INTRODUCTION

1.1 Rationale

In December 2019, the pandemic of novel coronavirus was reported in Wuhan province of China. 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
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.\textsuperscript{3} According to recent studies, both aerosols and droplets are modes of coronavirus disease transmission.\textsuperscript{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.\textsuperscript{5} Respiratory tract sampling by real-time PCR is a gold standard diagnostic method.\textsuperscript{1}

Besides the multi-systems involvement in COVID-19 diseases, dermatological manifestations have been poorly delineated.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{3} Recently, Some COVID-19 studies reported severe and life-threatening cutaneous drug reactions such as AGEP and DRESS.\textsuperscript{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.\textsuperscript{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.\textsuperscript{9}

Several numbers of life-threatening mucocutaneous reactions are\textsuperscript{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%.\textsuperscript{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.

## 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.
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.

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 six 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.

FIGURE 2 The search strategy for databases

4.1 | Virus-related group19-51

In the virus-related category, 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).
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

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

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. 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. 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. In a case series by Bitar et al, among two cases with TSS, one patient expired because of COVID-19-associated exfoliative shock syndrome. 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. 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. 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. A Necrotic acral lesion was reported by Antonella Tammaro which was super-infected by Pseudomonas aeruginosa and the patient expired. 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. A case of bullous haemorrhagic vasculitis was reported by Negrini who expired because of respiratory insufficiency.

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...
| 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 |
| Adelino 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 periorcular 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 9: 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 | | 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 | — |
| 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 purpuric 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, leukocytoclasia, 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)
| 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 mg BID) | No comorbidity | 5 d after symptom initial | Swelling, erythematous generalised pruritic urticarial lesions, 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 | Superficial 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)
| 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 man | 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 | Erythoderma | 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 feet | 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 | Not Performed | 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)
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. 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.

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 endothelitis 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. 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. In two cases, toxic shock syndrome was the first presentation besides the other COVID-19 symptoms. 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...
lesions in oral mucosa purely. Erythema multiforme 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 in 30% (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.

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 immunemediated 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.
| 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 |
|              |                     |                             |                     |                       |                           | Small haemorrhagic ulcerations on lips, Necrosis on anterior dorsal tongue |
|              | 71-y-old woman      | Cough, dysgeusia, fever, and mild dyspnoea, COVID-19 PCR: Positive | Piperacillin/tazobactam, ceftriaxone. | HTN, DM, Renal Failure, Obesity | 4 d after initial symptoms | Ulcer on the right lateral border of the tongue, and petechia and shallow necrotic at the anterior hard palate |
|              | 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 | Small haemorrhagic ulcerations at upper and lower lips, painful necrotic ulceration on the right lower lip mucosa |
|              | 72-y-old man        | Fever and dyspnea, COVID-19 PCR: Positive | Piperacillin/tazobactam, azithromycin, ceftriaxone | DM, HTN | 5 d after initial symptoms | Large black eschar (5 × 11 cm) with surrounding violaceous induration and retiform purpuric edges |
| 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 | Black eschar (6 × 4 cm) with surrounding induration and erythema |
|              | 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 |                           |
| 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/m² (IV)TID for 10 d, Photobiomodulation therapy daily for 10 d | 11 d after treatment | D.C | —                               |
| Tongue and anterior hard palate | | | Acyclovir 250 mg/m² (IV)TID for 7 d, Photobiomodulation therapy daily for 10 d | >15 d after treatment | D.C | —                               |
| Lips mucosa         |                                  |                              | Acyclovir 250 mg/m² (IV)TID 7 d, Photobiomodulation therapy daily for 10 days | 7 d after treatment              | D.C | —                               |
| Sacrum, buttocks    | Thrombotic Vasculopathy          | Fibrin thrombi in numerous blood vessels                                    | Not Mentioned                                                                             | Not Mentioned                   | Expire  | Haemorrhagic leucoencephalopathy |
| Sacro-cocygeal      | 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 | 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 |
| 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 2-10: 200 mg BID) | Lung adenocarcinoma, | 2 d after symptoms initial | Target lesions with central zone of pallor and erythematous peripheral rim, painful ulcers |
| 58-y-old woman | Diarrhea, fever, dry cough, COVID-19 PCR: positive | Hydroxychloroquine (Day 1: 400 mg BID, Day 2-10: 200 mg BID) | Antiphospholipid syndrome (2/21 patients), Factor V Leiden deficiency (1/21 Patient) | Median 19 d after admission | Purpuric and/or necrotic ulcerations |
| 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) | Medial 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                               |              | 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 microthrombi admixed with nuclear and eosinophilic debris | Not mentioned                   | Not mentioned                   | D.C     |                |
| First author | Case characteristic | COVID-19 sign and symptoms | Patients’ comorbidity | COVID-19 management | 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 |

