Received: 25 April 2021 | Accepted: 8 August 2021

DOI: 10.1111/ijcp.14720

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE WILEY

SYSTEMATIC REVIEW

Dermatology

Severe and life-threatening COVID-19-related mucocutaneous eruptions: A systematic review

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Funding information
None.

Abstract

Objectives: Earlier diagnosis and the best management of virus-related, drug-related or mixed severe potentially life-threatening mucocutaneous reactions of COVID-19 patients are of great concern. These patients, especially hospitalised cases, are usually in a complicated situation (because of multi-organ failures), which makes their management more challenging. In such consultant cases, achieving by the definite beneficial management strategies that therapeutically address all concurrent comorbidities are really hard to reach or even frequently impossible.

Methods: According to the lack of any relevant systematic review, we thoroughly searched the databases until 5 October 2020 and finally found 57 articles including 93 patients. It is needed to know clinical presentations of these severe skin eruptions, signs and symptoms of COVID in these patients, time of skin rash appearance, classifying drug-related or virus-related skin lesions, classifying the type of skin rash, patients' outcome and concurrent both COVID-19 therapy and skin rash treatment.

Result: Severe and potential life-threatening mucocutaneous dermatologic manifestations of COVID-19 usually may be divided into three major categories: virus-associated, drug-associated, and those with uncertainty about the exact origin. Angioedema, vascular lesions, toxic shock syndrome, erythroderma, DRESS, haemorrhagic bulla, AGEP, EM, SJS and TEN, generalised pustular figurate erythema were the main entities found as severe dermatologic reactions in all categories.

Conclusion: We can conclude vascular injuries may be the most common cause of severe dermatologic manifestations of COVID-19, which is concordant with many proposed hypercoagulation tendencies and systemic inflammatory response syndrome as one of the most important pathomechanisms of COVID-19 so the skin may show these features in various presentations and degrees.

1 | INTRODUCTION

1.1 | Rationale

In December 2019, the pandemic of novel coronavirus was reported in Wuhan province of China.[1]COVID-19 is a single-stranded RNA virus related to betacoronavirus genus, it is in the Orthocoronavirinae subfamily which is common between acute respiratory syndrome-associated coronavirus (SARS-CoV) and the Middle East respiratory syndrome-associated coronavirus (MERS-CoV) leading to previous epidemics or pandemics of severe and fatal coronavirus diseases in 2002 and 2012.[1,2]

Farzaneh Mashayekhi and Farnoosh Seirafianpour equally contributed in preparing this article.

The Virus attaches to the angiotensin-converting enzyme 2 (ACE2) receptor which is located in the cell membrane of the lungs, heart, kidney and arteries, and then enters the host cells.[3]According to recent studies, both aerosols and droplets are modes of coronavirus disease transmission.[4] Clinical manifestation of COVID-19 is varied from flu-like syndrome and mild upper respiratory tract infection to acute respiratory distress syndrome and death.[5] Respiratory tract sampling by real-time PCR is a gold standard diagnostic method.[1]

Besides the multi-systems involvement in COVID-19 diseases, dermatological manifestations have been poorly delineated.[2] In one study, 20% of the patients have skin presentation, and skin rash was the initial manifestation of COVID-19 in 44% of them.[6]

Skin manifestations are divided into four groups: (a) virus-related skin lesion, (b) skin reaction because of protective equipment and hand sanitiser, (c) adverse drug reaction of therapies for COVID-19, (d) primary skin diseases which are affected by virus or its therapies.[3] The skin manifestations are diverse, such as urticarial, livedoid eruptions, purpuric eruptions, livedoid vasculopathy, varicella-like vesicles, photo-contact dermatitis, generalised pustular figurate erythema, lichenoid photodermatitis and erythroderma.[3] Recently, Some COVID-19 studies reported severe and life-threatening cutaneous drug reactions such as AGEP and DRESS.[7,8] Widespread use of drugs such as hydroxychloroquine in treatment and prophylaxis of COVID-19, was associated with increased drug-induced skin reactions such as AGEP and erythema multiforme.[7]

Despite drug-induced severe mucocutaneous skin reactions, vasculitis and vasculopathy lesions because of endothelial damage with COVID-19 in clinically ill patients have been reported that should be considered as a severe form of skin lesions.[9]

Several numbers of life-threatening mucocutaneous reactions are[10-16]:

1. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)
2. Acute generalised exanthematous pustulosis (AGEP)
3. Drug reaction with eosinophilia and systemic symptoms (DRESS)
4. Generalised fixed drug eruption
5. Major erythema multiform and mucosal involvement
6. Generalised urticaria, with angioedema, and anaphylaxis
7. Purpurafulminans
8. Toxic shock syndrome (TSS)
9. Hypersensitivity vasculitis (HV)
10. Leucocytoclastic vasculitis
11. Generalised vasculitis
12. Vasculopathic lesion
13. Any erythrodermic skin reactions.

The mortality rate is varied from less than 5% to higher than 14.8%.[17,18]

Severe skin reactions are potentially life-threatening, and delayed diagnosis is associated with high mortality rates and internal organ damage which has permanent sequelae in patients. Earlier diagnosis is even more important for proper medical management of COVID-19 patients with severe mucocutaneous reactions; since these patients especially hospitalised ones are usually in a complicated situation (because of multi-organ failures), management of any potential life-threatening reactions is more challenging. In these challenging cases, make a definite beneficial managing decision—therapeutically addresses all concurrent comorbidities (COVID-19 and its systemic consequences) and the emerging concomitant severe and potential life-threatening dermatologic reactions (virus or drug-related)—is hard to approach, in addition to some further proposed controversies.

Review criteria

- This systematic review was conducted using four databases to evaluate clinical presentations of severe potential life-threatening skin eruptions, primary symptoms of COVID-19, time of skin rash appearance, categorised drug-related or virus-related skin lesions, classifying type of skin rash, patients' outcome and handling of both COVID-19 therapy and skin rash treatment.
- The systematic review adheres to the PRISMA guideline. The data extraction was performed by two independent reviewers.

Message for the clinic

- In the pandemic logically we may encounter severe and potentially life-threatening mucocutaneous dermatologic reactions mainly because of viremia, virus-host interaction-induced cytokine storms, and the consequences also probable drug reactions.
- In these cases, we should approach 3 major categories: virus-associated, drug-associated and those with uncertainty about the exact origin.
- Based on this study, angioedema, vascular lesions, toxic shock syndrome, erythroderma, DRESS, haemorrhagic bulla, AGEP, EM, SJS and TEN, Generalised pustular figurate erythema were the main entities found as severe dermatologic reactions in all categories.

2 | OBJECTIVES

According to the lack of relevant systematic review, there is an obvious requirement for diagnosing, assessing, and treatment in the case of severe and life-threatening mucocutaneous reactions; so the purpose of this study was to systematically review the literature on clinical presentations of severe potential life-threatening skin eruptions, primary symptoms of COVID-19, time of skin rash appearance, categorised drug-related or virus related skin lesions, classifying type of skin rash, patients' outcome and handling both COVID-19

therapy and skin rash treatment. To our best knowledge, this is the first systematic review to address this important topic and may have really practical points for specialists (dermatologists and first-line physicians manage these patients).

3 | METHOD

3.1 | Protocol and registration

This study is implemented according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. The PRISMA flow chart is shown in Figure 1.

3.2 | Information sources

A search was carried out in Medline (PubMed) (http://ncbi.nlm.nih.gov/pubmed), Scopus (http://www.scopus.com), Embase (http://embase.com) and Google Scholar (https://scholar.google.com) for articles published until 5 October 2020. Other searched sources were Cochrane (https://www.cochranelibrary.com/), WHO (http://www.who.int/emergencies/diseases/novel-coronavirus-2019), Medscape and CEBD coronavirus dermatology resource of Nottingham University (https://www.nottingham.ac.uk/).

3.3 | Search strategy

The search strategy for databases is shown in Figure 2 in the supplement file. It should be noted that all articles resulting from this search in PubMed, Scopus, and Embase were included, but in Google Scholar, only the 100 newest articles were selected from a total of 2289 articles. The search was not limiting the entries to any condition. The search was performed by keywords COVID-19 and alternative names have been called, and all the severe skin manifestations such as Stevens-Johnson syndrome, erythema multiforme major, toxic epidermal necrolysis, toxic shock syndrome, acute generalised exanthematous pustulosis, dress syndrome, angioedema, serum sickness, and their synonyms separately. The search was completed on 5 October 2020; and all related articles were included.

3.4 | Eligibility criteria

Inclusion criteria comprised all studies about COVID-19 virus-related or drug-related severe or life-threatening cutaneous manifestations of cutaneous involvements in this global pandemic.

The exclusion criteria consisted of all publications not meeting the above, studies not mentioning skin manifestations of COVID-19 or mild skin manifestations in the n-cov2019 pandemic, animal studies, in-vitro studies, and review articles.

