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Skin manifestations in patients with COVID-19: a prospective observational study during the first wave of the pandemic in the UK and review of the recent literature

Background: COVID-19 (SARS-CoV-2) is a viral infection that presents in heterogeneous forms with effects on multiple organ systems including the skin. *Objectives:* The objectives of this prospective observational study were to identify cutaneous lesions in confirmed COVID-19-positive patients admitted to a district general hospital in the eastern region of England, to determine the prevalence of these lesions and compare the findings with the current literature. *Materials & Methods:* The study was conducted at the Luton and Dunstable University Hospital during the first peak of the pandemic in the United Kingdom to identify skin manifestations in patients infected with COVID-19. Several variables were taken into consideration and photographs of skin lesions were taken. Unlike previous similar studies, all patients included in this study had a positive nasopharyngeal PCR swab for SARS-CoV-2. All photographs were analysed by a dermatology consultant. *Results:* A total of 93 patients were included in the study; 40% ($n = 37$) had cutaneous lesions but only 5.5% of the total patients ($n = 6$) presented with likely coronavirus-related skin changes. Lesions identified were pseudochilblain and purpuric/livedoid type. We also noted several coagulation abnormalities in these patients. *Conclusion:* COVID-19 can present with a variety of skin manifestations. Pseudochilblain lesions and purpuric livedoid lesions have been described in the literature and although the underlying mechanism is not fully understood, it is possible that these lesions represent thromboinflammatory processes as a result of the hypercoagulability state associated with COVID-19. More research is required to better understand the pathophysiology and epidemiology of these manifestations.

Key words: COVID-19, SARS-CoV-2, cutaneous lesions, UK, pseudochilblain and purpuric/livedoid type, coagulation abnormalities

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COVID-19 (Coronavirus Disease 2019) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing millions of deaths worldwide.

The disease was first seen in December 2019 in Wuhan City of Hubei Province of China [1]. In December 2019, the virus spread to Europe [2], in January 2020, the first cases were confirmed in the United Kingdom and in March 2020, it was declared a pandemic by the World Health Organization [3]. In March 2020, the first national lockdown was announced in the United Kingdom and since then several restrictions have been in place. The first peak of the pandemic was observed during April 2020.

SARS-Cov-2 is a single-stranded RNA virus (Betacoronavirus), composed of 16 non-structural proteins (NSP) with specific roles in replication of the virus. NSP3 blocks the innate immune response of the host and promotes cytokine expression. NSP5 inhibits interferon (IFN) signalling and NSP16 is involved in depressing the innate immunity [4]. Aerosolized uptake of SARS-CoV-2 causes infection of target cells that express angiotensin-converting enzyme type 2. Dendritic cells, monocytes and macrophages are the first-line cells against viral infections. The pathogenesis of COVID-19 is not fully understood but is known to be a multifactorial disease, and immunopathogenesis is associated with an uncontrolled immune response. The infection can progress to pneumonia, respiratory failure and death, secondary to extremely elevated inflammatory cytokines. In some patients, the overactive immune response can lead to a cytokine storm with development of macrophage activation syndrome, which frequently causes a fatal outcome [4].

Although COVID-19 primarily affects the respiratory system, it can also cause damage to the nervous, gastrointestinal and renal system. It has also been associated with a hypercoagulability state [5, 6]. Asymptomatic cases have been described with a variety of symptoms such as fever, cough, dyspnoea, anosmia, ageusia and cutaneous lesions, amongst others [7].

Various dermatological signs have been reported, some of which are non-specific. The major skin lesions described

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initially in the literature were: maculopapular eruptions, acral pseudochilblain lesions, urticarial lesions, vesicular lesions and livedo or necrosis. Since then, as knowledge in this area has rapidly evolved, several other cutaneous signs have been reported. It is important for dermatologists to be aware of these skin manifestations [8].

The exact prevalence of the reported cutaneous lesions is not known, but studies show rates that range from 1.8% to 20.4% [9, 10]. A prevalence of 20% was described in a cohort of 88 hospitalized patients in Italy, and the most common skin involvement was diffuse erythematous rash followed by urticaria [10].

