livedo/purpura/necrosis (LPN) were uncommon (4% of cases), appearing in elderly patients (MA 77.5 years) and occurring at the same time as non-cutaneous COVID-19 symptoms (18/29 patients). Erythema multiforme-like eruptions (EME), although infrequent (3.7% of cases), affected mostly children (MA 12.2 years).

Conclusions: VR may suggest an initial diagnosis of COVID-19, PC may be most appropriate for epidemiological uses, and LPN may be a useful prognostic marker for severe disease. As a potential correlate to disease severity, prognosis, or infectibility, it is critical that all health care professionals be well-versed in these increasingly common cutaneous manifestations of COVID-19.

1. Introduction

In December 2019, a new infectious pathogen named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China.[1] Transmitted through respiratory droplets, SARS-CoV-2, commonly referred to as coronavirus disease 2019 (COVID-19), has rapidly spread across the globe to infect 188 countries. The combination of its high infectivity and lengthy asymptomatic latency period has culminated in a global pandemic affecting 4.5 million people and resulting in over 300,000 deaths to date.[2] Although known to primarily cause interstitial pneumonia and respiratory failure, recent reports from around the world have indicated that this novel coronavirus may be associated with specific cutaneous manifestations. These dermatologic symptoms may be useful in identifying otherwise asymptomatic COVID-19 carriers, which may help slow the transmission of this highly infectious and dangerous virus. As such, a systematic review of peer-reviewed scientific literature was conducted to collect clinically relevant information on the cutaneous signs and symptoms of patients with COVID-19.

2. Materials And Methods

To identify all peer-reviewed articles reporting on the cutaneous manifestations associated with COVID-19, a systematic review of the PubMed database was conducted on May 14th, 2020 using the search terms “Covid-19 skin,” “Covid-19 rash,” “Covid-19 exanthem,” and “Covid-19 chilblains.” Records identified through the electronic database were initially screened by title and abstract content. The full-text articles that remained were assessed for eligibility and inclusion in the systematic review. Peer-reviewed publications that contained original COVID-19 patient cases and a discussion of the associated dermatologic findings were included in the analysis. Review or opinion articles that did not report on original patient cases, observational studies or case reports that did not discuss cutaneous symptoms, and articles that were published prior to the first COVID-19 case in December 2019 were excluded.

Eligible articles were assessed for study type, location, setting, and Level of Evidence for clinical research. Demographic characteristics such as patient sample sizes, ages, and genders was collected. COVID-19 status and diagnostic modality were also noted. Descriptive characteristics of the cutaneous manifestations were recorded, including: rash type, location, duration, associated symptoms, relation to drug intake, and correlation to onset of other COVID-19 symptoms.

3. Results

3.1 Study characteristics and patient demographics

As depicted in **Figure 1**, 115 records were initially identified in the literature search. After screening for eligibility and inclusion criteria, 34 peer-reviewed publications were ultimately included in the systematic review.[3-36] Study and demographic characteristics are summarized in **Table 1**. The majority of publications were case reports (*n* = 15), followed by case series (*n* = 10), observational studies (*n* = 7), and survey-based studies (*n* = 2). All studies included were rated as Level 4 or 5 Evidence for clinical research.[37] Most studies originated from Europe (Italy, *n* = 10; Spain, *n* = 10; France, *n* = 7; Belgium, *n* = 2), followed by the United States (*n* = 3), the Middle East (Qatar, *n* = 1; Iran, *n* = 1), and Southeast Asia (Thailand, *n* = 1). Patients were identified from dermatology clinics (*n* = 19) and hospitals (*n* = 15). A total of 996 patients with dermatologic symptoms were included in the analysis, of which 54.3% were female and the mean age was 37.3 years (range 1.0 to 98.0).