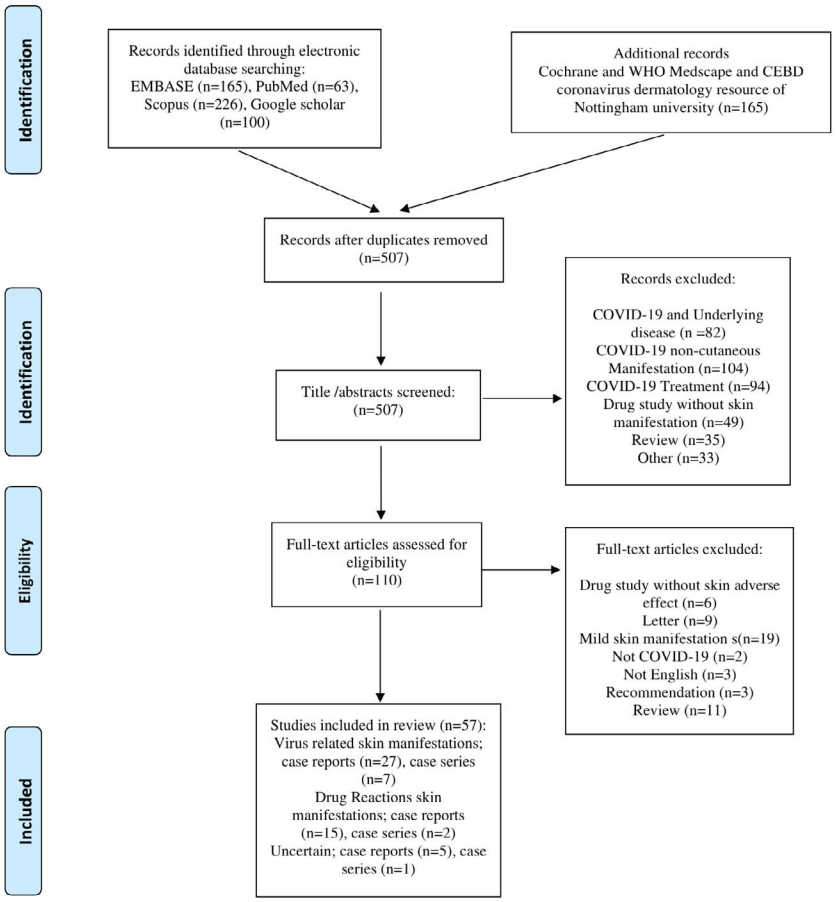

FIGURE 1 Severe COVID-19 skin manifestation PRISMA chart

Databases	Search sentences
Pubmed	(("coronavirus disease 2019" OR "covid-19") AND ("stevens johnson" OR "erythema multiforme major" OR "stevens-johnson" OR "toxic epidermal necrolysis" OR "bullous epidermolysis" OR "epidermal necrolysis" OR "toxic shock syndrome" OR "staphylococcal scalded skin syndrome" OR "fixed drug eruption" OR "acute generalized exanthematous pustulosis" OR "agep" OR "fulminating purpura" OR "purpura fulminans" OR "vascular lesion" OR "dress syndrome" OR "hypersensitivity syndrome" OR "angioedema" OR "giant urticaria" OR"urticaria edematosa" OR "serum sickness"))
Embase	('coronavirus disease 2019'/exp OR '2019-ncov disease' OR '2019-ncov infection' OR 'covid 19' OR 'covid 2019' OR 'wuhan coronavirus disease' OR 'wuhan coronavirus infection' OR 'coronavirus disease 2019' OR 'ncov 2019 disease' OR 'ncov 2019 infection' OR 'novel coronavirus 2019 disease' OR 'novel coronavirus 2019 infection' OR 'novel coronavirus infection 2019') AND ('stevens johnson syndrome'/exp OR 'stevens johnson syndrome' OR 'ectodermosis erosiva pluriorificialis' OR 'ectodermosis pluriorificialis' OR 'erythema exudativum multiforme major' OR 'erythema multiforme major' OR 'pluriorificial erosive ectodermosis' OR 'rendu fiessinger syndrome' OR 'steven johnson syndrome' OR 'stevens johnson disease' OR 'stevens johnson multiorificial syndrome' OR 'stevens-johnson syndrome' OR 'syndrome stevens johnson' OR 'toxic epidermal ecrolysis'/exp OR 'lyell syndrome' OR 'allergodermia, combustiform' OR 'bullous epidermolysis, toxic' OR 'combustiform allergodermia' OR 'epidermal necrolysis, toxic' OR 'epidermolysis bullosa toxica' OR 'epidermolysis toxica combustiformis' OR 'epidermolysis, acute toxic' OR 'lyell disease' OR 'necrolysis, toxic epidermal' OR 'scalded skin syndrome' OR 'syndrome, scalded skin' OR 'toxic bullous epidermolysis' OR 'toxic epidermal necrolysis' OR 'toxic epidermal neurolysis' OR 'toxic epidermis necrolysis' OR 'toxic epidermis neurolysis' OR 'toxic epidermolysis' OR 'toxic shock syndrome'/exp OR 'toxic shock syndrome' OR 'staphylococcal scalded skin syndrome'/exp OR 'exfoliative dermatitis, newborn' OR 'newborn exfoliative dermatitis' OR 'ritter disease' OR 'staphylococcal scalded skin syndrome' OR 'pemphigus vulgaris'/exp OR 'benign mucosal pemphigus' OR 'benign mucous membrane pemphigus' OR 'benign pemphigus' OR 'chronic pemphigus' OR 'pemphigus vulgaris' OR 'erythema multiforme'/exp OR 'hebra disease' OR 'erythema exsudativum multiforme' OR 'erythema exudativum multiforme' OR 'erythema multiforma' OR 'erythema multiforme' OR 'erythema multiforme exsudativum' OR 'erythema multiforme exudativum' OR 'erythema, multiform' OR 'multiform erythema' OR 'fixed drug eruption/exp OR 'fixed drug eruption' OR 'fixed drug eruptions' OR 'fixed eruption' OR 'fixed eruptions' OR 'acute generalized exanthematous pustulosis /exp OR 'agep' OR 'acute generalised exanthematic pustulosis' OR 'acute generalised exanthematous pustulosis' OR 'acute generalized exanthematic pustulosis' OR 'acute generalized exanthematous pustulosis' OR 'fulminating purpura'/exp OR 'fulminating purpura' OR 'purpura fulminans' OR 'vascular lesion'/exp OR 'lesion, vascular' OR 'skin lesion, vascular! OR 'vascular lesion' OR 'vascular skin lesion' OR 'dress syndrome'/exp OR 'dress syndrome! OR 'allopurinol hypersensitivity syndrome' OR 'anticonvulsant hypersensitivity syndrome! OR 'dapsone hypersensitivity syndrome' OR 'drug hypersensitivity syndrome' OR 'drug induced hypersensitivity syndrome' OR 'drug rash with eosinophilia and systemic symptom' OR 'drug rash with eosinophilia and systemic symptoms' OR 'drug rash with eosinophilia and systemic symptoms syndrome' OR 'drug reaction with eosinophilia and systemic symptoms syndrome' OR 'hypersensitivity syndrome' OR 'generalized bullous fixed drug eruption /exp OR 'angioneurotic edema'/exp OR 'quincke edema' OR 'quincke oedema' OR 'acute circumscribed edema' OR 'acute circumscribed oedema' OR 'acute essential edema' OR 'acute essential oedema' OR 'angio oedema' OR 'angio-oedema' OR 'angioedema' OR 'angioneurotic edema' OR 'angioneurotic oedema' OR 'angioneurotic swelling' OR 'angioneurotic syndrome' OR 'angiooedema' OR 'angiooedema, hereditary' OR 'angiooedemas, hereditary' OR 'edema, angioneurotic' OR 'edema, quincke' OR 'giant urtica' OR 'giant urticaria' OR 'oedema, angioneurotic' OR 'oedema, quincke' OR 'urtica gigantea' OR 'urticaria edematosa' OR 'urticaria oedematosa' OR 'wandering edema' OR 'wandering oedema' OR 'serum sickness'/exp OR 'plasma sensitivity' OR 'serum disease' OR 'serum sickness' OR 'leukocytoclastic vasculitis'/exp OR 'gougerot ruiter syndrome' OR 'allergic angiitis' OR 'allergic arteriolitis' OR 'allergic skin vasculitis' OR 'allergic vasculitis' OR 'angiitis, hypersensitivity' OR 'angiitis, leukocytoclastic' OR 'arteriolitis allergica' OR 'arteriolitis allergica cutis' OR 'haemorrhagic vasculitis' OR 'hemorrhagic vasculitis' OR 'hyperergic vasculitis' OR 'hypersensitivity angiitis' OR 'hypersensitivity vasculitis' OR 'leukoclastic vasculitis' OR 'leukocytoclastic angiitis' OR 'leukocytoclastic vasculitis' OR 'vasculitis allergica' OR 'vasculitis allergic cutis' OR 'vasculitis allergica cutis superficialis' OR 'vasculitis, allergic cutaneous' OR 'vasculitis, hypersensitivity' OR 'vasculitis, leukoclastic' OR 'vasculitis, leukocytoclastic' OR 'vasculitis, leukocytoclastic, cutaneous')
Scopus	((coronavirus disease 2019" OR "covid-19") AND ("stevens johnson" OR "erythema multiforme major" OR "stevens-johnson" OR "toxic epidermal necrolysis" OR "bullous epidermolysis" OR "epidermal necrolysis" OR "toxic shock syndrome" OR "staphylococcal scalded skin syndrome" OR "fixed drug eruption" OR "acute generalized exanthematous pustulosis" OR "agep" OR "fulminating purpura" OR "purpura fulminans" OR "vascular lesion" OR "dress syndrome" OR "hypersensitivity syndrome" OR "angioedema" OR "giant urticaria" OR "urticaria edematosa" OR "serum sickness"))
Google scholar	("covid-19") AND ("steven johnson" OR "erythema multiforme major" OR "bullous epidermolysis" OR "epidermal necrolysis" OR "toxic shock syndrome" OR "fixed drug eruption" OR "acute generalized exanthematous pustulosis" OR "purpura fulminans" OR "dress")

FIGURE 2 The search strategy for databases

3.5 | Study selection

Endnote® X8 (Clarivate Analytics, Philadelphia, USA) was used for study screening and data extraction. Overall, there were 754 articles, with 247 being duplicates; therefore, 507 articles were screened and categorised by two independent reviewers and any potential conflicts were resolved by consulting a third reviewer.

4 | RESULT

Finally, 57 articles were reviewed completely. It is shown in detail in the PRISMA flow diagram (Figure 1 in the supplement file). All articles whose data were extracted have been shown in Tables 1-6 in three different categories: virus-related skin manifestations, drug reactions, skin manifestations, and skin manifestations that are not known to be virus-related or drug-related.

After the final screening of the databases, 57 studies were included. Forty-seven studies were case reported and 10 studies were case series. A total data of 93 patients were extracted. All studies were published during December 2019 and October 2020; the mean patient age was 55.62 years old. The age of three cases was not reported. Fifty-two cases (59.77%) were males and 35 cases (40.22%) were females. The gender of 6 cases was not reported. Gender of the male is top of the virus-related list 68.3% (41/60) and female in drug-related group is in majority of 60% (12/20) that may indicate women's susceptibility to drug reactions. Seventy-five patients were confirmed COVID-19 with RT-PCR or serology, three cases were negative and 15 cases were not mentioned. Sixty-six cases were COVID-related cutaneous manifestations, 20 cases were drug-related skin reactions and seven cases were uncertain.