The primary objective of our study was to identify skin lesions associated with COVID-19 in patients admitted to the Luton and Dunstable University Hospital during the first wave of the pandemic, to determine their prevalence and compare with the current literature.

Luton and Dunstable University Hospital, now part of the Bedfordshire Hospitals NHS Foundation Trust, provides secondary care services for a population of around 400,000 people within the local catchment area covering Luton, South Bedfordshire and parts of Hertfordshire and Buckinghamshire (CQC report of 2018). Luton is an ethnically and culturally diverse town with approximately 45% of the population from non-white British communities. Within this group, there are significant Pakistani, Bangladeshi, Indian and African Caribbean communities (Luton and Dunstable annual report and account 2019). Luton has also been a region of concern with local outbreaks and a high number of cases of COVID-19.

Methods

Data collection

The study population consisted of patients admitted to the Luton and Dunstable University Hospital with a confirmed positive test for SARS-CoV-2 from the start of March to the end of June 2020, who were noted to have skin signs. Eligible patients were photographed and specific questions regarding their medical history were noted using a dedicated proforma (*see supplementary material*) by the authors of this study and other frontline staff. When possible, these patients were seen face-to-face, but if not possible then all proformas and images were surveyed by the authors of this study. All images were taken with patient consent and stored on the secure IT system, *Nervecentre.* The dates for images were cross-referenced to positive swab dates. The data collected and photographs of the all the skin lesions were then reviewed by the dermatology consultant.

Variables assessed were age, gender, ethnicity, presence of pre-existing skin conditions, comorbidities and other COVID-19 symptoms. Additionally, any recent changes in patient medication and new coagulation-related blood tests were also recorded.

Exclusion criteria

Patients with a negative test, despite clinical, radiological or laboratorial features suggestive of COVID-19, were not included in this study. Any patient with poor-quality photographs was excluded. The paediatric population was not included in this study.

A literature review on papers published up to March 2021 was performed using PubMed.

Results

A total of 93 patients were included in this observational study, from which 40% ($n = 37$) of the patients had cutaneous lesions. From these 37 patients, 31 had a variety of skin lesions, summarized in *table 1,* and only six patients (5.5%) were found to have skin lesions highly likely to be secondary to COVID-19. Five of these patients were Caucasian and one was Asian; 50% were female and 50% were male. Age range varied from 43 to 91 years. All of the patients had skin lesions on their extremities, mainly feet, and two had purpuric lesions on their buttock area (*table 2*).

Patient 1, a 43-year-old male, with a background of psoriasis, obesity, hypertension and Type 2 diabetes, was admitted to critical care for three weeks and required intubation and ventilation. He was found to have several chilblain-like lesions on his toes and some lesions on the palm of the hands and volar surface of fingertips. He also had a bulla on the right great toe. These lesions were seen on the ward post step down from the intensive care unit (ICU). The patient did not recall any similar lesions prior to admission. The lesions were asymmetrical in distribution (*figure 1*). No biopsies were performed. These lesions resolved spontaneously.

The remaining five patients were found to have purpuric heels with some presenting purpuric lesions on their buttock and chilblain-like lesions on their toes (*figures 2-6*). These were inpatients in medical or elderly care wards. Two died with COVID-19 pneumonitis but had several other associated comorbidities. Unfortunately, it was difficult to obtain a clear history to understand the time relationship between the onset of symptoms and cutaneous lesions. We therefore cross referenced the date of the positive swab with the date of photographs for these patients (*table 3*) and this showed good concordance between infection and the presence of cutaneous signs.

We analysed blood tests, such as INR (international normalized ratio), prothrombin time, D-dimers, fibrinogen and platelets, to determine whether there was an associated hypercoagulability state that could contribute to the skin lesions seen. We found that most of these patients had coagulation abnormalities with prolonged prothrombin time and elevated INR, D-dimers and fibrinogen (*table 3*).

Table 1. Other cutaneous lesions found in our patients.

Type of lesion	Number of patients
Pressure ulcer (sacrum)	11
Chronic venous ulcer	7
Chronic arterial ulcer	2
Excoriation	2
Plantar wart	1
Skin lesion secondary to heel osteomyelitis	1
Genital ulcer	1
Venous eczema	2
Other non-specific skin lesions	6

Table 2. Patients with skin lesions likely to be secondary to COVID-19.