ID	Study Type	Level of Evidence	Location	Setting	COVID-19 Status (Diagnostic Modality)	Sample Size*	Age (years) & Gender (M/F)	Other Study Notes
ch et	Case report	5	France	Derm clinic	Positive (lab)	1	57 F	---
than et	Case series	4	Qatar	Derm clinic	Positive (lab)	2	27 F, 35 F	---
re et	Case report	5	France	Derm clinic	Positive (lab)	1	39 M	---
iz et al.[4]	Observational retrospective	4	France	Derm clinic	Positive (lab)	14	N/A	---
sson et	Observational retrospective	4	France	Derm clinic	Positive (lab, *n* = 25) Suspected (contact with COVID+ case or symptomatic patient, *n* = 252)	277	2-98 (27 median) 50% M	---
raens et	Case report	5	Spain	Hospital	Positive (lab)	1	48 M	---
i et al.[25]	Case report	5	Iran	Derm clinic	Positive	1	27 M	---
anez et	Case report	5	Spain	Derm clinic	Positive	1	28 F	---
ndez-et al.[16]	Observational retrospective	4	Spain	Derm clinic	Positive (clinical, *n* = 19) Suspected (contact with COVID+ case or healthcare worker, *n* = 82)	132	1-56 (20 mean) 53.8% M	---
ndez-et al.[30]	Observational prospective	4	Spain	Hospital	Positive (lab)	24	19-65 (45 median) 75% F	0% case fatality
n Casas [3]	Survey snapshot	4	Spain	Derm clinic	Positive (lab or clinical)	375	(49 mean) 66.5% F	1.9% case fatality
ese et	Case report	5	Italy	Derm clinic	Positive (lab)	1	8 F	---
tti et	Case series	4	Italy	Hospital	Positive	3	59 F, 89 F, 57 M	---
et al.[12]	Observational prospective	4	France	Homes and hospital	Positive (lab)	5	N/A	4.9% prevalence of skin symptoms in 103 COVID-19 positive patients 0% case fatality
et al.[6]	Case report	5	France	Hospital	Positive (lab)	1	27 F	---
t al.[24]	Case report	5	New York	Hospital	Positive (lab)	1	20 M	---
ez Cauhe [4]	Case report	5	Spain	Hospital	Positive	1	84 F	---
t al.[23]	Case report	5	Thailand	Hospital	Positive (lab)	1	N/A	Patient was originally misdiagnosed with dengue 48 patients were positive for COVID-19 in all of Thailand at

								the time of the study
as et	Case report	5	Belgium	Derm clinic	Positive (lab)	1	23 M	---
et al.[34]	Case series	4	Spain	Derm clinic	Positive (lab, $n = 3$) N/A ($n = 3$)	6	15 M, 15 F, 23 F, 24 F, 44 M, 91 M	---
et al.[5]	Case series	4	New York	Hospital	Positive (lab)	3	32 M, 66 F, 40 F	---
et al.[21]	Case report	5	France	Hospital	Positive (lab)	1	64 F	---
no et	Case series	4	Italy	Hospital	Positive (lab)	22	8-83 (60 median) 72.7% M	13.6% case fatality
an et	Case report	5	New Jersey	Derm clinic	Positive (lab)	1	58 M	---
o et al.[33]	Survey snapshot	4	Italy	Derm and peds clinics	Positive (lab, $n = 4$) Suspected (contact with COVID+ case, $n = 10$) N/A ($n = 49$)	63	12-16 (14 median) 57.4% F	---
ana-neda et	Case report	5	Spain	Derm clinic	Positive (lab)	1	61 M	---
cati[3]	Observational prospective	4	Italy	Hospital	Positive (lab)	18	N/A	20.4% prevalence of skin symptoms in 88 COVID-19 positive patients
cati et	Observational prospective	4	Italy	Derm clinic	Negative (lab, antibody testing not performed)	14	13-39 (17.5 mean) 57.1% F	11 patients were children
eva et	Case series	4	Italy	Hospital	Positive (lab)	3	71 F, 77 F, 72 F	---
aro et	Case series	4	Italy, Spain	Hospital	Positive	3	N/A	---
s-ro et	Case series	4	Spain	Derm clinic	Negative (lab, antibody testing not performed)	2	16 F, 16 M	---
et al.[20]	Case series	4	Italy	Derm clinic	Not tested	4	26 M, 16 F, 18 F, 48 M	Patients not tested due to limited testing capacity but all presented during COVID-19 outbreak
amme et	Case series	4	Belgium	Derm clinic	Positive (lab, $n = 1$; clinical, $n = 1$)	2	71 M, 39 F	1 patient expired 2 weeks after presentation
rini et	Case report	5	Italy	Hospital	Positive (lab)	1	67 F	---

Table 1: Study Characteristics and Patient Demographics

*Sample size denotes number of dermatological patients discussed in the study.

Abbreviations: male (M), female (F), not available (N/A).