Generally, among all included literature, necrosis and ischaemic episode appeared to be the most common skin manifestation with 32.25% (30/93) of patients presenting such lesions on their skin. Vasculitis or vasculopathy lesions were seen in 17.2% (16/93) of patients. Angioedema occurred in 12.9% (12/93) of reported patients, and the presence of AGEP was seen in 8.6% (8/93).

4.1 | Virus-related group[19-51]

In the virus-related category, necrosis and ischaemic phenomenon with the prevalence of 45.45% (30/66) are the most frequent

presentation in patients. Vasculitis and vasculopathy lesions with 19.69% prevalence (13/66) were the second common skin reactions.

The prevalence of angioedema, toxic shock syndrome, EM, generalised Livedo reticularis and erythroderma was 9% (6/66), 7.5% (5/66), 6% (4/66), 6% (4/66) and 3% (2/66), respectively.

One case of haemorrhagic bullae, SJS, AGEP was also reported. In the virus-related category, four cases presented skin manifestations as an initial manifestation of COVID-19 infection before other symptoms.

4.2 | Drug-related classification[52-69]

AGEP with 30% (6/20) was the most frequent skin lesion in the drug-related group and afterwards EM 20% (4/20), angioedema 10% (2/20), DRESS 10% (2/20) and generalised pustular figurate erythema 10% (2/20), respectively. One case of vasculitis, TEN, and SJS was reported.

4.3 | Uncertain group[70-75]

In the uncertain group which there is no defined boundary between virus-related or drug-related reasons, angioedema was the most common skin reaction 50% (4/7). One case of SJS, AGEP, vasculitis and dissecting haematoma belong to this group.

This study reveals a 19.7% (14/71) mortality rate within patients who reported outcomes. The majority of expired patients were men. In the uncertain group, no deaths were reported. In drug-related classification, both cases died of a massive pulmonary embolism.[53,56] In the virus-related category, in one study by Theodora et al, within four expired patients, three patients developed deep vein thromboses and one experienced acute kidney injury.[50] In a case series by Sarah Young, a 69-year-old man who developed large a sacral ulcer during his severe COVID-19 disease courses, expired by the diagnosis of haemorrhagic leucoencephalopathy.[47] In a case series by Bitar et al, among two cases with TSS, one patient expired because of COVID-19-associated exfoliative shock syndrome.[45] Jessica A Rotman described a case report of ischaemic dermopathy syndrome with microvascular calcifications, leading to tissue ischaemia and necrosis which expired five days after admission.[44] In a case report by Aaron Shoskes et al 69-year-old male presented with diffuse microhaemorrhages on brain MRI. All findings are suggestive of secondary microangiopathy and thrombotic vasculopathy. He expired five days after admission.[40] A patient with acute bilateral lower limb necrosis was described by Del Giudice et al, who demonstrated a connection between severe COVID-19 and coagulopathy. The patient passed away in consequence of DIC.[39] A Necrotic acral lesion was reported by Antonella Tammaro which was super-infected by *Pseudomonas aeruginosa* and the patient expired.[31] Noel Lorenzo-Villalba et al, described a case of an 84 -year-old man who presented with bilateral cervical tumour and parotitis associated with thrombosis of the left jugular vein and He expired 29 days after admission.[30] A case of bullous haemorrhagic vasculitis was reported by Negrini who expired because of respiratory insufficiency.[76]

5 | DISCUSSION

Dermatological manifestations in novel coronavirus were more identified recently. Initial studies documented seldom skin involvement. True findings of skin manifestations and their proper management were important for dermatologists that have a crucial role in patients' care with COVID-19. The present review evaluates the severe and life-threatening mucocutaneous lesions and features related to patients with COVID-19. Drug reactions are hard to distinguish from virus-related skin lesions in some cases; therefore, the uncertain category includes cases in which discrimination between the unusual reaction to the prescribed drug or skin manifestation associated with COVID-19 pathophysiology, was not possible.

According to the Tables, some noticeable points have been presented, regarding severe and life-threatening mucocutaneous dermatologic manifestations' categories.

5.1 | Angioedema

Virus-related manifestations: In six patients with angioedema manifestation, 50% (3/6) presented before COVID-19 symptoms onset (range 2-11 days), and 66% (4/6) were younger than 50 years. Face and trunk were the most common locations. Also, the mean duration of treatment with systemic corticosteroids and antihistamines was from 1 to 22 days in severe forms and two patients had previous allergic history.

Drug-related reactions: Among two cases with angioedema, one patient with a history of four-month ACE inhibitor consumption, presented with severe forms of angioedema. This case indicated that COVID-19 may be the trigger for angioedema when combined with the use of ACE inhibitors.

Uncertain group: This presentation was the most common skin lesion in this category and the most commonly affected area was the face.

5.2 | Vascular lesions

Virus-related manifestations: In 47 patients with vascular lesions, about 23.40% were younger than 50 years (11/47). Most of them had comorbidities. Presentations varied from haemorrhagic vesiculobullous, retiform purpura, livedo reticularis to necrotic and ischaemic changes. Except for 2 cases, the rest of the patients presented vascular lesions after COVID-19 symptoms. Treatment consisted of corticosteroids, antihistamines and anticoagulation therapy in severe types. More than five-six days were required for skin resolution. The highest mortality rate was related to necrosis and occurred in patients over 60 years and the most commonly involved site was the

TABLE 1 COVID-19 virus-related skin manifestations case reports

First author	Case characteristic	COVID-19 sign and symptoms	COVID-19 management	Patients' comorbidity	Time of onset the reactions	Type of skin manifestation
Patel N	78-y-old woman	Temporary loss of consciousness, fever, COVID-19 PCR: positive	Not reported	Vascular epilepsy, hypothyroidism, heart failure	7 d before	Erythematous blanching maculopapular eruption, vesicles and urticarial
Negrini S	79-y-old man	Fever, dyspnoea, COVID-19 PCR: positive	Hydroxychloroquine (400 mg BID), enoxaparin (4000 IU QID), ceftaroline (600 mg BID), Methylprednisolone (80 mg QID)	HTN, myocardial infarction, COPD	10 d after	Haemorrhagic vesiculobullous lesions
Magro C	32-y-old man	Fever, cough, COVID-19 PCR: positive	Hydroxychloroquine, azithromycin, remdesivir (5 mg/kg intravenous once daily for 10 d)	Obesity-associated sleep apnoea	4 d after	Retiform purpura with extensive surrounding inflammation
Adeliño R	30-y-old woman	Fever, odynophagia, dry cough, ageusia, anosmia, COVID-19 PCR: positive	Not reported	Pine seeds allergy	11 d after	Facial angioedema especially periocular region, mild oedema of the lips, wheals
Lockey R	36-y-old man	Anosmia, ageusia, COVID-19 PCR: positive	Not reported	Obesity, 15 pack-year smoking	11 d before	Day 0: generalised erythema and pruritus, Day 9: generalised erythema, pruritus, urticaria and angioedema with dyspnoea, cough, and wheezing
Mayor-ibarguren A	83-y-old woman	Sore throat, malaise, nausea, IgM and IgG antibodies: Positive, COVID-19 PCR: negative	Not reported	HTN, TIA, atrial fibrillation, chronic renal impairment	30 d after symptom initial	Purple palpable papules, serohaematic blisters

Location	Final diagnosis	Skin biopsy	Managements of reactions	Time of reaction resolution	Outcome	Cause of death
Trunk, face	Angioedema	Not performed	Emollient	7 d after treatment	D.C	—
Neck, dorsal areas of hands	Vasculitis lesions	Erythrocytes extravasation, intraepithelial haemorrhagic bullae, nuclear hyperchromatic and cytoplasmic eosinophilia of the epidermis, severe neutrophilic infiltrate within the wall of small vessels, scant leucocytoclasia within the superficial dermis, Hyperchromasia and nuclear enlargement due to endothelial cells activation.	Not reported	Not reported	Expired	Respiratory insufficiency
Buttocks	Vasculopathic lesion	interstitial and perivascular neutrophilia and leucocytoclasia, striking thrombogenic vasculopathy with extensive necrosis of the epidermis and adnexal structures, IHC: extensive deposition of C5b-9 within the microvasculature	Not reported	Not reported	D.C	-
Face, trunk, abdomen, and limbs	Angioedema	Not reported	Antihistamine (10 mg TID)	1 d after treatment	D.C	—
Palms and soles, lips	Angioedema	Not reported	Day 0: Methylprednisolone, diphenhydramine 50 mg BID, Day 6: prednisolone 20 mg BID, diphenhydramine 50 mg BID, cefdinir 500 mg QID, Day 9: nebulised albuterol, diphenhydramine, epinephrine, famotidine, methylprednisolone intramuscularly, saline intravenously, Day 11: add high dose of oral cetirizine	22 d after treatment	D.C	-
Both distal legs, feet and toes	Vasculitis	Extravasation of red cells in the superficial dermis, basal epidermal layer necrosis, accumulation of neutrophils at the tips of the dermal papillae, perivascular neutrophil infiltration, fibrin deposition in the thin vessel wall of the dermis, leucocytoclasia affecting dermal vessels	Prednisone (30 mg daily)	10 d after treatment	D.C	—

(Continues)

TABLE 1 (Continued)