	Age	Ethnicity	Gender	Skin Lesion	Other symptoms	Pre-existing skin condition	Other comorbidities
Patient 1	43	Caucasian	Male	Acral chilblain-like lesions	Cough, fever, dyspnoea	Psoriasis	Type 2 diabetes mellitus, hypercholesterolemia, obesity
Patient 2	72	Asian	Male	Purpuric heel	Fever, dyspnoea	Nil	Anaemia, hypertension, cerebrovascular disease, dementia, gastroesophageal reflux, bed-bound
Patient 3	73	Caucasian	Female	Purpuric heel and chilblain-like toe lesion	Fever	Nil	Type 2 diabetes mellitus, hypertension, osteoarthritis, chronic kidney disease, frailty
Patient 4	78	Caucasian	Female	Purpuric heel + buttock area	Cough, fever, dyspnoea	Nil	Anaemia, gastroesophageal reflux, bed-bound
Patient 5	86	Caucasian	Female	Purpuric heel	Cough, dyspnoea	Nil	Atrial fibrillation, hypertension
Patient 6	91	Caucasian	Male	Purpuric heel + buttock lesions	Cough, dyspnoea	Nil	Hypertension, postural hypotension, anaemia, chronic back pain

Figure 1. A, **B**) Patient 1.

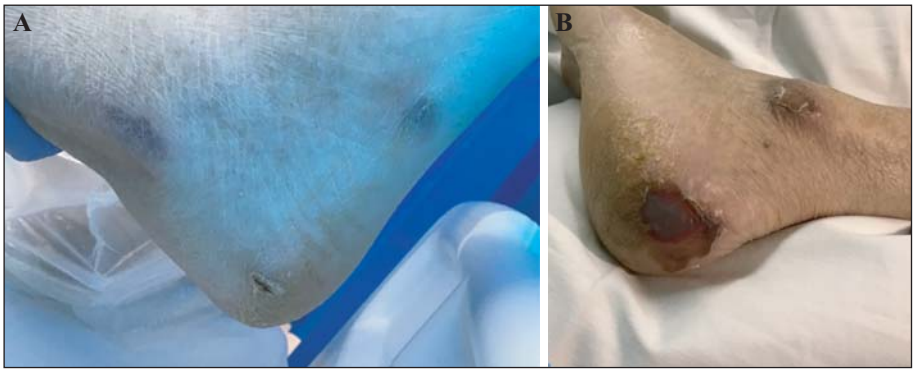

Figure 2. A, **B**) Patient 2.

Discussion

SARS-CoV-2 is a single-stranded RNA virus that enters the human cell via aerosol particles and then binds to the functional receptor of the angiotensin-converting enzyme type II (ACE2) present in target cells, such as alveolar cell type 2 (that produce lung surfactant). This then induces angiotensin II accumulation, which contributes to acute lung injury, diffuse endothelial inflammation and vessel dysfunction [11]. Angiotensin-converting enzyme type II is also present in the basal layer of the epidermis, in the endothelial cells of the dermal blood vessels and the eccrine adnexal tissue [1]. Besides ACE2, the virus must be primed by transmembrane protease serine 2 (TMPRSS2) to complete entry into the human endothelial cell [4, 5].

According to some studies, SARS-CoV-2 may directly infect T cell lymphocytes, and in a subset of patients cause an exaggerated activation of the immune response ("cytokine storm") with release of several proinflammatory

Figure 3. Patient 3.

cytokines, in particular IL-6. These cytokines can migrate to the skin and stimulate dendritic cells, macrophages, mast cells, lymphocytes and neutrophils [1]. The cytokine storm can cause damage to the endothelium, formation of multiple thromboses in the microvasculature of the skin, changes in the cellular component of the immune system and activation of the complement system [4].

As the awareness of the relationship between COVID-19 and skin lesions has improved through the course of the pandemic, there have been increasing reports on this subject. Coronavirus-related cutaneous manifestations are diverse and non-specific and may resolve spontaneously [1]. Different attempts have been made to classify these lesions.

