Cutaneous manifestations and considerations in COVID-19 pandemic: A systematic review

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Abstract
COVID-19 had a great impact on medical approaches among dermatologist. This systematic review focuses on all skin problems related to COVID-19, including primary and secondary COVID-related cutaneous presentations and the experts recommendations about dermatological managements especially immunomodulators usage issues. Search was performed on PubMed, Scopus, Embase and ScienceDirect. Other additional resources were searched included Cochrane, WHO, Medscape and coronavirus dermatology resource of Nottingham university. The search completed on May 3, 2020. Three hundred seventy-seven articles assigned to the inclusion and exclusion groups. Eighty-nine articles entered the review. Primary mucocutaneous and appendageal presentations could be the initial or evolving signs of COVID-19. It could be manifest most commonly as a maculopapular exanthematous or morbiliform eruption, generalized urticaria or pseudo chilblains recognized as “COVID toes” (pernio-like acral lesions or vasculopathic rashes). During pandemic, Non-infected non-at risk patients with immune-medicated dermatologic disorders under treatment with immunosuppressive immunomodulators do not need to alter their regimen or discontinue their therapies. At-risk o suspected patients may need dose reduction, interval increase or temporary drug discontinuation (at least 2 weeks). Patients with an active COVID-19 infection should hold the biologic or non-biologic immunosuppressives until the complete recovery occur (at least 4 weeks).

KEYWORDS
alopecia, biologic, collagen vascular disorder, corona virus, cosmetic procedure, COVID-19, cutaneous, cutaneous manifestation, dermatitis, dermatology, drug reaction, eczema, health care staff, hidradenitis suppurativa, immunobullous, immunomodulator, immunosuppressant, immunosuppressive, novel human coronavirus (SARS-CoV-2), pandemic considerations, papulosquamous, pemphigus, psoriasis, recommendation, skin, skin manifestation, skin rheumatologic disorder, special, specific skin diseases, surgical procedure, systematic review, systemic treatment, teledermatology, visits

1 | INTRODUCTION

COVID-19 outbreak, globally, had a significant impact on the medical approaches among different specialties. For the dermatologist
specifically, the cutaneous manifestations which are suggesting clues of COVID-19 are of great importance. Several articles have been introduced patients with primary nail, mucosal and skin complaints as an initial or evolving presenting signs of COVID-19. Maculopapular eruptions, urticaria, or the acral vasculopathic rashes (pseudo chilblains, pernio-like lesions) recognized as the "COVID toe," are the most common mucocutaneous manifestations of new corona virus; while the patients usually develop the common symptoms of COVID-19, few days after the initiation of these skin eruptions.

There is also dermatoses like COVID-19 treatment-related drug reactions, especially the generalized pustular rash due to hydroxychloroquine. In addition to mentioned dermatoses, there are many other dermatological concerns during pandemic as there are several skin conditions that may be treated by anti-inflammatory, Immunomodulatory drugs or biologic agents, from them, vesiculobulbous disease, autoimmune disorders, collagen vascular disease, psoriasis and so forth, could be mentioned and patients with these type of diseases considered as immunocompromised. These patients may need drug-dosage or drug-administration frequency alterations or even drug cessations during the time of pandemic especially in the case of personal infection or having a highly suspicious exposure that may leading to further disease aggravation or poorly disease controlling.

Secondary dermatoses are other concerns in the pandemic, so occurrence of an acute new dermatose could be seen frequently; some due to stress-related causes such as Herpes Simplex, Herpes Zoster, patchy alopecia areata and some due to physical-environmental causes like acute allergic or irritant contact dermatitis or acute urticaria.

Moreover, some acute conditions have a tendency to become chronic, from these, telogen-effluvium, eczema, chronic contact dermatitis, neurocutaneous or psychocutaneous disorders could be noted. There are also many preexisting chronic dermatoses may become poorly-controlled or aggravated due to some circumstances (like stress, irregular visits, treatment interruptions, delayed therapies, physical, environmental and behavioral issues such as wearing masks and latex gloves, frequent washing and disinfectants, excessive sweating...) for example, rosacea, acne, dermatitis and systemic or non-systemic immune-mediated cutaneous disorders (immune-bullous disorders, rheumatologic skin diseases, psoriasis, hidradenitis suppurativa, alopecia areata, lichen planus, and etc.). COVID-19 pandemic highlighted the role of preventive measures while visiting the patients. In a study of United States, it have been reported that almost half of the dermatologist closed their office or limited their practices only to the patients needed emergency cares and the cosmetic or elective surgical procedures have been postponed.

This raises the urgent need for having a better knowledge about future perspectives in dermatology; considering teledermatology and try to know more about virus or its drug-associated skin eruptions.

The aim of this systematic review is to present an overview of suggestive skin manifestations of the COVID-19 and to address several considerations in the dermatological issues practices, during this pandemic.

## METHOD

### 2.1 Protocol and registration

This study is implemented according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.