The majority of patients (58.2%) had a laboratory-confirmed diagnosis of COVID-19. Exceptions include De Masson et al. (252 out of 277 patients were suspected to have COVID-19 due to extracutaneous symptoms and/or prior contact with a COVID-19 patient), Fernandez-Nieto et al. (82 out of 132 patients were suspected to have COVID-19 due to prior contact with a COVID-19 patient or healthcare worker), Landa et al. (3 out of 6 patients were not tested for COVID-19), Piccolo et al. (59 out of 63 patients were either not tested or had missing information on COVID-19 status), Recalcati et al. (14 out of 14 patients were COVID-19 negative on PCR analysis), Torres-Navarro et al. (2 out of 2 patients were COVID-19 negative on PCR analysis), and Tosti et al. (4 out of 4 patients were not tested for COVID-19).[9, 18, 20, 33-36] These non-laboratory confirmed patients all presented during the COVID-19 outbreak and, for those with a negative COVID-19 PCR result, antibody testing was not available to establish the possibility of prior infection. Case fatality rates ranged from 0.0% to 13.6%.[8, 13, 30] For studies that examined a larger cohort of COVID-19+ patients (both with cutaneous and extracutaneous symptoms), the prevalence of skin symptoms ranged from 4.9-20.4%.[3, 12]

3.2 Characteristics of cutaneous symptoms

Table 2 summarizes the characteristics of the cutaneous symptoms described in the COVID-19 literature. These dermatologic manifestations were then grouped together into categories using common descriptive terminology and photographic evidence. These categories included: erythema multiforme-like eruptions (EME), erythematous maculopapular rashes (EMR), erythematous rashes not otherwise specified (ER-NOS), figurate erythema (FE), vascular rashes within the spectrum of livedo/purpura/necrosis (LPN), pityriasis rosea-like eruptions (PRE), pseudo-chilblains (PC), symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), urticarial rashes (UR), vesicular rashes (VR), and other rashes (OR).

Study ID	Rash Type (*n*)	Rash Location (*n*)	Rash Duration	Associated Cutaneous Symptoms (*n*)	Relation to New Drug Intake	Relation to Onset of Other COVID-19 Symptoms (*n*)	Other Rash Notes
Ahouach et al.[16]	EMR (1)	Trunk and limbs	9 days	Burning	No new drug intake	Before	Perivascular lymphocytic infiltrate on skin biopsy
Alramthan et al.[11]	PC (2)	Dorsal fingers (1) Subungual region (1)	---	---	No new drug intake	Before (2)	---
Amatore et al.[26]	FE (1)	Arms (incl. palms), neck, chest and abdomen	7 days	---	No new drug intake	At onset	Perivascular lymphocytic infiltrate on skin biopsy
Bouaziz et al.[4]	ER-NOS (4) EMR (1) UR (1) VR (2) LPN (3) PC (2) OR (1)	Trunk Limbs Feet	---	---	---	After (14)	OR was an eruptive cherry angioma PC also seen in close contacts of patients (n = 40, contacts did not have confirmatory testing for COVID-19)
De Masson et al.[36]	EMR (25) UR (26) VR (41) LPN (11) PC (142) OR (41)	Trunk and limbs (103) Face (12) Limbs (2) Hands/feet (56)	---	---	---	---	OR included eczematous, angiomatous and annular lesions No relation to cold exposure or comorbidities Perivascular mononuclear infiltrate with vascular microthrombi on skin biopsy
Diaz-Guimaraens et al.[22]	EMR (1)	Buttocks and legs	5 days	Pruritis	No new drug intake	After	Perivascular lymphocytic infiltrate on skin biopsy
Ehsani et al.[25]	PRE (1)	Trunk and arms	---	Pruritis	No new drug intake	After	---
Estebanez et al.[7]	UR (1)	Heels	---	Pruritis	No new drug intake	After	---
Fernandez-Nieto et al.[16]	PC (95) EME (37)	Digits (PC) Hands and feet (EME)	9 days	---	No new drug intake	At onset (3) After (16)	Statistically, PC was associated with greater patient age and EME was associated with more ventrally distributed lesions
Fernandez-Nieto et al.[30]	VR (24)	Head (4) Chest (21) Trunk (14) Arms (8) Legs (10) Palms/soles (2)	10 days	Pruritis (20)	7 patients had prior drug intake	Before (2) At onset (3) After (19)	75% of patients had a diffuse polymorphic rash at various stages of evolution, 25% had a localized monomorphic rash at the