| 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             | Erythodermic 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 superficial dermis was oedematous combined with dilated capillaries, surrounded by lymphocytes and eosinophils throughout the dermis. Surprisingly, large ballooning keratinocytes with nuclear features resembling a cytopathic viral infection were evident in a hair follicle | Not Mentioned                         | 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     |                |

| Location                  | Final diagnosis                              | Skin biopsy                                | Managements of reactions                                                                 | Time of reaction resolution | Outcome | Cause of death |
|---------------------------|----------------------------------------------|--------------------------------------------|------------------------------------------------------------------------------------------|-----------------------------|---------|----------------|
| 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 |
| 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 tromethamine, 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) | 2 days 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), methylprednisolon (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    | —               |
| 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-old woman      | 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-        | 55-y-old woman      | Bilateral interstitial pneumonia, positive PCR | Not mentioned | Hydroxychloroquine | 12 d after | Erythematous targetoid macules |
| Serrano J    |                     |                             |                       |              |                          |                  |
| 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 |
| 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, ceftriaxone, azithromycin | 21 d after | |

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, 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 | Tapering prednisone, bilastine and pantoprazole                                         | 7 d after treatment         | D.C     | -              |
|                          |                        | vacuolar degeneration of basal keratinocytes and focal lymphocytic exocytosis. Slight inflammatory |                                                                                         |                             |         |                |
|                          |                        | lymphomorphonuclear infiltrate of superficial dermis with minimal perivascular neutrophil component was observed, with occasional aspects of vessel wall damage |                                                                                         |                             |         |                |
| Trunk, limbs, armpits, scalp | Generalized pustular | Acanthotic epidermis with parakeratosis, numerous intraconal, subconal 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 | Erythema multiforme | Not mentioned | Not mentioned | Not mentioned | Not mentioned | Not mentioned |
### 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 initiation |
|              | 74±y-old woman      | Fever, COVID-19 PCR: positive | Hydroxychloroquine, lopinavir/ritonavir, Ceftriaxone, IFN-β | None | 23 d after other symptoms initiation |

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                               | Time of resolution the reaction | Skin biopsy            | Managements of reactions                                                                                                                                                                                                 |
|---------------------------------------------|--------------------------------|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Angioedema                                  | 5 d                            | Was Not Performed      | Diphenhydramine 50 mg intravenously QID, methylprednisolone 60 mg daily (2 d), Berinert 20 U/kg, Loratadine 10 mg BID                                                                                                                                 |
| Angioedema                                  | 2 d after                      | Not mentioned          | Methylprednisolone intravenously, famotidine, and diphenhydramine                                                                                                                                                         |
| Leucocytoclastic vasculitis                 | Not reported                   | 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                                                                                                                                                                                         |
| Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) | Not mentioned                  | 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)                                                                 |
| AGEP                                        | Not mentioned                  | Linear neutrophilic parakeratosis with crust, focal hypergranulosis, acanthosis, and mild spongiosis of epidermis, oedema, ectatic capillaries with margination of polymorphonuclear cells, and perivascular interstitial lymphocytic infiltration in the upper dermis. Mild neutrophilic infiltration and a few eosinophils, coarse and prominent granular layer | Not mentioned                                                                                                                                                                                                          |