### 2.2 Eligibility criteria

Inclusion criteria comprised all studies about virus or drug-related cutaneous manifestations of COVID-19 and most presented concerns in the management of dermatologic disorders or patients may treat with immunosuppressive, immunomodulator and biologic therapies, acute presentation or aggravation of pre-existing dermatoses like severe contact dermatitis, more severe atopic eczema, acute urticaria and etc, cutaneous adverse drug reactions, cutaneous involvements of health care providers and skin care issues; in this global pandemic. The exclusion criteria consisted of all publications not meeting the above, non-English literature, studies before December 1, 2019 and studies in which no mention of skin manifestations of COVID-19 or dermatology consideration in n-cov2019 pandemic. Three hundred seventy-seven articles assigned to the inclusion and exclusion groups. And after screening, 89 articles entered this systematic review as you see in Figure S1.

### 2.3 Information sources

Databases PubMed (http://ncbi.nlm.nih.gov/pubmed), Scopus (http://www.scopus.com), Embase (http://www.embase.com) and Sciedirect (https://www.sciencedirect.com) have been searched for the evidence. Other sources searched to make use of the additional research 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/).

### 2.4 Search strategy

Table S6 shows the search strategies used, not limit the entries to any condition. The search was performed by keywords COVID-19 and alternative names has been called, and skin manifestations, dermatology considerations, skin care and their synonyms. The search completed on May 3, 2020, and only the articles after date of December 1, 2019 have been included.

### 2.5 Study selection

Endnote X8 (Clarivate Analytics, Philadelphia) was used for study screening and data extraction. 377 articles assigned to the inclusion
and exclusion groups. In first step the titles and abstracts of articles were read. And, if accepted has evaluated to second step; the full-text screening, the authors read the full-text and executed the final inclusion articles. Disagreement situations regarding the inclusion process resolved through dialogue and no necessity for a third-party involvement occurred.

3 | RESULT

Totally there were 453 articles with 76 duplicate data that were deleted. Three hundred seventy-seven articles were screened by the authors. From 377 articles, 240 article met exclusion criteria in the first step. And, 39 article met exclusion criteria in the second step. Eighty-nine articles met inclusion criteria. Twenty-seven articles were about cutaneous manifestation of COVID-19; from them, 19 articles were case-reports and 8 articles were case-series. You can see the details in Figure S1. In Tables 1 and 2, we summarized case reports and case series of primary cutaneous COVID-19-related reactions, respectively. In Table 3, you can see cutaneous drug reactions related to COVID-19 treatment, till to our systematic search. Since there are wide categories of proposed drugs for treatment of COVID-19, in Table S8 the most prevalent and important cutaneous adverse reactions of these drugs is visible according to Tursen et al. review on all possible COVID-19 drugs skin reaction.\(^4\) Totally five articles were about skin drug reactions of COVID-19 treatments; two of them were original studies as case reports that were summarized in Table S7. Also, in Sharma, Ajay et al and Jakhar et al. Studies, adverse effect of hydroxychloroquine were reviewed.\(^2\) Eleven articles were about skin injuries among medical staff fighting COVID-19 & general population and usable recommendation about skin care in this global crisis that summarized in Table 3. And in Table 4, prevalence of areas affected by secondary skin complications were recorded. Also, 46 articles were about concerns in management of immune-based dermatologic disorders and autoimmune rheumatologic disorder and collagen vascular disease, and immunomodulator treatments in this pandemic. Twenty-six of them do not have certain usable recommendation and 20 of them had specific advice that reported in Table 5. Table S6 shows our exact search strategy.

4 | DISCUSSION

Coronavirus widespread quickly across the world and in the March 2020, WHO announced the pandemic condition\(^7\). There is necessity to paying more attention to skin and its appendix (hair, nail) and the mucosal manifestation of COVID-19 also being more aware of them and updates our knowledge according to the latest reports.

These manifestations could be the presenting signs of COVID-19 which may help for early disease diagnosis. In addition, we had many concerns about patient who are suffering from chronic dermatologic disorders which needed to have repeated follow ups or who are on immunomodulator agents specifically immunosuppressives that are needed to be controlled without any more risk to getting infected with COVID-19 or getting involved with its consequences.

4.1 | Primary skin manifestations of COVID-19

4.1.1 | Virus related

According to the study which has done among 88 positive patients with COVID-19, in Italy, 20.4% of patient had skin manifestation that the most common manifestation was erythematous rash or patchy exanthematous red rash. Also, there was urticarial eruption that could be localized or widespread, and 1 case of chickenpox-like blisters. The most involved area was trunk and all of the lesions were pruritic. There was not no any relation between disease severity and skin manifestations.\(^27\)

In a study carried out in France between 103 patients, skin manifestations were seen in 5(4.9%), which were red rashes or urticarial rashes, mostly in the face and upper trunk. And there was a case of HSV-1 in an intubated patient.\(^31\) There were reports of COVID-19 patients with mottling or livedo-reticularis (LR) that could be because of disseminated intravascular coagulation (DIC).\(^16\) Transient LR have been also seen in 2 COVID-19 patients who were not in bad general condition.\(^16\) Petechial skin rash (Dengue-like) could be considered as a presenting sign of COVID-19, like acute hemorrhagic edema of infancy.\(^8\) Symmetrical pruritic papules on both heels which were confluent yellowish- erythematous in color appeared 13 days after symptoms onset of COVID-19 in a 28-year-old previously healthy woman, that gradually became erythematous hardened pruritic plaques.\(^8\) Acro-ischemic lesions (pseudo-chilblain or Pernio-like lesion) or “COVID toe” which are micro thrombotic presentations of COVID occur in both children and adolescents when they are in good health condition, and the main affected parts were the feet and hands. The color of lesions were red and purple or blue and they could become blistering or having a black crust.\(^66\)