In April 2020, in the first report of its type, five main patterns of skin involvement in confirmed and suspected COVID-19 patients were described in a rapid prospective nationwide study in Spain involving 375 cases. These were: (1) acral areas of erythema with vesicles or pustules–pseudochilblain; (2) other vesicular eruptions; (3) urticarial lesions; (4) maculopapular eruptions; and (5) livedo or necrosis. Each pattern was associated with different demographics and severities. Maculo-papular lesions seemed to be the most frequent [12]. Overall, pernio-like lesions were seen in younger patients and later during the course of the disease, presenting after the onset of respiratory symptoms, while the remaining patterns presented sooner and in more elderly age groups [12].

In our study, 5.5% of the patients presented with COVID-19-related skin changes.

None of the skin changes seen in our patients were typical of adverse drug reactions.

Our results show that a total of six patients presented with pernio/chilblain-like lesions (COVID toes) and purpuric lesions. These lesions were localised on extremities (hands and mainly feet) and the buttock area.

Five patients, who were significantly older, presented with mainly purpuric/livedoid lesions, which were likely present early during the course of the disease and/or simultaneously. Two of these five patients ultimately died with pneumonia, but also had multiple comorbidities.

Only one patient had severe disease requiring ITU admission and intubation for mechanical ventilation. This gentleman had acral psudochilblain lesions on the distal aspect of his toes and fingers. These lesions were probably a late presentation in the course of the disease. These types of lesions have been widely described as "COVID toes" in inpatients but also in non-hospitalised patients [18].

In May 2020, a case-series study identified patients with pernio-like skin lesions and COVID-19 as generally young, with little comorbidity and with a benign course. In their study, most patients with pseudochilblains were white in ethnicity, with lesions mainly on their feet, and only a small number were hospitalised patients [19]. Since then, several similar findings have been published [15]. Most cases in the literature were associated with a benign course, however, a few cases of pseudochilblain lesions in more severe patients, like ours, have been described. *Table 4* compares the findings of our study with those from the literature.

Histology from acral chilblain type lesions shows diffuse a dense lymphoid infiltrate of the superficial and deep dermis and hypodermis with a prevalent perivascular pattern

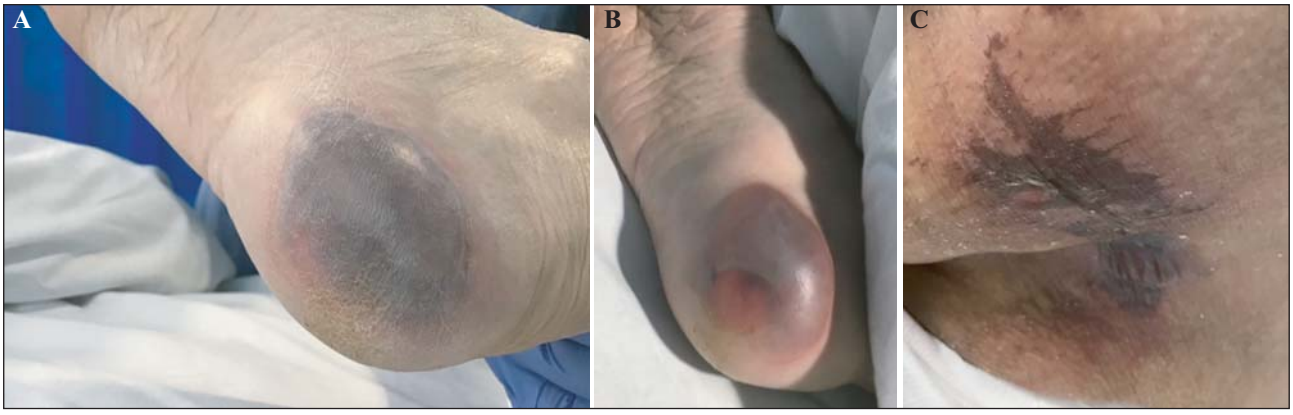

Figure 4. **A**-**C**) Patient 4.