							same stage of evolution 4 patients' lesions were tested and resulted negative for COVID-19 PCR
Galvan Casas et al.[13]	PC (71) VR (34) UR (73) EMR (176) LPN (21)	Hands and feet (PC) Trunk or limbs (VR) Trunk or palms (UR) Limbs (EMR) Trunk or digits (LPN)	6-13 days	Pruritis (213) Pain (32) Burning (22)	Many patients had prior drug intake (unable to ascertain exact *N*)	Before (22) At onset (212) After (139)	More HSV reactivation noted in cohort Some EMR were described as resembling pityriasis rosea or erythema multiforme Statistically, LPN was associated with the greatest patient age and the worst outcomes, followed by EMR, UR, VR, and finally PC
Genovese et al.[28]	VR (1)	Trunk	7 days	---	No new drug intake	After	---
Gianotti et al.[15]	EMR (3)	Trunk (3) Arms (2) Legs (1)	5-10 days	Pruritis (1)	---	Before (1) After (2)	Superficial perivascular dermatitis with small vessel thrombosis on skin biopsy
Hedou et al.[12]	ER-NOS (2) UR (2) OR (1)	Face and arms (3)	2-6 days	Pruritis (5)	---	Before (1) At onset (4)	OR was a reactivation of HSV-1
Henry et al.[6]	EMR (1)	Forehead, hand, foot	---	Pruritis	No new drug intake	Before	---
Hunt et al.[24]	EMR (1)	Trunk and limbs	---	---	---	At onset	---
Jimenez Cauhe et al.[14]	LPN (1)	Axilla	---	Mild pruritis	Had prior drug intake	After	---
Joob et al.[23]	LPN (1)	---	---	---	---	Before	---
Kolivras et al.[32]	PC (1)	Feet and toes	---	Pain	No new drug intake	After	No relation to cold exposure or comorbidities Perivascular lymphocytic infiltrate on skin biopsy
Landa et al.[34]	PC (6)	Toes (5) Soles (1)	---	Mild pruritis (2) Mild pain (3)	---	Before (1) After (5)	No relation to cold exposure or comorbidities
Magro et al.[5]	LPN (3)	Buttocks (1) Chest, arms and legs (1) Palms and soles (1)	---	---	2 patients had prior drug intake	After (3)	Thrombogenic vasculopathy with deposition of C4d and C5b-9 on skin biopsy
Mahe et al.[21]	SDRIFE (1)	Trunk and arms	5 days	---	Had prior drug intake	After	The rash both appeared and disappeared while on new oral drug

Marzano et al.[8]	VR (22)	Trunk (22) Limbs (4)	4-15 days	Mild pruritis (9)	No new drug intake	Before (1) At onset (2) After (16)	7 patients' skin biopsy showed viral infection 6 patients had a diffuse exanthem
Najarian et al.[29]	EMR (1)	Limbs, shoulders, trunk, chest and abdomen	4 days	Pruritis	Had prior drug intake	After	Patient was taking azithromycin when rash developed but had previously taken it without complications
Piccolo et al.[33]	PC (63)	Hands/feet (63)	---	Pruritis (30) Pain (30)	---	After	No relation to cold exposure or comorbidities Two different patterns of lesions were observed: erythematous-edematous and blistering types
Quintana-Castaneda et al.[27]	UR (1)	Limbs	7 days	Mild pruritis	No new drug intake	Before	---
Recalcati[3]	ER-NOS (14) UR (3) VR (1)	Trunk	"A few days"	Minimal pruritis	No new drug intake	At onset (8) After (10)	---
Recalcati et al.[9]	PC (14)	Feet (10) Hands (6)	14-28 days	Minimal pruritis	No new drug intake	Before (11) After (3)	No relation to cold exposure or comorbidities
Sachdeva et al.[31]	EMR (2) VR (1)	Trunk (3) Legs (2) Chest (1)	10 days	Pruritis (2)	1 patient had prior drug intake	At onset (1) After (2)	One of the rashes resembled Grover's disease
Tammaro et al.[10]	VR (3)	Trunk (3)	---	Mild pruritis (3)	---	After (3)	Rash appeared to belong to Herpesviridae family
Torres-Navarro et al.[35]	PC (2)	Fingers	---	---	---	---	---
Tosti et al.[20]	PC (4)	Heels (2) Toes (2)	---	Pain (2) Burning (1) Pruritis (1)	1 patient had prior drug intake	Before (2) After (2)	No relation to cold exposure or comorbidities
Van Damme et al.[17]	UR (2)	Trunk and legs (2)	---	Pruritis (1)	No new drug intake	At onset	---
Zengarini et al.[19]	ER-NOS (1)	Neck and trunk	7 days	Mild pruritis	Had prior drug intake	After	Perivascular lymphocytic infiltrate on skin biopsy

Table 2: Characteristics of Cutaneous Symptoms of COVID-19

Abbreviations: erythematous maculopapular rash (EMR), erythema multiforme-like eruption (EME), erythematous rash not otherwise specified (ER-NOS), figurate erythema (FE), livedo/purpura/necrosis (LPN), pityriasis rosea-like eruption (PRE), pseudo-chilblains (PC), symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), urticarial rash (UR), vesicular rash (VR), other rash (OR).