In a study of 63 patients who complained about chilblain like lesions in Italy, the range of patient’s age was 12 to 16 years old, and the most affected area was the feet (85.7%), then the both hands plus feet in the second place (7%), and next the only hands (6%). Most lesions were erythematous edematous, and in blistering form. Most of the cases were in good general conditions, some of the patients were symptomatic as, gastrointestinal (11.1%), respiratory (7.9%) or febrile (4.8%) before showing skin manifestations. It was not possible to perform confirmatory tests for SARS-CoV-2 in all patients, but in those who did (18 cases), 4 of them turned positive. A study stated the hypothesis of chilblain-like lesions could be occur because of delayed immune reaction to COVID-19 in genetically prone ones.\(^30\) A similar study with these finding performed in Spain.\(^12\)

In a case series of 14 patients, 11 children with average age of 14.4 years and 3 adult patients with average age of 29 years were reported, they did not have any systemic symptoms except cough and fever in 3 cases from 3 weeks before skin eruption onset. The morphology of rash was a red-purple maculopapular eruption on the feet,
| First author | Title | Cutaneous manifestation | Case characteristic | Accompanied by COVID-19 symptoms | Drug history | Involvement site | Skin biopsy | Duration of skin lesion |
|-------------|-------|-------------------------|---------------------|----------------------------------|-------------|------------------|-------------|------------------------|
| Andrea Estébanez | Cutaneous manifestations in COVID-19: a new contribution | Pruritic erythematous-yellowish papules | 28-year-old woman | 15 days after COVID-19 diagnose | 10 days after last dose of paracetamol | On both heels | Not reported | Not reported |
| Henry, D | Urticarial eruption in COVID-19 infection | Pruritic disseminated erythematous plaques eruption | 27-year-old woman | Before fever and respiratory syndrome | Not reported | Particular face and acral involvement | Not reported | Not reported |
| B. Ahouach | Cutaneous lesions in a patient with COVID-19: are they related? | Rash (Diffuse fixed erythematous blanching maculopapular lesions) | 57-year-old woman | 2 days after fever and in same time with dry cough | Not reported | Limbs and trunk and palms | Not reported | Not reported |
| Anwar Alramthan | A case of COVID-19 presenting in clinical picture resembling chilblains disease. First report from the Middle East | Rash (red-purple papules) + diffused erythema | A 27-year-old females | Asymptotic, RT-PCR confirmed COVID-19 | Not reported | Acal areas (dorsal aspect of fingers bilaterally) | Not reported | Not reported |
| Nerea Landa | Chilblain-like lesions on feet and hands during the COVID-19 Pandemic | Reddish and papular resembling chilblains after 1 week they become more purpuric and flattened (referred discomfort or pain when palpated) | 15 year old male | Same time with chest x-ray showing mild bilateral pneumonia | Not reported | Five in toes and heels | Not reported | Not reported |
| Wu, Ping | A child confirmed COVID-19 with only symptoms of conjunctivitis and eyelid dermatitis | Dermatitis | 2 years and 10 months old | 7 days after RT-PCR confirmed COVID-19 | Not reported | Eyelid | Not reported | 5 days |
| Sachdeva, Muskaan | Cutaneous manifestations of COVID-19: Report of three cases and a review of literature | Maculo-papular rash | 71-year-old Caucasian woman | 10 days after COVID-19 symptoms | No medication | Trunk (itchy) | Not reported | Not reported |
| | Diffuse maculopapular exanthem (morbilliform) + macular hemorrhagic rash | 77-year-old Caucasian woman | At the same time with COVID-19 symptoms | Not reported | Trunk + legs | Not reported | Not reported | Not reported |
| | Papular-vesicular, pruritic eruption | 72-year-old Caucasian woman | 4 days After COVID-19 symptoms | Not reported | Sub-mammary folds, trunk and hips | Not reported | Not reported | Not reported |
| First author | Title | Cutaneous manifestation | Case characteristic | Accompanied by COVID-19 symptoms | Drug history | Involvement site | Skin biopsy | Duration of skin lesion |
|--------------|-------|-------------------------|---------------------|---------------------------------|--------------|-----------------|-------------|------------------------|
| Rivera-Oyola, Ryan | Dermatologic findings in two patients with COVID-19 | Rash and scattered erythematous macules coalescing into papules | 60-year-old male | 3 days after COVID-19 symptoms | no recent changes to her medications | Back, flanks, groin and upper thighs | Mild perivascular infiltrate of predominantly mononuclear cells surrounding the superficial blood vessels and epidermis showed scattered foci of hydropic changes along with minimal acanthosis, slight spongiosis and foci of parakeratosis | 7 days |
| Manalo, Iviensan F. | A Dermatologic Manifestation of COVID-19: Transient Livedo Reticularis | transient non-pruritic blanching unilateral livedo reticular patch | 67-year-old Caucasian male | 7 days after COVID-19 symptoms | Not reported | Right anterior thigh | Not reported | 1 day |
| Mahé, A. | A distinctive skin rash associated with Coronavirus Disease 2019 | Erythematous rash | 64-years-old woman | 4 days after COVID-19 symptoms | 4 days after began to take oral paracetamol | Both antecubital fossa, extended on the trunk and axillary folds | Not reported | 5 days |
| Lu, S. | Alert for non-respiratory symptoms of Coronavirus Disease 2019 (COVID-19) patients in epidemic period: A case report of familial cluster with three asymptomatic COVID-19 patients | Generalized Urticaria | Not reported | 1 week after dry cough | Not reported | Generalized | Not reported | Not reported |
| Hunt, M. | A Case of COVID-19 Pneumonia in a Young Male with Full Body Rash as a Presenting Symptom | Diffuse morbilliform maculopapular rash | 20 years old man | Fever and rash simultaneously | Not reported | Trunk, extremities | Not reported | Not reported |