First author	Case characteristic	COVID-19 sign and symptoms	COVID-19 management	Patients' comorbidity	Time of onset the reactions	Type of skin manifestation
Dominguez-Santas M	71-y-old woman	Fever, cough, malaise, CXR: pulmonary infiltrate in the right lower field, COVID-19 PCR: positive	Hydroxychloroquine (Day 1-5: 200 mg BID, lopinavir-ritonavir 200/50 mg BID)	Not reported	7 d after symptom initial	Purpuric macules and papules, Koebner phenomenon, pruritic,
Bapst T	13-y-old boy	Fever, abdominal and thoracic pain, odynodysphagia, Chest CT: bibasal pneumonia, positive serology	Paracetamol, Azithromycin, ceftriaxone	Not reported	7 d after symptom initial	Generalised symmetrical and round papular lesions, central dark red zone surrounded by a pale ring of oedema and an erythematous halo on the extreme periphery with non-purulent conjunctivitis
Greene A	11-y-old girl	Sore throat, malaise, poor appetite, generalised abdominal pain, leg pain, fever, tachycardia, hypotension	Milrinone, norepinephrine, Furosemide, ceftaroline, clindamycin and piperacillin-tazobactam, Enoxaparin, Vitamin K, tocilizumab, IL-6 inhibitor, convalescent plasma, remdesivir, steroids, IVIG	No comorbidity	At the same time with other symptoms	Non-blanching papular and diffuse reticular rash, palmar erythema, itchy rash
Hassan K	46-y-old woman	Nasal congestion, fever, dry cough, slight wheeze, COVID-19 PCR: positive	Not reported	Hay fever, nut allergy and mild asthma	48 h before	Day 1: widespread red-raised blanching and itchy rash, Day 2: mild angioedema, swelling
Najafzadeh M	An elderly man	General malaise, fatigue, fever, sore throat, CT scan: pneumonia with subpleural and bilateral ground-glass opacification, consolidation in lower lobes	Not reported	Not reported	At the time of other symptoms	Generalised pruritic urticaria
Lorenzo-Villalba M	84-y-old man	General weakness and anorexia, thrombosis of the left jugular vein positive RT-PCR	Low-molecular-weight heparin,	HTN, type2 DM, CHF, COPD	25 d after	Dermatoporosis lesions, haemorrhagic bullae with intra-bullae blood clots

Location	Final diagnosis	Skin biopsy	Managements of reactions	Time of reaction resolution	Outcome	Cause of death
Right knee, both legs extending from the ankle up to the thigh	Vasculitis	Perivascular inflammatory infiltration by neutrophils with karyorrhexis, leucocytoclasia, nuclear dust and red blood cell extravasation, small vessel damage with fibrinoid necrosis of vessel walls	Betamethasone dipropionate 0.05% cream twice daily	3 wk after treatment	D.C	-
Left shoulder, back, hand	Erythema multiforme (EM)	Not reported	Antibiotic therapy	14 d after treatment	D.C	-
Bilateral upper extremities and abdomen, trunk, back	Toxic shock-like syndrome	Not reported	Steroids and IVIG	1 d after treatment	D.C	—
Upper and lower limbs and trunk, face, loins lower lips, hands, face, neck and upper chest	Angioedema	Was not performed	Fexofenadine hydrochloride 180 mg orally two to four times daily, fexofenadine hydrochloride 180 mg QID, prednisolone 40 mg daily for 3 d, chlorphenamine maleate 4 mg QID.	Next few days after treatment	D.C	-
Lip swelling	Angioedema	Not reported	Not reported	Not reported	D.C	-
All extremities	Haemorrhagic bullae	Was not performed	Surgical treatment	29 d after admission	Expire	Thrombosis

(Continues)

TABLE 1 (Continued)

First author	Case characteristic	COVID-19 sign and symptoms	COVID-19 management	Patients' comorbidity	Time of onset the reactions	Type of skin manifestation
Tammaro A	59-y-old man	Dyspnoea, fever and cough, positive RT-PCR, bilateral interstitial pneumonia was evident at chest CT scan.	Azithromycin, hydroxychloroquine	COPD, smoker	Not reported	Erythematous lesions, necrotic lesion
Lidder A	45 y old man	Fever, sore throat, diarrhoea, PCR: positive	IVIG, tocilizumab	No comorbidity	At the time of other symptoms	Eye redness, eyelid swelling, diffuse periorbital rash, non-exudative conjunctivitis, diffuse conjunctival hyperaemia, trace chemosis, perioral mucosal involvement, erythema multiforme-like rash, cervical lymphadenopathy
Feng Y	28-y-old woman	Day 0: hypoxic respiratory failure, Day 19: fever, and hypotension, generalised weakness, poor appetite, PCR: positive, Chest x-ray: bibasilar infiltrates	Hydroxychloroquine, steroids, broad spectrum antibiotics (vancomycin, ceftazidime, clindamycin)	ESRD, HTN, DM	19 d after symptoms initial	Scaling, yellow crusting and widespread erosions, dusky coloured and Diffuse erythematous plaques with bullae and superficial flaking, burning sensation, patchy lower eyelid desquamation, patchy palpebral conjunctival staining of the left eye
Elhag S	40-y-old-man	Non-productive cough, dyspnoea, low-grade fever, PCR: positive, CXR: bilateral lower-zone opacities and infiltrations	Acetaminophen, enoxaparin (1 mg/kg/d), favipiravir (Day 1: 1200 mg BID, Day 2-7: 600 mg BID), hydroxychloroquine (Day 1: 400 mg BID, Day 2-7: 200 md BID)	No comorbidity	5 d aftersymptom initial	Swelling, erythematous generalised pruritic urticarial welts, migratory rash
Nasiri S	64-y-old-woman	Day 0: fever, dry cough, dyspnoea, nausea, anorexia, Day 28: weakness, malaise, anorexia, PCR: Positive, CT: ground-glass patchy parenchymal opacities with peripheral infiltration, serology: positive	Hydroxychloroquine (200 mg BD), azithromycin (250 mg daily for 5 d)	DM, HTN	48 h before the second presentation	Oedema, Annular and polycyclic purpuric urticarial lesions, targetoid lesions

Location	Final diagnosis	Skin biopsy	Managements of reactions	Time of reaction resolution	Outcome	Cause of death
Limbs, foot	Necrotic acral lesions	Small vessel thrombosis	Tocilizumab as a single dose	Not reported	Expire	Necrotic acral lesions
Eye and bilateral upper and lower eyelids	Toxic shock syndrome	Superficial perivascular neutrophils, lymphocytes and eosinophils infiltration	Ophthalmic lubricating therapy, prednisolone acetate 1% eye drops QID, topical triamcinolone ointment	2 wk after treatment	D.C	—
40% of her total body surface area, Both eyes, oral	Toxic shock syndrome	Superfcial perivascular inflammation with eosinophils and neutrophils, subcorneal split with parakeratosis, intraepidermal dyskeratosis	Prednisolone acetate 1% eye drops (every 2 h), preservative free artificial tears (every 2 h), erythromycin ointment (QID)	3 d after ocular treatment	D.C	-
Bilateral eyelid, lip, trunk, back, extremities	Angioedema	Not reported	Desloratadine 5 mg orally TDS	3 d after treatment	D.C	—
Face, periorbital, extremities, trunk	Vasculitis	Dermal oedema, Vascular damage, red blood cell extravasation in the background of mixed neutrophil & eosinophil infiltration, evidence of leucocytoclastic vasculitis consistent with urticarial vasculitis,	Antihistamine	One week after treatment	D.C	-

(Continues)

TABLE 1 (Continued)

First author	Case characteristic	COVID-19 sign and symptoms	COVID-19 management	Patients' comorbidity	Time of onset the reactions	Type of skin manifestation
Ghalamkarpour F	45-y-old man	Fever, COVID-19 PCR: Positive	Acitretin 35 mg daily, cloxacillin, enoxaparin, methadone, pantoprazole, vancomycin, meropenem	Psoriasis	At the time of other symptoms	Erythroderma and ectropion and severe onycholysis
Tahir A	47-y-old man	Fever, malaise, and polyarthralgia, COVID-19 PCR: Positive	Not Mentioned	No comorbidities	At the time of symptoms initial	Targetoid papules and plaques with central necrosis and peripheral erythema on all extremities, buttocks, and lower trunk, Also a 1-cm tender ulcer on the undersurface of the tongue with moist pale granulation tissue on its floor and gingival and lingual purpura
Balestri R	74-y-old woman	Asymptomatic, COVID-19 PCR: Positive	Not mentioned	Chronic venous leg ulcers, AF, CHF	20 d after positive PCR	Blanching of fingers, dusky red macules, digital infarcts and an ischaemic necrosis of the left third fingertip
Del Giudice P	83-y-old man	Fever, ARDS, COVID-19 PCR: Positive	Acetylsalicylic acid, fluindione, ramipril, bisoprolol, furosemide, prednisolone 7.5 mg daily	DM, HTN, Mesenteric ischemia, PAD, IHD,	12 d after initial symptoms	Bilateral symmetrical well-limited black skin
Shoskes A	69-y-old man	Dyspnoea, cough, diarrhoea, and fevers, COVID-19 PCR: Positive	Not mentioned	HTN, CKD, hypothyroidism	1 wk after	Morbilliform rash and diffuse purpura
Verheyden M	57-y-old man	Cough, dyspnoea, headache, myalgia arthralgia, fever, COVID-19 PCR: Positive	Acetaminophen, hydroxychloroquine, low-molecular weight heparin	Not reported	8 d after	Extensive, symmetric livedo reticularis (LR)
Khalil S	34-y-old woman	Congestion, fever, anosmia, COVID-19 PCR: Positive	Not mentioned	No comorbidities	7 d after	Well-demarcated reticular lacy erythematous patches with overlying faint morbilliform exanthem.
Heald M	65-y-old man	Shortness of breath, Confirmed case of COVID-19	Not mentioned	HTN	Not mentioned	Progressive left-hand ischemic changes involving the distal first and second digits

Location	Final diagnosis	Skin biopsy	Managements of reactions	Time of reaction resolution	Outcome	Cause of death
Whole body	Erythroderma	Not Mentioned	Cyclosporine 100 mg BID, prednisolone 10 mg daily	20 d after treatment	D.C	-
All extremities, Trunk, buttocks, Oral Cavity	Vasculitis	Endothelial swelling, neutrophilic vessel wall infiltration, karyorrhectic debris, and fibrin deposition in small and medium-sized dermal vessels with extravasated erythrocytes and microthrombi occluding lumina of smaller dermal capillaries	Topical betamethasone valerate 0.12% cream	Not Mentioned	D.C	-
Fingers	Necrosis	Not Performed	Vascular surgery assessment was offered but the patient did not give consent.	No follow up	D.C	—
Legs and foots	Necrosis	Not Performed	Not mentioned	—	Expire	DIC
Trunk	Thrombotic vasculopathy	Fibrin thrombi (black arrows) in numerous blood vessels	Not mentioned	—	Expire	Cerebral microthrombi
Trunk and thighs	Livedo reticularis	Not Performed	Continual of COVID-19 related drugs	3 wk after	D.C	—
Left hand, bilateral thighs and arms	Livedo reticularis	Perivascular lymphocytic inflammation, increased superficial dermal mucin, and necrotic keratinocytes consistent with viral exanthem	No specific treatment	2 wk after	D.C	—
Fingers	Necrosis	Not performed	Enoxaparin	Not mentioned	Not mentioned	—