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

ORCID
Azadeh Goodarzi https://orcid.org/0000-0002-1249-4429

REFERENCES
1. Guo YR, Cao Q-D, Hong Z-S, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak— an update on the status. Mil Med Res. 2020;7:1-10.
2. Pruc M, Smereka J, Dziedziczkowski T, Jaguszelewski M, Filipiak KJ, Szarpak L. Kawasaki disease shock syndrome or toxic shock syndrome in children and the relationship with COVID-19. Letter. Med Hypotheses. 2020;144:109986.
3. Almutairi N, Schwartz RA. Coronavirus disease-2019 with dermatologic manifestations and implications: an unfolding conundrum. Dermatol Ther. 2020;33:e13544.
4. Jayaweera M, Perera H, Gunawardana B, Manatunge J. Transmission of COVID-19 virus by droplets and aerosols: a critical review on the unresolved dichotomy. Environ Res. 2020;188:109819.
5. Dalal A, Jakhar D, Agarwal V, Beniwal R. Dermatological findings in SARS-CoV-2 positive patients: an observational study from North India. Dermatol Ther. 2020;33:e13849.
6. Grant-Kels JM, Sloan B, Kantor J, Elston DM. Acute generalized exanthematous pustulosis caused by hydroxychloroquine. Ixekizumab for treatment of refractory acute generalized exanthematous pustulosis caused by hydroxychloroquine. JAAD Case Rep. 2020;6:634-636.
7. Negrini S, Guadagno A, Greco M, Parodi A, Burlando M. An unusual case of bullous haemorrhagic vasculitis in a COVID-19 patient. Article in Press. J Eur Acad Dermatol Venereol. 2020;34:e675-e676. doi:10.1111/jdv.16760
8. Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Article. Transl Res. 2020;220:1-13.
9. Deliñoño R, Andrés-Cordón JF, Aracelis De La Cruz Martínez C. Acute urticaria with angioedema in a morbidly obese man successfully treated with glucocorticoids. Ann Allergy Asthma Immunol. 2020;125:359-360.
10. Mayor-Ibarguren A, Feito-Rodriguez M, Quintana Castanedo L, Ruiz-Bravo E, Montero Vega D, Herranz-Pinto P. Cutaneous small vessel vasculitis secondary to COVID-19 infection: A case report. Article in Press. J Eur Acad Dermatol Venereol. 2020;34:e541-e542.
11. Dominguez-Santos M, Díaz-Guimaraens B, García Abella P, Moreno-García del Real C, Burgos-Blasco P, Suarez-Valle A. Cutaneous small-vessel vasculitis associated with novel 2019 coronavirus SARS-CoV-2 infection (COVID-19). Article in Press. J Eur Acad Dermatol Venereol. 2020;34:e536-e537.
12. Bapst T, Romano F, Romano F, Müller M, Rohr M. Special dermatological presentation of paediatric multisystem inflammatory syndrome related to COVID-19: Erythema multiforme. Note. BMJ Case Rep. 2020;13:e236986.
13. Greene AG, Saleh M, Roseman E, Sinert R. Toxic shock-like syndrome and COVID-19: A case report of multisystem inflammatory syndrome in children (MIS-C). Article in Press. Am J Emerg Med. 2020;38:2492.e5-2492.e6.
14. Hassan K. Urticaria and angioedema as a prodromal cutaneous manifestation of SARS-CoV-2 (COVID-19) infection. Article. BMJ Case Rep. 2020;13:e236981.
15. Puram V, Lyon D, Skeik N. A unique case report on hypersensitivity vasculitis as an allergic reaction to the herpes zoster vaccine. Vasc Endovasc Surg. 2019;53:75-78.
16. Cockayne S, Glet R, Gawkrodger D, McDonagh A. Severe erythromycin reactions to the proton pump inhibitors omeprazole and lan- soprazole. Br J Dermatol. 1999;141:173.
17. Hasegawa A, Abe R. Recent advances in managing and understanding Stevens-Johnson syndrome and toxic epidermal necrolysis. F1000Research. 2020;9:F1000. Faculty Rev-612.
18. Munshi M, Junge A, Gadaldi K, Yawalkar N, Heidemeyer K. In: StatPearls [Internet]. StatPearls Publishing; 2019.
19. Gottlieb M, Long B, Koyfman A. The evaluation and management of toxic shock syndrome in the emergency department: a review of the literature. J Emerg Med. 2018;54:807-814.
33. Feng Y, Armenti ST, Albin OR, Mian SI. Novel case of an adult with toxic shock syndrome following COVID-19 infection. Article. Am J Ophthalmol Case Rep. 2020;20:100843.