As seen in **Table 3**, PC was the most common category identified (40.4% of all cases), followed by EMR (21.3%), VR (13.0%), UR (10.9%), OR (4.3%, including 1 eruptive cherry angioma, 1 reactivation of HSV-1, and 41 unspecified cases of eczematous, angiomatous or

annular lesions), LPN (4%), EME (3.7%), and ER-NOS (2.1%). Cutaneous manifestations resembling SDRIFE, PRE and FE were the least common (0.3% combined).

Rash Type	Sample size (*n*, %)	Age (mean years)*	Females* (*n*, %)	Relation to Onset of Other COVID-19 Symptoms**		
				Before (%)	*At Onset (%)*	*After (%)*
PC	402 (40.4)	23.2	211 (54.1)	21 (21.0)	24 (24.0)	55 (55.0)
EMR	212 (21.3)	53.2	115 (55.6)	11 (5.9)	110 (58.8)	66 (35.3)
VR	129 (13.0)	48.3	61 (50.8)	8 (9.5)	24 (28.6)	52 (61.9)
UR	109 (10.9)	38.3	59 (59.0)	5 (6.4)	46 (59.0)	27 (34.6)
OR***	43 (4.3)	45.6	25 (69.4)	0 (0)	1 (50.0)	1 (50.0)
LPN	40 (4.0)	77.5	16 (47.1)	2 (6.9)	18 (62.1)	9 (31.0)
EME	37 (3.7)	12.2	15 (40.5)	---	---	---
ER-NOS	21 (2.1)	67	1 (100)	0 (0)	2 (28.6)	5 (71.4)
SDRIFE	1 (0.1)	64	1 (100)	0 (0)	0 (0)	1 (100)
PRE	1 (0.1)	27	0 (0)	0 (0)	0 (0)	1 (100)
FE	1 (0.1)	39	0 (0)	0 (0)	1 (100)	0 (0)
	Total 996 (100)	*Mean 37.3*	*Total 504 (54.3)*	*Total 47 (9.6)*	*Total 226 (46.1)*	*Total 217 (44.3)*

Table 3: Summary of Rashes by Type, Patient Characteristics and Onset Characteristics

* Studies by Bouaziz, Hedou, Joob, Recalcati and Tammaro excluded because of inability to extract exact data.[4,12,23,3,10]

** Studies by De Masson, Fernandez-Nieto, Piccolo, Recalcati and Torres-Navarro excluded because of inability to extract exact data.[3,16,33,35,36]

** Other rashes included: eruptive cherry angioma ($n = 1$), reactivation of HSV-1 ($n = 1$), and unspecified cases of eczematous, angiomatous or annular lesions ($n = 41$).

Abbreviations: erythematous maculopapular rash (EMR), erythema multiforme-like eruption (EME), erythematous rash not otherwise specified (ER-NOS), figurate erythema (FE), livedo/purpura/necrosis (LPN), pityriasis rosea-like eruption (PRE), pseudo-chilblains (PC), symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), urticarial rash (UR), vesicular rash (VR), other rash (OR).

Mean patient age associated with each dermatologic category was as follows: LPN (77.5 years), ER-NOS (67.0 years), SDRIFE (64.0 years), EMR (53.2 years), VR (48.3 years), OR (45.6 years), FE (39.0 years), UR (38.3 years), PRE (27.0 years), PC (23.2 years) and EME (12.2 years). All rashes had a female predominance except for LPN (52.9% male predominance), EME (59.5% male predominance), PRE (100% male predominance) and FE (100% male predominance).