(Continues)

TABLE 1 (Continued)

First author	Case characteristic	COVID-19 sign and symptoms	COVID-19 management	Patients' comorbidity	Time of onset the reactions	Type of skin manifestation
Rotman J	62-y-old woman	Cough, COVID-19 PCR: Positive	Hydroxychloroquine	ESRD, HTN, DM, RA, hypothyroidism	3 wk after initial symptoms	Firm oedema and erythema about both knees, greatest near the popliteal fossae, with mass-like areas of indurated dusky plaques. Hyperpigmentation and xerosis were also noted in the non-oedematous portions of the more distal lower extremities.

extremities. More severe disease-related haemostatic disturbances have been reported. In some cases, the presence of antiphospholipid antibodies and their role in the vascular phenomenon was discussed.[28] In a case series by Thaís Bianca Brandão et al, four patients presented with superficial mucosal necrosis. Photobiomodulation therapy was prescribed to pain control associated with oral ulcers in some cases.[46]

Drug-related reactions: In one case of two reported patients with vasculitis; amoxicillin, ibuprofen, and metamizole were prescribed 3 days before lesions' onset.

Uncertain group; A case with leucocytoclastic vasculitis suggests COVID-19 infection or its treatment regimen may trigger a severe drug-related cutaneous reaction or systemic vasculitis.

Skin biopsies in different studies showed that COVID-19 may induce endothelial damage and thrombosis. Evaluating histopathologic features of a skin biopsy revealed erythrocytes extravasation, epidermal necrosis, thrombogenic vasculopathy, microthrombi and vessel wall infiltration suggesting vascular occlusion because of endothelial damage in vasculopathy lesions and accumulation of inflammatory cells in the vessel wall in vasculitis lesions. This review demonstrated that COVID-19 could cause viral endotheliitis and endothelial damage. Ischaemic lesions are the consequence of the combined effect of vasculitis and severe coagulopathy because of COVID-19. According to studies with the first presentation of ischaemic changes or necrosis, anticoagulant administration should begin immediately.

5.3 | Toxic shock syndrome

Virus-related manifestations: Kawasaki-like syndrome or Toxic shock-like syndrome in the setting of COVID-19, represents Multisystem Inflammatory Syndrome (MIS-C) in previously healthy paediatrics from 5 to 19 years.[33] In adults there was also reporting of Kawasaki-like syndrome or Toxic shock-like syndrome associated with COVID-19. In this category, five patients with toxic shock syndrome presentation were mostly under the age of 50. One of the predominant characteristics of TSS is conjunctivitis and mostly appeared early in the disease course and triggered by bacterial superantigens.[33] In two cases, toxic shock syndrome was the first presentation besides the other COVID-19 symptoms.[27,32] IVIG and steroid appeared to produce a better response than other options.

5.4 | Erythroderma

Virus-related manifestations: Two psoriasis patients presented with the flare-up of psoriatic erythroderma which may be challenging for management. It seems that immunosuppressive therapy subsides skin reaction and should be considered as a good choice for its treatment.

5.5 | Dress

Drug-related reactions: Another common drug-related skin manifestation was DRESS 10% (2/20), reported mostly in connection with hydroxychloroquine and healed after 15-30 days of steroid therapy.

5.6 | Haemorrhagic bulla

Uncertain group: Ahaemorrhagic bulla with dissecting haematoma was reported which may be related to anticoagulant treatment or haemostasis abnormalities induced by COVID-19.

5.7 | AGEP, EM, SJS, and TEN

Virus-related manifestations: Four cases with erythema multiform were reported that 75% (3/4) were less than 20 years. One case presented

Location	Final diagnosis	Skin biopsy	Managements of reactions	Time of reaction resolution	Outcome	Cause of death
Both knees, popliteal fossae, distal lower extremities	Thrombotic Necrosis retiform purpura	Vascular alterations in the dermis and subcutaneous fat. full-thickness epidermal necrosis and adnexal structures, in the skin overlying the fat. Occlusive luminal thrombi and focal mural fibrin deposition Within the subcutaneous fat, thrombotic diathesis localised to capillaries and venules, lipomembranous fat necrosis, calcific microangiopathy with granular basophilic deposits of calcium within the capillaries.	Dialysis, sensipar and sodium thiosulfate which improved calciphylaxis	Not mentioned	Expire	Ischemic dermopathy syndrome

lesions in oral mucosa purely. Erythemamultiforme in COVID-19 patients had a favourable prognosis. It healed after 8-14 days of treatment. In this group, two patients demonstrated Kawasaki syndrome and erythema-multiform-like lesions together, in which IVIG therapy was suggested.

Drug-related reactions: AGEP and major erythema multiform were the most common skin reactions, presented in30% (6/20) and 20% (4/20) of cases, respectively. Hydroxychloroquine was the principal culprit. In most cases, it was a late-onset skin reaction to the prescribed drug and took time to resolve. Patients with AGEP had poor clinical condition.

SJS and TEN were also reported and initiation of intravenous Immunoglobulin as a therapeutic option for symptoms' attenuation was recommended.

Four cases with erythema multiform associated with hydroxychloroquine, 5-30 days after treatment, were reported.

Uncertain group: SJS/TEN syndrome was reported in a critically ill patient with several comorbidities.

5.8 | Generalised pustular figurate erythema

Drug-related reactions: It is a combination of Stevens-Johnson syndrome/toxic epidermal necrolysis with its targetoid lesions and AGEP with its pustulosis. Two COVID-19 patients on hydroxychloroquine treatment developed generalised pustular figurate erythema, two and three weeks after the onset of hydroxychloroquine. This report is the first study delineating this type of skin reaction.[68]

These cutaneous features linked to the COVID-19 infection interplay with the skin. It means that increased angiotensin-II levels occur with the binding and inhibition of ACE-2 receptors by COVID-19 which induces vascular injuries. It is unclear that the skin eruptions in COVID-19 patients could be specifically because of COVID-19 itself or not.

Virus-related skin lesions may help identify COVID-19 patients earlier to avoid progression to disseminated infection and potentially life-threatening skin reactions.

Generally, in the drug-related group, except for four cases (with AGEP, TEN, vasculitis, angioedema), hydroxychloroquine was suspected to be accountable for drug-induced skin reactions.

According to the widespread use of corticosteroids and immunomodulatory agents in severe skin reactions in a setting of COVID-19 infection, we hypothesised that severe skin lesions, are mainly because of immune-mediated reaction and dysregulated host inflammatory responses affecting the skin and occasionally the mucosa. Therefore, COVID-19 as an important etiological agent activates the immune system rather than direct invasion. We underline that the lesions could present as a delayed immune-mediated reaction to the virus or an immediate response.

The authors of this study have been worked on the most important hot topics of dermatologic issues in this pandemic area and now based on the experiences of the experts in academic centres and consultant complicated cases of mucocutaneous COVID-19 related reactions, they found that some holistic managing decision in these patients is challenging, even for expert dermatology professors, since these patients, especially hospitalised ones, many times show multiple laboratory abnormalities or organ failures that the handling of a severe and potential life-threatening mucocutaneous reaction or aggravation of a pre-existing severe chronic dermatologic disorder by COVID-19, which usually needs immunosuppressive immunomodulators, are hard and needing to multi-aspect cautions. In addition, all drugs are not available in all situations such as IVIG (eg in Iran), etc, which makes this condition more complicated, as well.[77-92]

TABLE 2 COVID-19 virus-related skin manifestations case series

First author	Case characteristic	COVID-19 sign and symptoms	COVID-19 management	Patients' comorbidity	Time of onset the reactions	Type of skin manifestation
Bitar C	Mean 4 patients 'age 51 y	Fever and upper respiratory symptoms	Not mentioned	Not mentioned	Median: 9 d after initial symptoms	Erythematous plaques with superficial exfoliation on the abdomen.
						Erythematous to dusky plaques with superficial exfoliation
						Dusky vesicles and bullae coalescing into plaques with denudation with mucosal involvement, rash and mucositis
						Painful retiform purpura consisting of angulated violaceous plaques with necrotic centers
Brandão T	81-y-old man	Cough and progressive chest tightness, COVID-19 PCR: Positive	Azithromycin, ceftriaxone	HTN, COPD	5 d after initial symptoms	Painful shallow aphthous-like ulcers of varying sizes and irregular margins covered with mucopurulent membrane
	71-y-old woman	Cough, dysgeusia, fever, and mild dyspnoea, COVID-19 PCR: Positive		HTN, DM, Renal Failure, Obesity	4 d after initial symptoms	Small haemorrhagic ulcerations on lips, Necrosis on anterior dorsal tongue
	83-y-old woman	Abdominal distension and mild dyspnea, COVID-19 PCR: Positive	Piperacillin/tazobactam, ceftriaxone.	Obesity, Parkinson, HTN, pancreatitis, COPD	2 d after initial symptoms	Ulcer on the right lateral border of the tongue, and petechia and shallow necrotic at the anterior hard palate
	72-y-old man	Fever and dyspnea, COVID-19 PCR: Positive	Piperacillin/tazobactam, azithromycin, ceftriaxone	DM, HTN	5 d after initial symptoms	Small haemorrhagic ulcerations at upper and lower lips, painful necrotic ulceration on the right lower lip mucosa
Young S	69-y-old man	Fever, chills, cough, and shortness of breath, COVID-19 PCR: Positive	Hydroxychloroquine, Azithromycin, IV antibiotics, Heparin	HTN, gout, obesity	12 d from admission	Large black eschar (5 × 11 cm) with surrounding violaceous induration and retiform purpuric edges
	56-y-old man	Fever, Shortness of breath, and cough, COVID-19 PCR: Positive	IV antibiotics, hydroxychloroquine, azithromycin, tocilizumab	MM, leukaemia, pre-diabetes, HTN, obesity	19 d from admission	Black eschar (6 × 4 cm) with surrounding induration and erythema