34. Abasaed Elhag SA, Ibrahim H, Abdelhadi S. Angioedema and urticaria in a COVID-19 patient: a case report and review of the literature. JAAD Case Rep. 2020;6:1091-1094.

35. Nasiri S, Dadkhahfar S, Abasifar H, Mortazavi N, Gheisari M. Urticarial vasculitis in a COVID-19 recovered patient. Letter. Int J Dermatol. 2020;59:1285-1286.

36. Ghalamkarpour F, Pourani MR, Abdollahimajid F, Zargari O. A case of severe psoriatic erythroderma with COVID-19. J Dermatol Treat. 2020:1-3.

37. Tahir A, Sohail Z, Nasim B, Parmar NV. Widespread cutaneous small vessel vasculitis secondary to COVID-19 infection. Letter. Int J Dermatol. 2020;59:1279-1279.

38. Balestri R, Termine S, Rech G, Girardelli CR. Late onset of acral necrosis after SARS-CoV-2 infection resolution. J Eur Acad Dermatol Venereol. 2020;34:e448-e449.

39. Del Giudice P, Boudoumi D, Le Guen B, et al. Catastrophic acute bilateral lower limbs necrosis associated with COVID-19 as a likely consequence of both vasculitis and coagulopathy. J Eur Acad Dermatol Venereol. 2020;34:e679-e680. doi:10.1111/jdv.16763

40. Shoskes A, Migdady I, Fernandez A, Ruggieri P, Rae-Grant A. Cerebral microhemorrhage and purpuric rash in COVID-19: the case for a secondary microangiopathy. J Stroke Cerebrovasc Dis. 2020;29:105111.

41. Verheyden M, Grobler M, Gutermuth J, Velkeniers B. Relapsing symmetric livedo reticularis in a patient with COVID-19 infection. J Eur Acad Dermatol Venereol. 2020;34:e684-e686. doi:10.1111/jdv.16777

42. Khalil S, Hinds BR, Manalo IF, Vargas IM, Mallela S, Jacobs R. Livedo reticularis as a presenting sign of severe acute respiratory syndrome coronavirus 2 infection. JAAD Case Rep. 2020;6:871-874.

43. Heald M, Fish J, Lurie F. Skin manifestations of COVID-19 resembling acute limb ischemia. J Vasc Surg Cases Innov Tech. 2020;6:514-515.

44. Rotman JA, Dean KE, Magro C, Nuovo G, Bartolotta RJ. Concomitant calciphylaxis and COVID-19 associated thrombotic retiform purpura. Skeletal Radiol. 2020;49:1879-1884.

45. Bitar C, Chan MP, Harms PW, et al. Cutaneous manifestations of hospitalized coronavirus disease 2019 patients: a report of six cases with clinicopathologic features and viral RNA in situ hybridization. J Eur Acad Dermatol Venereol. 2020;34:e656-e659. doi:10.1111/jdv.16741

46. Brandão TB, Gueiros LA, Melo TS, et al. Oral lesions in patients with SARS-CoV-2 infection: could the oral cavity be a target organ? Oral Surg Oral Med Oral Pathol Oral Radiol. 2021;131:e45-e51.

47. Young S, Narang J, Kumar S, et al. Large sacral/buttocks ulcerations in the setting of coagulopathy: a case series establishing the skin as a target organ of significant damage and potential morbidity in patients with severe COVID-19. Int Wound J. 2020;17:2033-2037.

48. Labé P, Ly A, Sin C, et al. Erythema multiforme and Kawasaki disease associated with COVID-19 infection in children. Article in Press. J Eur Acad Dermatol Venereol. 2020;34:e539-e541.

49. Rolfo C, Cardona AF, Ruiz-Patiño A, et al. Atypical skin manifestations during immune checkpoint blockade in coronavirus disease 2019-infected patients with lung cancer. J Thorac Oncol. 2020;15:1767-1772.