Although not all studies reported on the mean duration of these cutaneous manifestations, most studies described signs and symptoms that resolved within 2 to15 days. One study reported persistent PC that required 2 to 4 weeks for complete resolution.[9] Of the dermatologic findings that were symptomatic, the majority were pruritic ($n = 295$), followed by painful ($n = 68$) or burning ($n = 24$). Most patients had no new drug intake in the 2 weeks preceding rash onset. Some studies went into more descriptive detail to characterize the skin findings. Fernandez-Nieto et al. observed two different types of VR: a diffuse polymorphic rash at various stages of evolution (observed in 75% of patients) and a localized monomorphic rash at the same stage of evolution (observed in 25% of patients).[30] The single case of a VR reported by Sachdeva et al. was described as resembling Grover's Disease.[31] Piccolo et al. observed two different lesion patterns for PC: erythematous-edematous types and blistering types. A few articles also described skin biopsy findings, which almost uniformly revealed a perivascular mononuclear/lymphocytic infiltrate with occasional small vessel thrombosis.[8, 15, 16, 19, 22, 26, 32, 36] One study in particular revealed a complement-mediated thrombogenic vasculopathy with deposition of C4d and C5b-9 on histopathology.[5]

The association and time relationship between each dermatologic manifestation and the non-cutaneous symptoms of COVID-19 (like fever, cough, shortness of breath, malaise and myalgia) is depicted in **Table 3**. The appearance of most cutaneous findings coincided with the onset of other COVID-19 symptoms (46.1% of all cases). Other rashes appeared shortly after (44.3%) or before (9.6%) the onset of non-cutaneous COVID-19 manifestations. EMR were the most likely to present concurrently with other symptoms (58.8%) compared to before (5.9%) or after (35.3%). UR also frequently coincided with the onset of non-cutaneous symptoms (59.0%) compared to before (6.4%) or after (34.6%). The same trend was observed for LPN, with the majority of cases appearing alongside other COVID-19 symptoms (62.1%) compared to before (6.9%) or after (31.0%). Of the cases reported, ER-NOS presented most frequently after other symptoms of COVID-19 (71.4%) rather than before (0%) or at the same time (28.6%). PC also more commonly appeared after (55.0%) compared to before (21.0%) or at the same time (24.0%) as extracutaneous symptoms. VR were also more likely to present after other symptoms (61.9%) compared to before (9.5%) or at the same time (28.6%).

A breakdown of COVID-19 skin symptoms by location is depicted in **Table 4**. Hands and feet were the most frequently reported site for dermatologic findings (55.1% of cases), followed by a mixed location pattern (26.8%), trunk alone (10.2%), limbs alone (3.3%), face and neck (3.0%), palms and soles (6.0%), chest and abdomen (0.4%).

Rash Location	Sample size* (*n*, %)
Face/Neck	15 (3.0)
Chest/Abdomen	2 (0.4)
Trunk/Back	52 (10.2)
Arms/Legs	17 (3.3)
Hands/Feet	280 (55.1)
Palms/Soles	6 (1.2)
Mixed**	136 (26.8)

Table 4: Summary of Rashes by Location

* Studies by Bouaziz and Galvan Casas excluded because of inability to extract exact data.[4,13]
** Most common mixed pattern was trunk and limbs.

4. Discussion

The repercussions of the SARS-CoV-2 pandemic is substantial, impacting millions of patients medically, financially, and socially. Unfortunately, this highly-virulent pathogen is extremely difficulty to contain given its prolonged asymptomatic latency period and respiratory droplet transmission pattern. Cutaneous manifestations of COVID-19 may help assist in the identification of carriers, enabling health care officials to implement appropriate measures to stem the spread and, if appropriate, provide earlier COVID-19-specific care to these individuals.

Reports of the dermatologic signs and symptoms associated with COVID-19 is mounting in the literature, but these studies have yet to be comprehensively evaluated. This manuscript presents the most current and extensive systematic review of the COVID-19 scientific literature to identify and present the cutaneous manifestations of SARS-CoV-2. Thirty-four studies on 996 dermatologic patients from 8 different countries and 4 different continents were included in this report.

The most commonly reported dermatologic findings included erythema multiforme-like eruptions (EME), erythematous maculopapular rashes (EMR), vascular rashes within the spectrum of livedo/purpura/necrosis (LPN), pseudo-chilblains (PC), urticarial rashes (UR), vesicular rashes (VR), and otherwise unspecified erythematous rashes (ER-NOS). Most of these rashes may be attributable to a COVID-19-specific viral exanthem; however, some dermatologic manifestations may be by-products of the thrombogenic and immune deregulatory effects of SARS-CoV-2, as evidenced by the cutaneous reaction patterns and histopathological findings.[38]