Location	Final diagnosis	Skin biopsy	Managements of reactions	Time of resolution the reaction	Outcome	Cause of death
Abdomen	Toxic shock syndrome	Subcorneal split with intracorneal neutrophils, parakeratosis and scant dermal inflammation	No treatment for deceased patient was mentioned	Not mentioned	Expire	Exfoliative shock syndrome
Trunk	Toxic shock syndrome	subcorneal split with parakeratosis and intracorneal neutrophils	Linezolid		D.C	—
Back	SJS like eruptions	Full-thickness epidermal necrosis	Not mentioned		Not mentioned	—
Bilateral legs	Calciphylaxis with thrombotic vasculopathy	Epidermal necrosis with vascular thrombi and calcification of small- to medium-sized vessels	Not mentioned		Not mentioned	—
Upper and lower lip mucosa, anterior dorsal tongue	Superficial necrosis	Not Performed	Acyclovir 250 mg/m^2 (IV)TID for 10 d, Photobiomodulation therapy daily for 10 d	11 d after treatment	D.C	—
			Acyclovir 250 mg/m^2 (IV)TID for 7 d, Photobiomodulation therapy daily for 10 d	>15 d after treatment	D.C	—
Tongue and anterior hard palate			Photobiomodulation therapy daily for 10 d	5 d after treatment	D.C	—
Lips mucosa			Acyclovir 250 mg/m^2(IV)TID 7 d, Photobiomodulation therapy daily for 10days	7 d after treatment	D.C	—
Sacrum, buttocks	Thrombotic Vasculopathy	Fibrin thrombi in numerous blood vessels	Not Mentioned	Not Mentioned	Expire	Haemorrhagic leucoencephalopathy
Sacro-coccygeal	Probable thrombotic vasculopathy	Not Performed	Debridement	32 d after	D.C	—

(Continues)

TABLE 2 (Continued)

First author	Case characteristic	COVID-19 sign and symptoms	COVID-19 management	Patients' comorbidity	Time of onset the reactions	Type of skin manifestation
	73-y-old man	Fever, chills, cough, Shortness of breath, COVID-19 PCR: Positive	Hydroxychloroquine, azithromycin, Heparin, Vancomycin, Meropenem	HTN, COPD, CHF, CAD, obesity	7 d from admission	Large black eschar
Labe P	6-y-old man	Loss of appetite, anosmia, COVID-19 PCR: positive	Not reported	Not reported	Not reported	Painful and erosive cheilitis, gingival erosions, thick haemorrhagic crusts, rash, multiple target lesions, bilateral conjunctivitis
	3-y-old man	Fever, asthenia, CT scan: ground-glass opacities, consolidation in the right posterobasal zone				Generalised exanthema, oedema, cheilitis and glossitis, stomatitis, bilateral conjunctivitis, Desquamation of the cervical lymphadenopathy
Rolfo C	62-y-old man	Fever, fatigue, myalgia, chills, nasal congestion, pharyngeal exudation, dry cough, COVID-19 PCR: positive	Hydroxychloroquine (Day 1: 400 mg BID, Day 2-14: 200 mg BID), Azithromycin (Day 1:500 mg once daily, Day 2-5:250 mg once daily), methylprednisolone (Day 1-14:1 mg/kg), Enoxaparin 40 mg/d subcutaneously	Squamous cell lung carcinoma with pleuropulmonary involvement	2 d after symptom initial	Urticarial papular lesions and erythema, burning sensation
	58-y-old woman	Diarrhea, fever, dry cough, COVID-19 PCR: positive	Hydroxychloroquine (Day 1: 400 mg BID, Day 2-10: 200 mg BID)	Lung adenocarcinoma,	2 d after symptoms initial	Target lesions with central zone of pallor and erythematous peripheral rim, painful ulcers
Karagounis T	21 Patients: median age 56 y, Man (18/21)	COVID-19 PCR: Positive (21/21 patients)	Therapeutic anticoagulation in 16/21 (76%) for a thrombotic event or elevated D-dimer: 13 prior to the recognition of cutaneous findings, the remainder were transitioned from prophylactic to therapeutic doses of anticoagulation after cutaneous eruptions were noted.	Antiphospholipid syndrome (2/21 patients), Factor V Leiden deficiency (1/21 Patient)	Median 19 d after admission	Purpuric and/or necrotic ulcerations
Gianotti R	Not mentioned	Severe systemic and pulmonary symptoms, COVID-19 PCR: Positive	Hydroxychloroquine, antibiotics	Not Mentioned	Not Mentioned	Livedoid exanthematous eruption

Location	Final diagnosis	Skin biopsy	Managements of reactions	Time of resolution the reaction	Outcome	Cause of death
Left gluteal region	Probable thrombotic vasculopathy		Debridement, IV antibiotics	47 d after	D.C	—
Extremities	Erythema multiforme	Not reported	Not reported	2 wk after treatment	D.C	—
Bilateral palmar, extremities			Intravenous gamma globulin (2 g/kg)	Not reported	D.C	-
Lower dorsal, lumbar, and gluteal region	Urticarial vasculitis	Dermal oedema, mild extravasation of red blood cells in to dermis and Fibrinoid changes of vessel wall with neutrophil infiltration, granulomas and nuclear debris in superficial and deep dermis	Methylprednisolone (Day 1-14:1 mg/kg)	6 d after treatment	D.C	—
Oral	Erythema multiforme	Basal cell vacuolisation and apoptotic keratinocytes with inflammatory cells, interface dermatitis	Hydroxyzine (25 mg BID), desloratadine (5 mg daily), methylprednisolone (1 mg/kg daily)	8 d after treatment	D.C	—
Ears, face, distal extremities, and/or genitalia	Acrofacial purpura and necrotic ulceration	Not Performed	In 3/21 patient's anticoagulation therapy was increased from prophylactic dose to anticoagulation	Not Mentioned	D.C (17/21 Patients), Expire (4/21)	DVT, AKI
Not Mentioned	Diffuse livedoid exanthematous eruption	Nest of Langerhans cells in the epidermis. In the deep dermis and occasionally in the superficial dermis, there were micro-thrombi admixed with nuclear and eosinophilic debris	Not mentioned	Not mentioned	D.C	—

(Continues)

TABLE 2 (Continued)

First author	Case characteristic	COVID-19 sign and symptoms	COVID-19 management	Patients' comorbidity	Time of onset the reactions	Type of skin manifestation
	78-y-old woman	Fever, cough, and ageusia, COVID-19 PCR: Not Performed	Not Mentioned	Guttate psoriasis	Not mentioned	Erythroderma
	51-y-old woman	Cough, asthenia, and ageusia, COVID-19 PCR: Not Performed	Not Mentioned	Polycystic kidney	Not Mentioned	Reticulated pigmented dermatitis reminiscent of prurigo pigmentosa, On the trunk. Psoriasiform lesions were noticed, On the elbows, the buttocks, and capillitium. there were papular confluent lesions in plaques on the arms, erythematous macular lesions similar to vasculitis in lower limbs

TABLE 3 Drug-related skin manifestations case reports

First author	Case characteristic	COVID-19 sign and symptoms	Patients' comorbidity	Type of drug	Time of onset the reactions	Type of reactions
Jiménez A	37-y-old woman	Fever, COVID-19: Not Confirmed	Not Mentioned	Hydroxychloroquine (200 mg), lopinavir-ritonavir (200/50 mg BID), azithromycin 250 mg daily for 5 d	2 –3 wk	Maculopapular rash, purpuric rash, periorbital angioedema, itchy, Bilateral cervical lymphadenopathy, oral mucosa enanthema
Delaleu J	76-y-old man	Cough, diarrhea, COVID-19 PCR: Positive	DM	Hydroxychloroquine (orally 200 mg TID for 6 d), piperacillin-tazobactam intravenous 4 g/6 h, azithromycin (orally 500 mg daily then 250 mg daily for 5 d), ceftriaxone (intravenous 1 g daily 6 days), voriconazole 600 mg BID, after skin lesions 300 mg BID (for 9 d), Enoxaparin (subcutaneous 6000/L/24 h for 15 d)	9 d after drug initiation	Pustules on a background of oedematous erythema, Without mucosal involvement

Location	Final diagnosis	Skin biopsy	Managements of reactions	Time of resolution the reaction	Outcome	Cause of death
Not mentioned	Erythrodermic psoriasis with maculohemorrhagic rash	Classical epidermal features of psoriasis. In the superficial dermis we observed oedema, swollen and dilated vessels surrounded by lymphocytes and eosinophils.	Not mentioned	Not mentioned	Not Mentioned	-
Trunk, Elbows, Buttocks, Capillitium, Arms, Lower Limbs	Vasculopathy	A lichenoid dermatitis with marked epidermotropism, numerous necrotic keratinocytes, and conspicuous signs of lymphocytic satellitosis were present. The super ficial dermis was oedematous combined with dilated capillaries, surrounded by lymphocytes and eosinophils throughout the der- mis Surprisingly, large ballooning keratinocytes with nuclear features resembling a cytopathic viral infection were evident in a hair follicle	Not Motioned	10 d after biopsy	D.C	—

location	Final diagnosis	Skin biopsy	Managements of reactions	Time of reaction resolution	Outcome	Cause of death
Face, trunk, limbs	Angioedema	Was not performed	Not reported	Not reported	D.C	—
Flexural region, 30% of body surface	AGEP	Intracorneal and subcorneal spongiform neutrophilic pustules, perivascular and dermal inflammatory infiltrate of neutrophils, keratinocyte necrosis	Withdrawal of hydroxychloroquine and piperacillin- tazobactam and ceftriaxone	5 d after treatment	expired	Massive pulmonary embolism

(Continues)

TABLE 3 (Continued)