| Magro, C. | Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases | Retiform purpura with extensive surrounding inflammation | 32 years old male | One week after fever and cough he became ventilator dependent, 4 days after ventilator support skin rash appeared | hydroxychloroquine, azithromycin and remdesivir | Buttocks | There was a significant degree of interstitial and perivascular neutrophilia with prominent leukocytosis. IHC showed striking and extensive deposition of C5b-9 within the microvasculature | Not reported |
| First author | Title                                                                 | Case characteristic                                                                 | Accompanied by COVID-19 symptoms                                                                 | Drug history                                      | Involvement site   | Skin biopsy                                             | Duration of skin lesion |
|-------------|----------------------------------------------------------------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|--------------------------------------------------|--------------------|--------------------------------------------------------|-------------------------|
| Chen, Y.    | Infants Born to Mothers with a New Coronavirus (COVID-19)              | 40-year-old woman                                                                      | after 2 weeks of dry cough, fever, myalgias, diarrhea, and progressive dyspnea                   | Not reported                                    | chest, legs and arms | Extensive vascular deposits of C5b-9 (figure 6C), C3d, and C4d were observed throughout the dermis, with marked deposition in an occluded artery. Not reported |
|            |                                                                     | Above 37-week gestational age infant                                                   | edema of the lateral thigh                                                                      | Nothing                                         | Diffuse            | Not reported                                            | 1 day                   |
|            |                                                                     | Above 37-week gestational age infant                                                   | TTN (transient tachypnea of the newborn)                                                       | Nothing                                         | Not reported        | Not reported                                            | 8-9 days                |
| Chen, Y.    |                                                                      | First on forehead and progress to diffuse small millary red papules                   |                                                                                                  |                                                  |                    |                                                        |                         |
|            |                                                                      |                                                                                       |                                                                                                  |                                                  |                    |                                                        |                         |
| Chen, Y.    |                                                                      | 58-year-old Hispanic male                                                              | cough and pain in hands and legs 3 days ago                                                     | azithromycin and benzonatate                    | legs, thighs, forearms, arms, shoulders, back, chest, and abdomen Not reported | 2 days                   |
| Hoegg, Leonard J. | Rash as a Clinical Manifestation of COVID-19 Photographs of a Patient | Erythematous, edematous, malar eruption                                               | sore throat, malaise, ache, nonproductive cough, anosmia, ageusia, fever                        | adalimumab                                      | Face               | Not reported                                            | 6 days                  |
| Jimenez-Cauhe, Juan | Reply to “COVID-19 can present with a rash and be mistaken for Dengue”: Petechial rash in a patient with COVID-19 infection | Erythematous-purpuric, millimetric, coalescing macules                                  | 3 days after hospitalization (11 days after COVID-19 symptoms)                                | hydroxychloroquine and lopinavir/ritonavir      | Flexural regions mainly in peri-axillary area           | Not reported                                            |                         |
| Quintana-Castanedo, Lucia | Urticarial exanthem as early diagnostic clue for COVID-19 infection | Urticarial rash consisting of confluent, edematous and erythematous papules                | Not reported                                                                                   | No drug during the last 2 months                | Thighs, arms, and forearms                              | Not reported                                            | 7 days                  |
| Miriam Morey | Cutaneous manifestations in the current pandemic of coronavirus infection disease (COVID 2019) | 6-year old boy                                                                        | 2 weak after symptoms and 48 hours after confirmed COVID-19 test                               | Not reported                                    | Trunk and neck that gradually spread to the cheeks and upper and lower extremities, reaching the palms of the hands Not reported | 5 days                   |
| Miriam Morey |                                                                      | 2-month old girl                                                                       | 4 days after low fever, at the same time with COVID-19 cinfim                                  | Not reported                                    | Face and upper extremities and spread in a few hours to the trunk and lower extremities Not reported | 5 days                   |
**TABLE 2**  Case series of COVID-19 skin manifestations