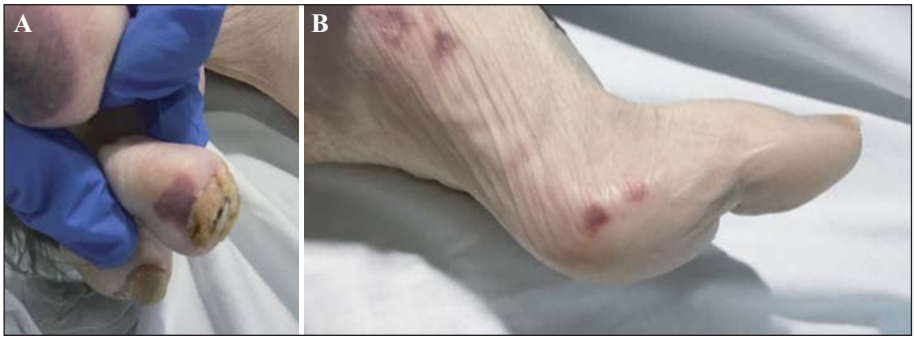

Figure 6. **A**, **B**) Patient 6.

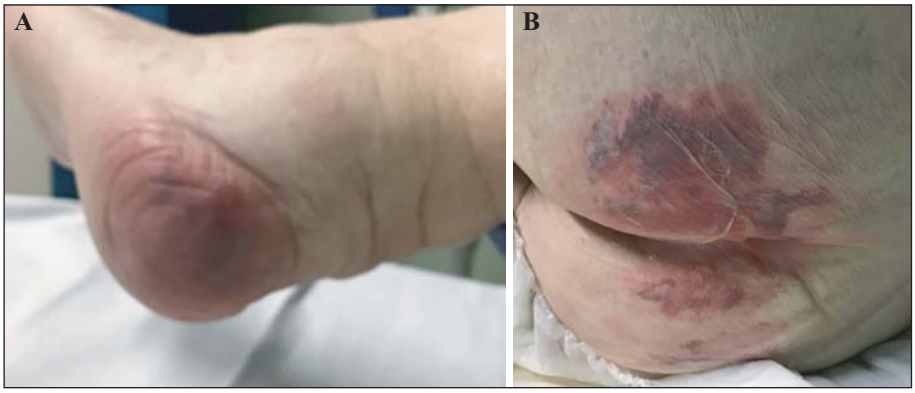

Figure 5. **A**, **B**) Patient 5.

and signs of endothelial activation. Purpuric and livedoid lesions are likely due to thrombogenic vasculopathy associated with extensive deposition of C5b-9 and C4d within the microvasculature [1]. In both lesions, there is obliterative microangiopathy which in combination with increased vascular permeability, could contribute to occlusion of the vascular lumen and haemorrhage [1]. Given that these patients have several coagulation abnormalities, it is likely that these acral lesions and livedoid eruptions simply represent coagulation disorder secondary to systemic effects of the virus and not a direct lesion caused by SARS-CoV-2 [1, 12, 18, 19]. Hypercoagulation may also play an important role in the mortality associated with this viral infection [3]. All our patients in this study presented with coagulation abnormalities.

It has been considered that pseudochilblain-like lesions may be useful as predictors of prognosis given that they have been associated with less severe disease compared with the other skin patterns [12]. Equally, livedoid eruptions could result from systemic thrombotic vasculopathy, initially described to be associated with more severe disease. Therefore, early recognition of these lesions could also have prognostic value [3, 12, 20].

Another fact in favour of these pseudochilblain lesions being linked with COVID-19 is that these lesions were seen in higher numbers during spring, which is an unusual presentation for chilblains [12]. Pernio (chilblain) is a superficial inflammatory vascular response that usually occurs on acral skin after exposure to cold, and is therefore more frequent during winter [19].

Pernio-like skin changes on the hands and feet, without any explanation, are suggestive of COVID-19 infection and therefore patients presenting with these lesions should receive a nasopharyngeal viral PCR swab. Some authors have even proposed consideration of pernio-like lesions as a criterion for COVID-19 [19].

In July 2020, a review article based on a literature search from various databases subdivided the existing cutaneous lesions related to COVID-19 into six different patterns which could be subsequently merged into two main groups: inflammatory/exanthematous and vasculopathic/vasculitic (*table 5*) [13]. The final version of this review was later published in September 2020 in the *British Journal of Dermatology*.