Pseudo-chilblains were the most common type of rash presented in the literature, primarily affecting young adult patients and presenting after the onset of non-cutaneous COVID-19 symptoms. According to Galvan Casas et al., PC were significantly associated with younger aged patients and with a milder disease course. Patients with PC typically required less treatments than those with LPN, EMR, UR and VR skin findings.[13] Of note, these PC lesions were largely unrelated to cold exposure (secondary to social isolation and stay-at-home orders) or a prior history of Raynaud's disease.[9, 20, 32, 33, 34, 36] As such, these cutaneous findings may be categorized as COVID-19-induced pseudo-chilblains rather than primary pernio disease. The majority of PC cases were associated with milder disease, resolving disease, or negative laboratory testing. In one study, PC was found in many close patient contacts.[4] Since this rash affected a large number of patients, it may be useful for detecting individuals more likely to unknowingly transmit the disease. As such, pseudo-chilblains may be most appropriate for epidemiological uses rather than diagnostic applications.

Erythematous maculopapular rashes were the second most common skin manifestation, affecting mostly middle-aged patients and presenting at the same time as other symptoms. Vesicular rashes and urticarial rashes were the next most frequent dermatologic findings. Both rash types affected adults, but VR typically presented after the onset of extracutaneous COVID-19 manifestations while UR occurred simultaneously. UR and EMR eruptions are often drug-induced, which lessens the ability of these cutaneous reactions to serve as a COVID-19 diagnostic marker. Vesicular lesions, however, tend to be more specific to viral exanthemas. As such, VR lesions may be a more useful COVID-19 diagnostic tool. Unfortunately, the VR pattern varies amongst COVID-19 studies, ranging from diffuse polymorphic to localized monomorphic distributions. Further studies evaluating the VR form most strongly associated with COVID-19 is warranted prior to determining the diagnostic utility of this particular cutaneous lesion.

Vascular lesions belonging to the spectrum of livedo/purpura/necrosis, while relatively uncommon, were primarily seen in the elderly at the onset of non-dermatologic COVID-19 symptoms. According to Galvan Casas et al., LPN lesions were significantly correlated with more advanced age and/or severe symptomatology. Unsurprisingly, these vascular rashes were then associated with higher rates of hospital admission and mechanical ventilation compared to EMR, UR, VR and PC.[13] Given their correlation to disease severity, these LPN findings might represent a COVID-19-specific complication in which the virus-induced pro-thrombotic state provokes vascular occlusion and ischemia.[38] Consequently, these rashes may be a useful prognostic marker that can help guide medical management.

Erythema multiforme-like eruptions were infrequent and typically occurred in young patients, particularly children. OR (including one HSV-1 reactivation and one eruptive cherry angioma), EME, PRE and SDRIFE were also rarely observed. As such, these cutaneous manifestations may not be directly correlated to the COVID-19 virus. However, the true incidence of EME and PRE may be under-reported, as some studies grouped many unspecified rashes of annular or angiomatous appearance into the OR category.[36] The frequency of PRE in particular warrants further investigation, as this rash has previously been linked to other viruses. [39]

As with any cutaneous eruption, one must consider that it may have been triggered by a medication. Drugs used to treat COVID-19, such as antimalarials, azithromycin, remdesivir, antiretrovirals, steroids, and biologics, are known to cause acute urticaria, vasculitis and other pruritic lesions. The rashes included in this systematic review that coincided with recent medication intake were determined to be non-drug induced, as most authors reported that, for each questionable patient, the administered drug had either previously been taken without complication or was not known to cause the specific rashes observed. Of note, some COVID-19 patients with previous skin conditions like rosacea, acne, eczema and atopic dermatitis experienced a flare during the course of their disease. [41]

Finally, the case fatality rate reported by the studies included in this analysis ranged from 0.0% to 13.6%. This span encompasses the most recent and accurate estimation of overall COVID-19 mortality rate of 6.8%.[2] As a rapidly evolving situation, COVID-19 peer-reviewed reports are rarely in the form of high-powered, strictly controlled clinical trials. As such, one of the limitations of this study was the inability to collect complete and standardized data sets to allow for in-depth comparisons between rash subgroups. Additionally, not all studies included in this analysis reported on patients with a laboratory-confirmed diagnosis of COVID-19; however, this may also be attributable to the unprecedented turmoil induced by this novel coronavirus, as testing is often limited or inaccessible.