| First name | Title | Percentage of skin lesions | Skin lesions characteristic | Accompanied by COVID-19 symptoms | Location of skin lesions | Accompanied by specific symptoms | Age | Duration of skin lesions, mean (days) |
|------------|-------|-----------------------------|-----------------------------|-----------------------------------|--------------------------|-----------------------------------|-----|-------------------------------------|
| S. Recalcati | Cutaneous manifestations in COVID-19: a first perspective<sup>27</sup> | 15% | Erythematous rash | 40% had used new medicine in 15 previous days, 12% were hospitalized | Trunk | Itching was low or absent and usually lesions healed in few days | Not reported | Not reported |
| | | 3% | Widespread urticaria | | | | Not reported | Not reported |
| | | 1% | Chickenpox-like vesicles | | | | Not reported | Not reported |
| C. Galván Casas | Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases<sup>3</sup> | 19% | Erythema with vesicles or pustules (Pseudo-chilblain) | 59% after other symptoms | Acral areas | Pain (32%) or itch (30%). | younger patients | 12.7 days |
| | | 9% | Other vesicular eruptions | 15% before other symptoms | Trunk and limbs | Itching (68%). | middle aged patients | 10.4 days |
| | | 19% | Urticarial lesions | Not reported | trunk or disperse and palmar dorsum of the hands | Itching (92%). | Not reported | 6.8 days |
| | | 47% | Maculopapular eruptions | Not reported | truncal or acral ischemia | Itching (57%). | Not reported | 8.6 days |
| | | 6% | Livedo or necrosis | Not reported | | Not reported | Not reported | Not reported |
| Fernandez-Nieto, D. | Characterization of acute acro-ischemic lesions in non-hospitalized patients: a case series of 132 patients during the COVID-19 outbreak<sup>28</sup> | 72.0% | Chilblain-like | 12% after other symptoms and 2% at the same time with other symptoms | Acral area (34% hands and 76% feet and 12.6% heels or wrists) | Not reported | Mean of age were 23.4 years old | 9.2 days |
| | | 28.0% | Erythema multiforme-like | | Acral area (21% hands and 94% feet and 27% heels or wrists) | Not reported | Mean of age were 12.2 years old | 7.4 |
| Gianotti, Raffae | Clinical and Histopathological study of skin dermatoses in patients affected by COVID-19 infection in the Northern part of Italy<sup>29</sup> | Not reported | Diffuse maculo-papulo-vesicular rash | Lung biopsy of COVID + pneumonia indicates a severe damage of the alveolar epithelial cell floating in the alveolar space just like in bullous severe erythema multiforme in which ballooning keratinocytes detach from the spinous layer. | Arm | classic dyskeratotic cells, ballooning multinucleated cells and sparse necrotic keratinocytes | Not reported | Not reported |
| | | Not reported | Hemorrhagic dot-like area are due to extravasated erythrocytes | | | trunk | lymphocytic satellitosis, perivascular spangiotic dermatitis with exocytosis along with a large nest of Langerhans cells and a dense perivascular lymphocytic infiltration eosinophilic rich around the swollen blood vessels with extravasated erythrocytes | Not reported | Not reported |
| | | Not reported | Poplar erythematous exanthem | | | trunk | Not reported | Not reported |
| | | Not reported | Diffuse macular livedoid hemorrhagic lesions | | | leg | Not reported | Not reported |
| Piccolo, V. | Chilblain-like lesions during COVID-19 epidemic: a preliminary study on 63 patients<sup>30</sup> | 100% | 31/54 erythematous oedematous lesion, 23/54 blister | Gastrointestinal symptoms 11.1%, respiratory symptoms 7.9%, fever 4.8% | Feet (85.7%), hand (6%), hand and feet together (7%) | Pain & itching sensation 27%, both together 20.6% | Median 14 | Not reported |
| Hedou, M. | Comment on "Cutaneous manifestations in COVID-19: a first perspective" by Recalcati<sup>31</sup> | 4.9% | Erythematous rash, urticaria | Not reported | Face, upper body | Itching | Mean age 47 | Not reported |

(Continues)
hand of both sides and in 2 children papular targetoid lesions appeared on the hands and the elbow after few days. The rash diminished without any treatment during 2 to 4 weeks. The tests of 4 of them showed a negative result for COVID-19. Acral ischemic lesions, 2 healthy young females who complained of bilateral papules on the dorsum of their fingers in a red-purple color reported, a 35-year-old patient had another complaint about diffuse redness under the nail of her right thumb. They both confirmed for having SARS-CoV-2. Digit ischemia may happen due to transient increase in antiphospholipid antibodies in severe illnesses or in viral disorders. Another assumption was that this digit ischemia could be related to immunological mechanism or prothrombotic activation states. Pruritic lesions in severe COVID-19-related respiratory failures revealed an inflammatory thrombogenic vasculopathy with trace amount of C5b_9 and C4d depositions. Maculopapular lesions which were fixed erythematous blanching on the trunk and limbs presented 2 days after onset of COVID infection symptoms in a 57 years old woman with not any significant past medical history.