50. Karagounis TK, Shaw KS, Caplan A, Lo Sicco K, Femia AN. Acrofacial purpura and necrotic ulcerations in COVID-19: a case series from New York City. Int J Dermatol. 2020;59:1419-1422. doi:10.1111/ijd.15181

51. Gianotti R, Recalcati S, Fantini F, et al. Histopathological study of a broad spectrum of skin dermatoses in patients affected or highly suspected of infection by COVID-19 in the northern part of Italy: analysis of the many faces of the viral-induced skin diseases in previous and new reported cases. Article. Am J Dermatopathol. 2020;42:564-570.

52. Castro Jiménez A, Navarrete Navarrete N, Gratacos Gómez AR, Florida López F, García Rodriguez R, Gómez TE. First case of DRESS syndrome caused by hydroxychloroquine with a positive patch test. Note. Contact Dermatitis. 2020;84:50-51.

53. Delaleu J, Deniau B, Battistella M, et al. Acute generalized exanthematous pustulosis induced by hydroxychloroquine prescribed for COVID-19. J Allergy Clin Immunol Pract. 2020;8:2777-2779.e1.

54. Herman A, Matthews M, Mairlot M, et al. Drug reaction with eosinophilia and systemic symptoms syndrome in a patient with COVID-19. Article in Press. J Eur Acad Dermatol Venereol. 2020;34:e768-e700. doi:10.1111/jdv.16838

55. Robustelli Test E, Vezzoli P, Carugno A, et al. Acute generalized exanthematous pustulosis with erythema multiforme-like lesions induced by Hydroxychloroquine in a woman with coronavirus disease 2019 (COVID-19). Letter. J Eur Acad Dermatol Venereol. 2020;34:e457-e459.

56. Litaïem N, Hajlaoui K, Karray M, Slouma M, Zeglaoui F. Acute generalized exanthematous pustulosis after COVID-19 treatment with hydroxychloroquine. Letter. Dermatol Ther. 2020;33:e13565.

57. Suarez-Valle A, Fernandez-Nieto D, Melian-Olivera A, et al. Comment on “Generalized purpuric figure erythema: a newly delineated severe cutaneous drug reaction linked with hydroxychloroquine”: report of a COVID-19 patient with particular findings. Letter. Dermatol Ther. 2020;e13852.

58. Davoodi L, Jafarpour H, Kazeminejad A, Soleymani E, Abhari Z, Razavi A. Hydroxychloroquine-induced Stevens-Johnson syndrome in COVID-19: a rare case report. Article. Oxf Med Case Rep. 2020;2020:193-195.

59. Torres-Navarro I, Abril-Pérez C, Roca-Gínés J, Sánchez-Arráez J, Botella-Estrada R. A case of cefditoren-induced acute generalized exanthematous pustulosis during COVID-19 pandemics. Severe cutaneous adverse reactions are an issue. Letter. J Eur Acad Dermatol Venereol. 2020;34:e537-e539.

60. Demirbaş A, Elmas ÖF, Atasoy M, Türsen Ü, Lotti T. A case of erythema multiforme major in a patient with COVID 19: the role of corticosteroid treatment. Article in Press. Dermatol Ther. 2020;e13899.

61. Enos T, Jeong HS, Vandergriff T, Jacobe HT, Chong BF. Acute generalized exanthematous pustulosis induced by empirical hydroxychloroquine for presumed COVID-19. Letter. Dermatol Ther. 2020;e13834.

62. Grandolfo M, Romita P, Bonamonte D, et al. Drug reaction with eosinophilia and systemic symptoms syndrome caused by hydroxychloroquine with a positive patch test. Article in Press. J Eur Acad Dermatol Venereol. 2020;34:e539-e541.

63. Grewal E, Sutarjono B, Mohammed I. Angioedema, ACE inhibitor and COVID-19. BMJ Case Rep. 2020;13:e237888.

64. Vanegas Ramirez A, Efe D, Fischer M. Drug-induced vasculitis in a patient with COVID-19. J Eur Acad Dermatol Venereol. 2020;34:e361-e362.

65. Saha M, D’Cruz A, Paul N, et al. Toxic epidermal necrolysis and co-existant SARS-CoV-2 (COVID-19) treated with intravenous immunoglobulin: ‘killing 2 birds with one stone’. J Eur Acad Dermatol Venereol. 2020;35:e97-e98. doi:10.1111/jdv.16887

66. Monte Serrano J, Cruaı̈nes Monferrer J, García-García M, García-Gil MF. Hydroxychloroquine-induced erythema multiforme in a patient with COVID-19. Article. Med Clin. 2020;155:231.