A German review, published in July 2020, classified skin manifestations related to COVID-19 into two groups: I. Skin changes indicating infectious disease (not specific to COVID-19) and II (*table 6*), Skin changes possibly indicating COVID-19. The second group of lesions is likely to be associated with thrombovascular events with endothelial involvement and microangiopathy. The authors also identified less frequent skin changes that cannot be categorized in the previous two groups, such as dengue-like rash with petechia or cherry angiomas and Kawasaki syndrome, predominantly observed in children [14].

An evidence-based review, published in August 2020 in the *American Journal of Clinical Dermatology*, concluded that vesicular rashes may suggest an initial diagnosis of COVID-19, acral lesions could be useful for epidemiological studies, and vascular rashes could be a useful prognostic marker for severe disease. In their review, pseudochilblain lesions were the most frequent type of cutaneous manifestation appearing in young adults after the onset of extracutaneous COVID-19 symptoms.

Table 3. Cross reference between date of positive swab and photograph of lesion and relevant blood tests on and during admission.

	Age	Skin lesion	Date of positive swab	Date of photograph	Bloods	Platelets (150-450)	INR (0.8-1.2)	Prothrombin time (9.0-14.0)	Lymphocytes (1.0-3.0)	D-dimers <250	Fibrinogen (2.2-5.0)	Ferritin (30-400)
Patient 1	**43**	**Foot and hand chilblain-like lesions**	07/04/20	01/05/20	**On admission**	292	1.0	12.7	1.5	153	-	**1030**
					During admission	**532**	1.2	**14.5**	**0.81**	**586**	-	-
Patient 2	**72**	**Purpuric heel**	04/05/20	06/05/20	**On admission**	324	1.1	13.9	1.35	657	8.47	696
					During admission	-	-	**15.1**	-	-	-	-
Patient 3	**73**	**Purpuric heel and toe**	28/04/20	25/04/20	**On admission**	241	1.0	12.5	**0.54**	-	-	-
					During admission	-	-	-	-	-	-	-
Patient 4	**78**	**Purpuric heel + buttock area**	05/05/20	05/05/20	**On admission**	433	1.1	11.6	**0.68**	**559**	**8.80**	**2073**
					During admission	-	-	**15.8**	**0.42**	**439**	**9.70**	**2659**
Patient 5	**86**	**Purpuric heel**	20/04/20	21/04/20	**On admission**	251	1.2	0.51	-	-	-	-
					During admission	-	-	-	-	-	-	-
Patient 6	**91**	**Purpuric heel + buttock area**	18/05/20	10/05/20	**On admission**	**406**	**1.9**	**24.9**	**0.93**	**999**	3.20	**550**
					During admission	-	-	-	-	-	-	-

Table 4. Comparison of our findings with those from the current literature.

	Type of lesion	Location of lesion	Time of onset of lesion	Month	Age	Ethnicity	Severity	Reported in the literature	Differences in the literature
Patient 1	Pseudochilblain	Hand, feet	Lesions seen several days post positive swab	April/May	43	White	ITU admission with severe hypoxia	-Late in the evolution of disease [7, 12, 19] -Location of lesions: hand and feet [12, 19] -Usually young patients [12, 19, 20] -Occur in spring [11, 12, 19] -High mortality* [3]	Less severe disease* (12, 19)
Patient 5	Purpuric livedoid-like lesions	Feet (heel)	Overlap between positive swab date and photograph of cutaneous lesions	April/May	72	Asian	Mild symptoms	-Appear at similar time to other symptoms [12] -Locations of lesion: trunk and acral areas [12, 20] -Older patients [12] -Severe disease [12, 18]	The two patients who died with COVID-19 pneumonitis also had multiple comorbidities
Patient 6	Purpuric livedoid-like lesions + pseudochilblain-like lesions	Feet (heel), chilblain-like lesion on the toe			73	White	Mild symptoms		
Patient 4	Purpuric livedoid-like lesions	Feet (heel)			78	White	Death, COVID, pneumonia		
Patient 2	Purpuric livedoid-like lesions	Feet (heel)			86	white	Mild symptoms		
Patient 3	Purpuric livedoid-like lesions	Buttock, feet (heel)			91	White	Death, COVID, pneumonia		

**Most cases seen in the literature were associated with a benign course, however, a few cases of pseudochilblain lesions in more severe patients have been described.*

Table 5. Classification of cutaneous lesions related to COVID-19 into six patterns.