In another case who was a 48 years old man with HTN, 3 days after onset of fever, the macules, papules and petechial lesions appeared in a symmetric pattern in buttocks, popliteal fossae, proximal anterior thighs, and the lower abdomen. The petechial lesions were similar to parvovirus B19 infection. In a 6 years old boy after 14 to 16 days’ work-up for fever and elevated liver enzymes, erythematous, nonpruritic maculopapular rashes appeared first in the trunk and neck and then gradually spread to the other areas. The lesions diminished with no specific therapies after 5 days. A 34 months old child with conjunctivitis and eyelid dermatitis confirmed SARS-CoV-2 in China. Acute urticaria and low-grade fever was noticed in 2 months girl lasted 4 days, and spread in few hours from face and upper extremities toward lowers limbs and trunk.
| First author | Title | Skin injuries among medical staff fighting COVID-19 & general population | Percentage | Recommendations |
|--------------|-------|---------------------------------------------------------------------|------------|-----------------|
| Bahareh Abtahi-Naeini | Frequent handwashing amidst the COVID-19 outbreak: prevention of hand irritant contact dermatitis and other considerations | Eczema, irritant contact dermatitis, methicillin-resistant Staphylococcus aureus colonization | Not reported | • Frequent use of emollients/ • Use soap-free cleanser; synthetic detergents have a neutral or slightly acidic pH and have relatively high free fatty acid content/ • Use alcohol-based cleansers or other antibacterial hand rub/ • Use lukewarm water (45°C-50°C)/ • Use paper towels drying of hands after washing instead electric air dryers/ • Apply an ointment-based emollient during work time after hand washing and after work, at home/ • Avoid a water-based moisturizer/ • Avoid coming into direct contact with chemicals that are used for surface disinfection/ • Use anti-inflammatory topical medication under the supervision of a specialist |
| Pingping Lin | Adverse skin reactions among health care workers during the coronavirus disease 2019 Outbreak: A survey in Wuhan and Its surrounding regions | Occupational contact dermatitis, dryness or scales, papules or erythema, maceration | 31.5% | • applying moisturizers/ • Using alcohol-based products instead of soaps/ • Double gloving is sufficient/ |
| Patruno, Cataldo | The role of occupational dermatology in the COVID-19 outbreak | Dryness, irritation, itching, and even fissuring and bleeding, hand dermatitis, maceration | Not reported | • Application of hand cream/moisturizers on intact skin after hand washing/ • Disposable packaging is recommended |
| Pei, S. | Occupational skin conditions on the frontline: A survey among 484 Chinese health care professionals caring for COVID-19 patients | Various degrees of pruritus, mild pruritus, moderate pruritus, severe pruritus, various skin lesions, erythema, prurigo, blisters, rhagades, papule/edema, exudation/crust, lichenification, scratch | 61.8% | Not reported |
| Bin Zhang | COVID-19 epidemic: Skin protection for health care workers must not be ignored | Indentations, ecchymosis, maceration, abrasion and erosion, blisters and itching and bleeding, dermatitis and folliculitis, fungal infections, desquamation, rhagades, eczema-like changes, ulcers followed by secondary bacterial or fungal infections | Not reported | • Shorter rotating shifts/ • Soap-based cleansers and synthetic cleansers can be used/ • Excessive washing of the skin and repeated application of disinfectants (eg, bleach and alcohol) should be avoided/ • should check whether there is excessive pressure when using the PPE/ • If there are eczema-like changes, a glucocorticoid cream or ointment can be applied topically/ • When ulcers followed by secondary bacterial or fungal infections occur, an antibiotic ointment or antifungal drug may be applied on the skin lesions and covered with wound dressings/ • dry skin alleviated by non-irritating creams or emulsions containing urea or ceramide with long moisturizing time/ (Continues)
| First author | Title                                                                 | Skin injuries among medical staff fighting COVID-19 & general population | Percentage | Recommendations |
|--------------|------------------------------------------------------------------------|--------------------------------------------------------------------------|------------|-----------------|
| Qixia Jiang  | The Prevalence, Characteristics, and Prevention Status of Skin Injury Caused by Personal Protective Equipment Among Medical Staff in Fighting COVID-19: A Multicenter, Cross-Sectional Study39 | Various type of Skin injury related pressure injuries 42.8% moist-associated skin damage (redness, pain, itching, or pricking) skin tear 2% related pressure injuries and moist-associated skin damage and skin tear 78.8% related pressure injuries and skin tear 13.2% related pressure injuries and skin tear 7.0% moist-associated skin damage and skin tear 1.0% | 30% 1.8% 2% 78.8% 13.2% 7.0% 1.0% | - Medical staff wearing PPE should be replaced every 4 hours/
- Controlling the sweat and moisture on the skin is very important/
- Used prophylactic dressings and lotions to protect the skin/
- Hydrocolloid dressing, oil, or cream to treat/
- Train medical staff about knowledge of skin protection /
- Protective products should be selected according to the guidelines, such as prophylactic dressings and fatty acid cream/
- Develop various prophylactic dressings suitable for the head and face to effectively keep the moisture balance and protect skin/ |
| Yan, Y.     | Consensus of Chinese experts on protection of skin and mucous membrane barrier for health care workers fighting against coronavirus disease 201940 | Erythema, dryness, scale, papules, maceration, erosion, contact dermatitis | Not reported | - Apply hand cream every time after if possible.
- Emollients containing hyaluronic acid, ceramide, vitamin E or other repairing ingredients applying after long duration of using hand gloves.
- Urea-containing emulsions are recommended in treating skin rhagadia.
- One layer of qualified latex gloves is adequate for skin protection, avoid wearing gloves for a long time and apply hand cream can reverse maceration.
- Hydropathic compress with 3% boric acid solution or normal saline or topical use of zinc oxide ointment is recommended for maceration and subsequent erosion and exudation.
- For contact dermatitis ones, use of cotton gloves inside latex gloves are encouraged, Moisturizers together with Topical glucocorticoid cream is recommended.
- Apply moisturizers or gel before wearing facial protective equipment to lubricate and reduce friction between skin and masks or goggles
- Management of mild skin indentation, blister and erosion include hydropathic compress with 3 to 4 layers of gauze soaked by cold water or normal saline for about 20 minutes each time every 2 to 3 hours and then applying moisturizers
- Antihistamines such as Cetirizine and Loratadine and antileukotriene agents if needed for delayed pressure urticaria.
- For severe pruritus oral antihistamine can be taken
- Management of skin dryness and scales is applying high-potent moisturizers before and after wearing PPE
- Acne vulgaris apply moisturizers containing oil control ingredients before and after using of masks. Use topical antibiotic creams or benzoyl peroxide for mild papules and pustules, and topical retinoids creams for blackhead and whitehead. Severe acne vulgaris should be treated under the guidance of dermatologists in time |