First author	Case characteristic	COVID-19 sign and symptoms	Patients' comorbidity	Type of drug	Time of onset the reactions	Type of reactions
Herman A	50-y-old man	ARDS, fever, COVID-19 PCR: Positive	Not Mentioned	Azithromycin, Hydroxychloroquine (17 d before), heparin, propofol, clonidine, norepinephrine, sufentanil rocuronium, pantoprazole (9 d before), sevoflurane (8 d before), cefuroxime (6 d before), flucloxacillin (4 d before)	17 d after first drug initiation	Generalised maculopapular rash, hands and face oedema
Robustelli Test E	70-y-old woman	Pneumonia	Not Mentioned	Lopinavir/ritonavir (200/50 mg two tablets), Hydroxychloroquine (200 mg BID for 10 d)	13 d after drug initiation	Scattered pinhead-sized pustules with scales on an erythematous-oedematous base, symmetric Targetoid lesions and small pustules, without mucosal involvement
Litaiem N	39-y-old woman	Dry cough, dyspnoea, fever, COVID-19 PCR: Positive	Not Mentioned	Hydroxychloroquine (600 mg once daily), enoxaparin	18 d after drug initiation	Erythematous and pustular plaques, cephalocaudal spread, petechiae, erythema and oedema with sterile pustules
Suarez-Valle A	75-y-old woman	Chest CT: Bilateral pneumonia	Not reported	Hydroxychloroquine	20 d after drug initiation	Non-follicular pustules and pruriginous rash on an erythematous and oedematous base, facial oedema
Davoodi L	42-y-old woman	Fever, dry cough, COVID-19 PCR: Positive	Not reported	Hydroxychloroquine (200 mg BID) acetaminophen (500 mg QID)	2days after drug initiation	Erythematous maculopapular rash and flat atypical targets, orolabial area and genital mucosal involvement with ulcers, itchy, positive Nikolsky sign
Torres-Navarro I	49-y-old woman	Severe respiratory failure, COVID-19 PCR: Positive	Morbid obesity	Interferon beta (250 mg BID), hydroxychloroquine (200 mg BID), azithromycin (500 mg daily), ceftriaxone (2 g BID), lopinavir-ritonavir (800-200 daily), methylprednisolone (40 mg BID) tocilizumab (600 mg single dose), cefditoren (400 mg BID, 1 d before skin reaction)	8 d after drug initiation	Erythematous macular rash and rare pustules over the macules

location	Final diagnosis	Skin biopsy	Managements of reactions	Time of reaction resolution	Outcome	Cause of death
More than 70% of his body surface area	DRESS	Lymphohistiocytic cells, eosinophils perivascular infiltration and oedema of the dermis	Withdrawal of azithromycin and hydroxychloroquine, methylprednisolone 1 mg/kg/d	15 d treatment	D.C	—
Face, trunk and upper limbs, buttocks, thighs and legs	AGEP	Perivascular lymphocytic infiltrate with eosinophils and rare neutrophils, mild focal acanthosis and spongiosis with subcorneal pustule, rare keratinocyte necrosis and neutrophilic exocytosis	Prednisone 0.3 mg/kg orally daily	Not reported	D.C	—
Lower legs, trunk	AGEP	Was Not Performed	Withdrawal of hydroxychloroquine	Not reported	Expired	Massive pulmonary embolism
Flexural regions	AGEP	Mild-moderate diffuse spongiosis with neutrophilic exocytosis and non-follicular subcorneal pustules in the epidermis, mild mixed interstitial inflammation consists of lymphocytes and neutrophils and moderate superficial oedema in the underlying dermis.	Methylprednisolone intravenously	28 d after treatment	D.C	—
Entire body	SJS	Not Performed	Withdrawal of hydroxychloroquine, lopinavir/ritonavir 400 mg BID, loratadine 10 mg BID, diphenhydramine 50 mg TID	5 d after treatment	D.C	—
Trunk, neck, face, axillary and neck folds, arms	AGEP	Rare eosinophils within superficial dermis. papillary oedema, inflammatory infiltration and subcorneal pustules	Withdrawal of all drugs, prednisone 0.3 mg/kg once daily	Not reported	D.C	—

(Continues)

TABLE 3 (Continued)

First author	Case characteristic	COVID-19 sign and symptoms	Patients' comorbidity	Type of drug	Time of onset the reactions	Type of reactions
Demirbaş A	37-y-old woman	Confirmed COVID-19	No comorbidity	Hydroxychloroquine (Day 1: 400 mg BID, Day 2-4:200 mg BID), Azithromycin (Day 1: 500 mg daily, Day 2-4: 250 mg daily), oseltamivir (Day 1-5: 75 mg BID)	5 d after drug initiation	Erythematous targetoid lesions, painful ulcerations
Enos T	29-y-oldwoman	Fever, cough, and sore throat, COVID-19 PCR: negative	Protein S deficiency and SJS due to cefaclor	Azithromycin orally, doxycycline and prednisone, hydroxychloroquine 200 mg BID	4 d after drug initiation	Oedematous papules and erythematous macules developing to plaques, pruritus, scattered non-follicular pustules, facial swelling, Nikolsky's sign was negative, Hyperaemic oral mucosa without erosion
Grandolfo M	69-y-old woman	Fever	Lichen planopilaris, hiatal hernia, HTN, hypothyroidism	Hydroxychloroquine (400 mg daily)	20 d after drug initiation	Maculopapular rash erythema multiforme-like appearance, massive exfoliation, facial oedema, multiple, lymphadenopathies
Grewal E	57-y-old man	PCR: positive	HTN, DM	Benazepril	4 mo after drug initiation	Tongue swelling, shortness of breath and difficulty in speaking, without pain or pruritus
Ramirez A	57-y-old woman	Fever, non-productive cough, COVID-19 PCR: positive	Antibiotics allergy, Depression, HTN	Amoxicillin, Ibuprofen and Metamizole	1 d after drug initiation	Day 1: pruritic pink-to-red maculopapular exanthema, Day 3: purpuric, non-blanching, pruritic and painful maculas and plaques
Saha M	62-y-old man	Fever, cough, COVID-19 PCR: positive	HTN, DM, MM, stem cell transplant	Amoxicillin, lenalidomide, septrin and allopurinol 6 wk prior to presentation	At the time of positive PCR	Large areas of flaccid blistering and severe mucosal involvement
Monte-Serrano J	55-y-old woman	Bilateral interstitial pneumonia, positive PCR	Not mentioned	Hydroxychloroquine	12 d after	Erythematous targetoid macules

location	Final diagnosis	Skin biopsy	Managements of reactions	Time of reaction resolution	Outcome	Cause of death
Ventral and dorsal sides of the hands, elbows, palate, lip, tongue	Major Erythema multiforme	Was Not Performed	Withdrawal of all drugs, Methylprednisolone (40 mg daily tapered by 5 mg once daily), Antiseptic mouthwashes and Topical anaesthetic	8 d after treatment	D.C	—
Face, trunk, bilateral arms and thighs, abdomen and the lateral neck	AGEP	Ruptured subcorneal pustule with neutrophils and eosinophils	Withdrawal of Hydroxychloroquine, methylprednisolone orally for 6 d, methylprednisolone 125 mg intravenously, topical triamcinolone 0.1% ointment, methylprednisolone 500 mg intravenously, oral prednisone	35 d after treatment	D.C	—
Facial, trunk spread to the whole-body surface (more than 50%)	DRESS	Interface dermatitis, apoptotic keratinocytes	Withdrawal of hydroxychloroquine, methylprednisolone (60 mg once daily)	1 mo after treatment	D.C	—
Prevertebral, submucosal tissues of the oropharynx, hypopharynx, subcutaneous tissues of the perioral area	Angioedema	Was not performed	Withdrawal of benazepril, tranexamic acid, diphenhydramine, famotidine,	1-d after treatment	D.C	—
Trunk and extremities	Vasculitis	Vasculitis	Withdrawal of all drugs, Prednisolone 120 mg daily intravenously, Antihistamines, Topical glucocorticoid	9 d after treatment	D.C	—
30% of the body surface area, mucosal involvement	TEN	Apoptotic keratinocytes occupying almost the entire thickness of the epidermis	Withdrawal of all previous drugs, supportive treatment, intravenous immunoglobulin (IVIG) at 2 g/kg	3 d after treatment	D.C	—
Trunk and upper limbs	Erythema multiforme	Eosinophil infiltration, interface dermatitis	Discontinue hydroxychloroquine	Not mentioned	Not mentioned	—

(Continues)

TABLE 3 (Continued)

First author	Case characteristic	COVID-19 sign and symptoms	Patients' comorbidity	Type of drug	Time of onset the reactions	Type of reactions
Skroza N	47-y-old-man	Ct scan: pulmonary ground-glass opacifications, COVID-19 PCR: Positive	HTN, Impaired glucose tolerance	Antibiotic, antiviral and anticoagulant, lopinavir/ritonavir, hydroxychloroquine and enoxaparin	17 d after initial covid-19 treatment	Multiple, raised erythematous weal, alone or in cluster, some of them with central purple hyperpigmentation

TABLE 4 Drug related skin manifestations case series

First author	Case characteristic	COVID-19 sign and symptoms	Patients' comorbidity	Type of drug	Time of onset the reactions	Type of reactions
Abadías-Granado I	64-y-old man	Pneumonia, COVID-19 PCR: positive	Diffuse Large B-cell lymphoma, Recent Chemotherapy	Hydroxychloroquine (day 1: 400 mg BID, day 2-10: 200 mg BID) and lopinavir/ritonavir (200/50 mg BID), teicoplanin	14 to 21 d after drug initiation	Pruritic purpuric erythematous rash with non-follicular pustules, negative Nikolsky's sign
	60-y-old woman		Rheumatoid arthritis	Hydroxychloroquine (day 1:400 mg BID, day 2-10: 200 mg BID) and lopinavir/ritonavir (200/50 mg BID), teicoplanin, Azithromycin		Pruritic purpuric erythematous rash with non-follicular pustules, targetoid lesions on the back, negative Nikolsky's sign
Sánchez-Velázquez A	82-y-old man	Not mentioned	Not mentioned	Hydroxychloroquine, ceftriaxone, ertapenem	30 d after	Targetoid, erythematous-violaceous papular plaques
	48-y-old man			Hydroxychloroquine, ritonavir, lopinavir, ceftriaxone, azithromycin	21 d after	

6 | CONCLUSION

Based on this systematic review the reported severe and potential life-threatening mucocutaneous dermatologic manifestations of COVID-19 usually may be divided into three major categories: virus-associated, drug-associated, and those with uncertainty about the exact origin.