5. Conclusion

A study of 552 hospitals in mainland China initially indicated a 0.2% prevalence of COVID-19 skin symptoms.[40] However, the prevalence suggested by this systematic analysis implies that the true rate is much greater, affecting up to 20.4% of COVID-19 patients. As a potential correlate to disease severity, prognosis, or infectibility, it is critical that all health care professionals be well-versed in these increasingly common cutaneous manifestations of COVID-19. Hand surgeons and podiatrist must be even more aware of these lesions, as they most often appear on the hands and feet. Additional standardized studies of the COVID-19 rashes are warranted to further establish the diagnostic validity and utility of these visible findings.

Declarations

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Availability of data and material: The data that support the findings of the studies referenced in this article are openly available in PubMed and/or PubMed Central.

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Figures

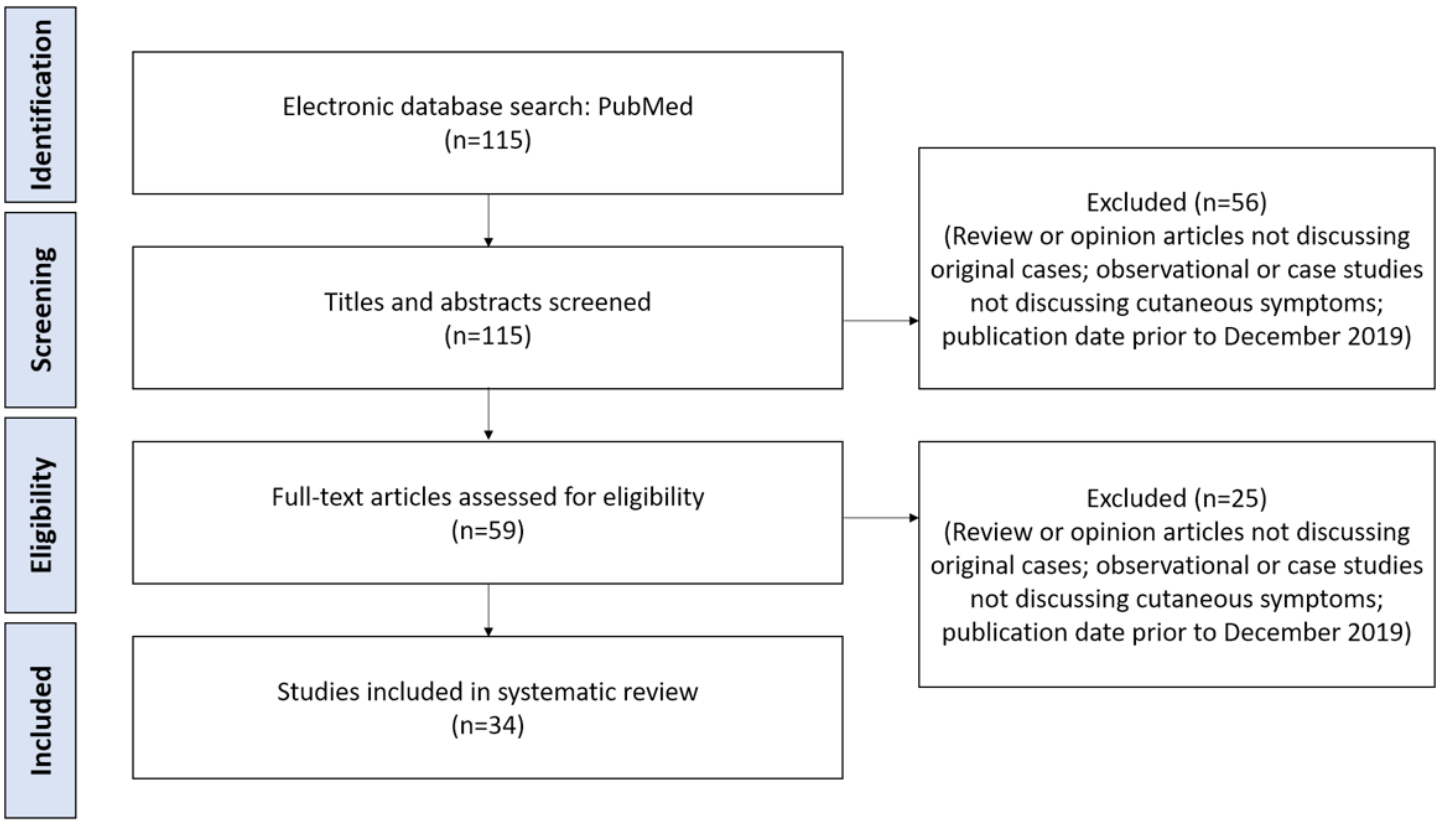

Figure 1

Flow Diagram of the Search Strategy