- Dirk M. Elston, MD: Occupational skin disease among health care workers during the Coronavirus (COVID-19) epidemic5 Dermatitis 97.0% | - Shorter rotating shifts in high-intensity protective gear.
- Latex-free gloves |
women who complained of diffuse arthralgia, odynophagia and pruritic reddish plaque in the acral area and the face proceed by fever, chills and chest pain. Urticaria have been seen in a female patient who just had dry cough in the past days and her CT scan confirmed the COVID-19 infection. Also in a 61 years old Spanish MD male patient, progressive pruritic urticarial lesions manifested which lasted about 10 days without no other symptoms.

A 60-year old woman with a history of flu-like and gastrointestinal symptoms 9 days ago, presented to dermatology department with complaint of diffuse urticarial plaques on the trunk, head and limbs. About Febrile rash it could be say that in a 39 years old male patient with 39°C fever and rashes which appeared at the same time of the fever onset presented, the lesions morphology were red, annular, stable plaques in neck, chest, abdomen, upper limbs and palms without involvement of face and the mucosa. The rash were edematous and erythematous and non-pruritic. He had no medication use in recent days and weeks before initiation of rash. Varicella-like exanthema was found in a 8 years old girl who had only mild cough 6 days before papulovesicular skin rash starts which had a symmetrical and bilateral pattern on the trunk. The test of she and her family confirmed for SARS-CoV-2. The lesions diminished after a week.

### Table 3

| First author | Title | Skin injuries among medical staff fighting COVID-19 & general population | Percentage | Recommendations |
|--------------|-------|------------------------------------------------------------------------|------------|-----------------|
| Teresa Oranges | Reply to: “Skin damage among health care workers managing coronavirus disease-2019” | Hand eczema, skin damage | more than 60% | - Barrier film spray before wearing the medical devices/ - Omental lipids cream/emulsion improving skin barrier function/ - Non-adherent dressings (soft silicone/paraffin use of thin hydrocolloid dressing for prevention pressure injuries on the nasal bridge in case of acute non-invasive ventilation |
| Jiajia Lan | Skin damage among health care workers managing coronavirus disease-2019 | dryness/tightness and desquamation | 97.0% | Not reported |
| Singh, M | Overzealous hand hygiene during COVID-19 pandemic causing increased incidence of hand eczema among general population | Hand eczema, erythema, scaling and vesiculation | Not reported | - Sanitizers should be allowed to dry first and then hypoallergenic hand cream/emollients should be applied so as to prevent the trapping of sanitizers in web spaces |