Angioedema, vascular lesions, toxic shock syndrome, erythroderma, DRESS, haemorrhagic bulla, AGEP, EM, SJS and TEN, generalised pustular figurate erythema were the main entities found as severe dermatologic reactions that usually seen in all categories.

Necrosis and ischemic lesions appeared to be the most common severe skin manifestations of the novel coronavirus in 32.25% (30/93). Vasculitis or vasculopathy lesions were seen in 17.2% (16/93) of patients. Angioedema occurred in 12.9% (12/93) of reported patients, and the presence of AGEP was seen in 8.6% (8/93). We can conclude vascular injuries may be the cause of the most severe dermatologic manifestations of COVID-19, which is concordant with many proposed hypercoagulopathy inflammatory systemic storms as one of the most important pathomechanisms of COVID-19, so the skin is not an exception which shows these features in various degree and presentations.

location	Final diagnosis	Skin biopsy	Managements of reactions	Time of reaction resolution	Outcome	Cause of death
Head, Trunk, Upper arms	Urticarial Vasculitis	Orthokeratotic hyperkeratosis, spongiosis, focal vacuolar degeneration of basal keratinocytes and focal lymphocytic exocytosis. Slight inflammatory lymphomorphonuclear infiltrate of superficial dermis with minimal perivascular neutrophilic component was observed, with occasional aspects of vessel wall damage	Tapering prednisone, bilastine and pantoprazole	7 d after treatment	D.C	-

location	Final diagnosis	Skin biopsy	Managements of reactions	Time of reaction resolution	Outcome
Trunk, limbs, armpits, scalp	Generalized pustular figurate erythema	Acanthotic epidermis with parakeratosis, numerous intracorneal, subcorneal and intraepidermal pustules, Exocytosis of neutrophils and mild spongiosis at the periphery of the intraepidermal Pustules, mild oedema with erythrocyte extravasation at upper dermis, dilated capillaries and perivascular lymphocytic infiltrated with occasional neutrophils and rare eosinophils	Betamethasone dipropionate cream 0.05% twice a day, loratadine (10 mg/d) and methylprednisolone (40 mg/d)	4 wk after treatment	D.C
Trunk, limbs, armpits, scalp neck and face			Betamethasone dipropionate cream 0.05% BID, loratadine (10 mg/d) and methylprednisolone (40 mg/d)	4 wk after treatment	D.C
Not mentioned	Erythema multiforme	Not mentioned	Not mentioned	Not mentioned	Not mentioned

We need to know more about the probable pathomechanisms of virus-related and the responsible drugs of severe dermatologic manifestations for better management of systemic involvements of COVID-19 and concurrent dermatologic complications. Since the skin could be the mirror of internal organ pathologic events; we can use the dermatologic data of patients to acquire more information about the less accessible internal organs. The role of skin biopsies and following the patients with various dermatologic clinical presentations could be a way to make a judgment about final COVID outcomes, also investigating any probable associations between dermatologic signs and COVID-19 outcomes could be more addressed in future studies. Our finding significantly showed a probable hypercoagulopathy inflammatory storm in COVID-19 patients which needs to approach therapeutically; especially in hospitalised patients with a bad condition or even in non-hospitalised patients with a good condition before going into the deterioration phases.

ACKNOWLEDGEMENTS

The authors would like to express their gratitude to Rasool Akram Medical Complex Clinical Research Development Center (RCRDC), Iran University of Medical Sciences for its technical and editorial assistance.

TABLE 5 Skin manifestations that are not known to be virus-related or drug-related case reports

First author	Case characteristic	COVID-19 sign and symptoms	Covid-19 management	Patients' comorbidity	Time of onset the reactions	Type of skin manifestation
Azmy V	29-y-old woman	Hypoxemic respiratory failure, COVID-19 PCR: Positive	Hydroxychloroquine 400 mg BID, followed by 200 mg BID, piperacillin-tazobactam and vancomycin, ampicillin, remdesivir (4 total doses of 100 mg daily), lovenox (40 mg BID)	DM, DLP, Obesity	18 d after drug initiation	Severe tongue angioedema without urticaria
Cohen AJ	62-y-old man	Fevers, chills, fatigue, myalgia, anorexia, anosmia, ageusia, dry cough, COVID-19 PCR: positive	Not reported	HTN	12 d after	Upper lip and cheeks and lower face swelling, asymmetric, non-pitting oedema
Caputo V	59-y-old man	Severe respiratory failure, Delirium, COVID-19 PCR: positive	Cefepime, piperacillin/tazobactam, linezolid, gentamicin, meropenem, amikacin, methylprednisolone 1 mg/kg daily	Not reported	35 d after	Symmetrically maculopapular purpuric exanthema in face, trunk and extremities
Lagziel T	58-y-old woman	Coughing, fevers, and fatigue, acute respiratory distress, AKI, COVID-19 PCR: positive, CT scan: multifocal pneumonia	Levofloxacin and oseltamivir, broad-spectrum antibiotics (vancomycin, piperacillin, tazobactam), and supportive therapy	Morbid obesity, HTN, gout, CML, CKD	21 d after other symptoms initiation	Disseminated erythematous and papular skin rash after 48 h, developed into vesicles and bullae with desquamation, widespread, large, open wounds, (5% total body surface area of epidermal loss affecting bilateral thighs, bilateral arms, and face), positive Nikolsky's sign
Ayatollahi A	33-y-old man	Positive IgG and negative IgM serology test for COVID-19	Oral azithromycin	Not mentioned	90 d after COVID-19 symptoms	Widespread pruritic pustular lesions on an erythematous base on face, neck, trunk, and hands generalised non-follicular sterile pustules

TABLE 6 Skin manifestations that are not known to be virus-related or drug-related case series

First author	Case characteristic	COVID-19 sign and symptoms	COVID-19 management	Patients comorbidity	Time of onset the reactions
Rosell AM	61-y-old woman	Low-grade fever, COVID-19 PCR: positive	Hydroxychloroquine, lopinavir/ritonavir, ceftriaxone	Asthma	22 d after other symptoms init
	74-y-old woman	Fever, COVID-19 PCR: positive	Hydroxychloroquine, lopinavir/ritonavir, Ceftriaxone, IFN- ß	None	23 d after other symptoms init

Abbreviations: AF, atrial fibrillation; AGEP, acute generalised exanthematous pustulosis; AKI, acute kidney injury; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; BID, twice a day; CAD, coronary artery disease; CHF, chronic heart failure; CKD, chronic kidney disease; CML, chronic myelogenous leukaemia; COPD, chronic obstructive pulmonary disease; CXR, chest x ray; D.C, discharge; DIC, disseminated intravascular coagulation; DLBL, diffuse large B-cell lymphoma; DLP, dyslipidaemia profile; DM, diabetes mellitus; DRESS: drug reaction with eosinophilia and systemic symptoms; DVT, deep vein thrombosis; ESRD, end stage renal disease; HSV, Herpes simplex virus; HTN, hypertension; IHC: immunohistochemistry; MM, multiple myeloma; PAD, peripheral artery disease; QID, four times a day; SAH, subarachnoid haemorrhage; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrosis; TIA, transient ischemic attack; TID, three times a day.

Final diagnosis	Skin biopsy	Managements of reactions	Time of resolution the reaction	outcome
Angioedema	Was Not Performed	Diphenhydramine 50 mg intravenous QID, methylprednisolone 60 mg daily (2 d), Berinert 20 U/kg, Loratadine 10 mg BID	5 d	D.C
Angioedema	Not mentioned	Methylprednisolone intravenously, famotidine, and diphenhydramine	2 d after	D.C
Leucocytoclastic vasculitis	Superficial and deep dermal perivascular neutrophilic infiltrate with red blood cell extravasation and fibrinoid necrosis of vessel walls and sparse leucocytoclasis	Methylprednisolone 1 mg/kg daily	Not reported	Not reported
Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN)	Spongiosis and subtle basilar vacuolar changes with rare dyskeratotic cells, dermis superficial oedema and perivascular, mildly dense, superficial and interstitial infiltration of histiocytes, lymphocytes, rare eosinophils and melanophores. basket-weave stratum corneum and detached epidermis in dermal-epidermal junction.	First: withdrawal of Prophylactic hydrocortisone therapy and antibiotics, second: silver antimicrobial foam dressing BID, oral prednisone (tapered over a week)	Not mentioned	D.C
AGEP	Linear neutrophilic parakeratosis with crust, focal hypergranulosis, acanthosis, and mild spongiosis of epidermis, oedema, ectatic capillaries with margination of polymorphonuclearcells, and perivascular interstitial lymphocytic infiltration in the upper dermis. Mild neutrophilic infiltration and a few eosinophils, coarse and prominent granular layer	Not mentioned	Not mentioned	D.C

Type of skin manifestation	Final diagnosis	Skin biopsy	Managements of reactions	Time of resolution the reaction	Outcome
Generalised maculopapular confluent exanthema Violaceous lesions targetoid lesions, facial oedema, itching	Angioedema	Not performed	Withdrawal of all medications, prednisone (30 mg orally daily), topical corticosteroid	Not mentioned	D.C
			Withdrawal of all medications, methylprednisolone: 30 mg intravenous BID, Topical corticosteroids		D.C

DISCLOSURES

The authors declare that they have no conflict of interest for this study.

AUTHOR CONTRIBUTIONS

AG made the idea of this systematic review. A. G., FM, F. S. and A.P M., wrote the initial draft AG, edited the document. All the authors made extensive contributions to the final draft of this manuscript.

ETHICS APPROVAL

Not applicable.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of the article at the publisher's website.

How to cite this article: Mashayekhi F, Seirafianpour F, Pour Mohammad A, Goodarzi A. Severe and life-threatening COVID-19-related mucocutaneous eruptions: A systematic review. *Int J Clin Pract*. 2021;00:e14720. https://doi.org/10.1111/ijcp.14720