67. Skroza N, Bernardini N, Balduzzi V, et al. A late-onset widespread skin rash in a previous COVID-19-infected patient: viral or multi-drug effect? J Eur Acad Dermatol Venereol. 2020;34:e438-e439.

68. Abadías-Granado I, Palma-Ruiz AM, Cerro PA, et al. Generalized purpuric figure erythema first report in two COVID-19 patients on hydroxychloroquine. J Eur Acad Dermatol Venereol. 2020;35:e5-e7. doi:10.1111/jdv.16903
69. Sánchez-Velázquez A, Falkenhain D, Rivera DR. Erythema multiforme in the context of SARS-coronavirus-2 infection. Med Clin (Barc). 2020;155:141.

70. Azmy V, Benson J, Love K, Steele R. Idiopathic nonhistaminergic acquired angioedema in a patient with coronavirus disease 2019. Article. Ann Allergy Asthma Immunol. 2020;125:600-602.

71. Cohen AJ, DiFranco MF, Solomon SD, Vaduganathan M. Angioedema in COVID-19. Article in Press. Eur Heart J. 2020;41:3283-3284.

72. Caputo V, Schroeder J, Rongioletti F. A generalized purpuric eruption with histopathologic features of leucocytoclastic vasculitis in a patient severely ill with COVID-19. Article in Press. J Eur Acad Dermatol Venereol. 2020;34:e579-e581.

73. Lagziel T, Quiroga L, Ramos M, Hultman CS, Asif M. Two false negative test results in a symptomatic patient with a confirmed case of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and suspected stevens-johnson syndrome/toxic epidermal necrolysis (SJS/TEN). Cureus. 2020;12:e8198.

74. Ayatollahi A, Robati RM, Kamyab K, Firooz A. Late-onset AGEP-like Atefi NS, Behrangi E, Mozafarpoor S, Seirafianpour F, Peighambari Z, Goodarzi Z. A comprehensive review of histopathologic changes and cellular events of various organs in patients with COVID-19. J Cell Mol Anesth. 2021;6:81-88.

75. Mohamadi M, Fattahi N, Goodarzi A, et al. A comprehensive review on COVID-19 infection and comorbidities of various organs. Acta Med Iran. 2021;59:4-14. doi:10.18502/actav.5991.5396.

76. Kooranifar S, Sadeghipour A, Riahi T, Goodarzi A, Tabrizi S, Davodny. Histopathologic survey on lung necropsy specimens of 15 patients who died from COVID-19: a large study from Iran with a high rate of anthracosis. Med J Islam Repub Iran. 2021;35:63.

77. Najar Nobari N, Seirafianpour F, Dodangeh M, et al. A systematic review of the histopathologic survey on skin biopsies in patients with Corona Virus Disease 2019 (COVID-19) who developed virus or drug-related mucocutaneous manifestations. Exp Dermatol. 2021;35:481-490. doi:10.1111/exd.14384.

78. Sadeghzadeh-Bazargan A, Rezai M, Najar Nobari N, Mozafarpoor S, Goodarzi A. Skin manifestations as potential symptoms of diffuse vascular injury in critical COVID-19 patients. J Cutan Pathol. 2021:48:1266-1276. doi:10.1111/cup.14059.

79. Kalantari S, Sadeghzadeh-Bazargan A, Ebrahimi S, et al. The effect of influenza vaccine on severity of COVID-19 infection: an original study from Iran. Med J Islam Repub Iran. 2021:35:114. doi:10.47176/mjiri.35.114.

80. Riahi T, Sadeghzadeh-Bazargan A, Shokri S, et al. The effect of opium on severity of COVID-19 infection: an original study from Iran. Med J Islam Repub Iran. 2021:35:115. doi:10.47176/mjiri.35.115.

81. Tavakolpour S, Aryanian Z, Seirafianpour F, et al. A systematic review on efficacy, safety, and treatment-durability of low-dose rituximab for the treatment of Pemphigus: special focus on COVID-19 pandemic concerns. Immunopharmacol Immunotoxicol. 2021:1-12. doi:10.1080/08923973.2021.1953063.

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