Inflammatory/exanthematous	Urticarial rash Confluent erythematous/ maculopapular/morbilliform rash Papulovesicular exanthema
Vasculopathic/vasculitic	Chilblain-like acral pattern Livedo reticularis/racemose-like pattern Purpuric vasculitic pattern

Table 6. Classification of cutaneous lesions related to COVID-19 into 2 groups.

Skin lesions indicating infectious disease	Maculopapular rash Urticaria Erythema multiforme
Skin changes possibly indicating COVID-19	Varicella-like exanthema Livedo reticularis Chilblain-like lesions

Maculopapular rashes affected middle-aged people and appeared simultaneously to non-cutaneous COVID-19 symptoms. Vesicular lesions were seen more frequently in middle-aged people and occurred at the same time as other COVID-19 symptoms. Vascular rashes (livedo or purpura type) were uncommon and appeared mostly in elderly people and simultaneously to other COVID-19 symptoms. Children presented more with erythema multiform-like eruptions, although these were infrequent [15].

More recently, in September 2020, an abstract on a case series from the Kings College Hospital NHS Foundation Trust published in a supplement of the *British Journal of Dermatology*, suggested the addition of three new types of cutaneous manifestations related to COVID-19 to the literature: panniculitis, eccrine squamous syringometaplasia and digital vein thrombosis [16].

In September 2020, The British Association of Dermatologists and the COVID Symptom Study App launched a COVID rash gallery with the objective of sharing images of COVID-19-related skin rash (www.covidskinsingns.com). These photographs were collected via the COVID-Symptom Study App in March 2020. In total, 3,195 images were uploaded, from which 400 were selected and are available to view by doctors and the general public worldwide to help identify whether an unusual rash could be related to COVID-19. Several patterns have been identified, such as: papular and vesicular, viral exanthema-like rash, oral lesions, pityriasis rosea, purpuric lesions, COVID digits, urticarial rash and eczematous eruptions of the neck and exposed areas.

In December 2020, another worldwide review on skin manifestations of COVID-19 from Singapore was published online and identified five common skin lesions: pseudochilblains, rashes with macules and papules, and urticarial, vesicular and vaso-occlusive lesions (livedo, retiform purpura and acral ischaemia). They noted that the prevalence of COVID-19-related skin lesions differed globally as did the morphology of skin manifestations. Pseudochilblain lesions were the most common lesions seen in Europe and The United States, but only one case was reported in Asia. Pseudochilblains were seen with less frequency in the African American population and no cases were reported in China. It is possible that genetic factors play a role in the development of these skin signs. These lesions were found to appear later during the course of the disease with indolent disease progression, as mentioned in previous reviews. Vaso-occlusive lesions were the least frequently reported signs, however, associated with less favourable outcomes. These lesions were linked to elevated D-dimers and disseminated intravascular coagulopathy. The prevalence of these lesions also varied between different ethnicities (less common in India) which could be due to different genetic thrombophilia-related factors [17].

We acknowledge some limitations in our study. The temporal relationship between skin lesions and the onset of respiratory symptoms was difficult to establish due to the difficulty in obtaining an accurate clinical history. Also, our sample consisted mainly of elderly patients and hence the data are not representative of the general population. Finally, data were collected by different observers and this could have introduced bias. Given that the project was performed during the peak of the pandemic, most of the staff, including dermatologists, were deployed to medical services, hence it was not possible to perform biopsies on these skin lesions. Despite the above challenges, our study included a large sample size over a relatively long period with laboratory confirmation for all patients, in contrast to some of the previous publications, and all photographs of skin signs were analysed by a dermatology consultant.

Conclusion

The results from of our observational study align with what is currently published. Pseudochilblain lesions and purpuric livedoid lesions have been described in the literature and although the underlying mechanisms are not fully understood, it is likely that they represent consequences of coagulation abnormalities and a hypercoagulability state associated with this disease. ■

Disclosures. *Conflicts of interests: none.*
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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1684/ejd.2022.4202.

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