### Table 4

| First author | Title | Location skin injuries among medical staff fighting COVID-19 | Percentage |
|--------------|-------|-----------------------------------------------------------|------------|
| Pingping Lin | Adverse skin reactions among health care workers during the coronavirus disease 2019 outbreak: A survey in Wuhan and its surrounding regions | Hands | 84.6% |
| | | Cheeks | 75.4% |
| | | Nasal bridge | 71.8% |
| Pei, S. | Occupational skin conditions on the frontline: A survey among 484 Chinese health care professionals caring for COVID-19 patients | Face | 47.1% |
| | | Hands | 27.5% |
| | | Limbs | 15.7% |
| | | Truncus | 12.6% |
| | | Whole body | 2.3% |
| Bin Zhang | COVID-19 epidemic: Skin protection for health care workers must not be ignored | Nasal bridge | 83.1% |
| Qixia Jiang | The Prevalence, Characteristics, and Prevention Status of Skin Injury Caused by Personal Protective Equipment Among Medical Staff in Fighting COVID-19: A Multicenter, Cross-Sectional Study | Nose Bridge | 30.1% |
| | | Cheeks | 28.3% |
| | | Ear | 25.3% |
| | | Forehead | 14.8% |
| Jiajia Lan | Skin damage among health care workers managing coronavirus disease-2019 | Nasal bridge | 83.1% |
| First author          | Title                                               | Patient characteristics                                                                 | Recommendation                                                                 | The reason                                                                 | Dose adjustment                                                                 |
|----------------------|-----------------------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Rademaker, M.        | Advice regarding COVID-19 and use of immunomodulators, in patients with severe dermatological diseases | Patient With inflammatory skin disorder being actively managed with an immunomodulator who confirmed COVID-19 Disease | should stop the immunomodulator(s) immediately, exception of systemic corticosteroids | COVID-19 infection being aggravated by immunomodulators and secondary bacterial infection as part of COVID-19 complication become aggravated too | Not reported                                                                      |
|                      |                                                     | patient with inflammatory skin disorder being actively managed with an immunomodulator who with signs of common cold but is not formally diagnosed with COVID-19 disease | Lowering the dose of immunomodulatory/ or temporarily stopping for 2 weeks. Exception is systemic corticosteroids. |                                                                            |                                                                             |
|                      |                                                     | patient with inflammatory skin disorder being actively managed with an immunomodulator who confirmed COVID-19 Disease |                                                                       |                                                                            |                                                                             |
|                      |                                                     |                                                                       |                                                                       |                                                                            |                                                                             |
| Federico Bardazzi    | Biologic therapy for psoriasis during the COVID-19 outbreak is not a choice | patient is stable or in good health                                                  | It is not reasonable/indicated to suspend the ongoing immunosuppressive/ immunomodulatory therapy | as the risk of reactivation of the underlying pathology could add an additional risk factor to infections, including COVID-19. Inhibition of IL-17 pathway may have beneficial effects in treating COVID-19 | Not reported                                                                      |
| Shanshal, M.         | Biological treatment uses amid the COVID-19 era, a close look at the unresolved perplexity | patients who are already on biological treatment and have tested positive for COVID-19 | Discontinuing or postponing the biological therapy until full recovery from the COVID-19 infection. avoidance of initiation of biological therapy for high-risk patients all individuals stop biological treatment as soon as they are diagnosed with COVID-19 infection | patients with existing comorbidities will need extra precaution along with frequent clinical observation and monitoring, some patients with active infection show no symptoms or radiologic abnormalities in the initial presentation and might not realize that they have been infected | Not reported                                                                      |
|                      |                                                     | composed of patients who are being considered for the initiation of biological therapy |                                                                       |                                                                            |                                                                             |
|                      |                                                     | patients with severe psoriasis, those on potentially immunosuppressive therapies, and those presenting comorbid conditions might be at higher risk of infection. |                                                                       |                                                                            |                                                                             |
|                      |                                                     |                                                                       |                                                                       |                                                                            |                                                                             |
| Di Lernia, Vito       | Biologics for psoriasis during COVID-19 outbreak | patients on biologics and on immunosuppressants for psoriasis, hidradenitis, atopic dermatitis, pemphigoid, pemphigus, and other conditions | all patients taking biologics wear such coverings or masks when outside the home and practice social distancing | it is neither practical nor logical to cease these over a few weeks while this pandemic is upon us | Not reported                                                                      |
| Megna, M.            | Biologics for psoriasis patients in the COVID-19 era: more evidence, less fears | psoriasis patients during COVID-19 pandemic era                                     | We strongly believe that proactive biologic discontinuation should be avoided. | interruption of biologic therapy in psoriatic patients involves a dysregulation of inflammatory cytokines that not only exacerbates psoriasis but is also likely to contribute to a more aggressive organic response to SARS-CoV-2, biologics for psoriasis do not increase the risk of viral infections or their complications | Not reported                                                                      |
| Abdelmaksoud, A.     | Comment on “COVID-19 and psoriasis: Is it time to limit treatment with immunosuppressants? A call for action” | Older patients with moderate-to-severe psoriatic                                     | Not stop systemic biologic or nonbiologic therapy and phototherapy/ interleukin 17 inhibitors should considered in the priority because have lower effects on personal immune functions | users of apremilast, etanercept, and ustekinumab are at lower risk rate of serious infection compared with those on methotrexate, | Not reported                                                                      |
### Table 5 (Continued)

| First author       | Title                                                                 | Patient characteristics                                                                                                                                                                                                                                                                                                                                 | Recommendation                                                                 | The reason                                                                                                                                                                                                 | Dose adjustment |
|--------------------|-----------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| Conforti, C.       | COVID-19 and psoriasis: Is it time to limit treatment with immunosuppressants? A call for action52                        | patient with psoriasis taking immunosuppressive drugs                                                                                                                                                                                                                                                                                                      | limit and/or reduce the time of administration, preferring topical and/or drugs with a lower impact on the immune system | these drugs may cause decreased immune response and greater susceptibility to life-threatening infections                                                                                                        | Not reported    |
|                    |                                                                       | patient with psoriasis taking immunosuppressive drugs who confirmed COVID-19                                                                                                                                                                                                                                                                              | stop all immunosuppressive and biological therapy                                                                                       |                                                                                                                                                                                                                                                                          | Not reported    |
| Price, K. N.       | COVID-19 and immunomodulator/immunosuppressant use in dermatology53    | Psoriasis Patients treat with Corticosteroids, Tacrolimus, Cyclosporine, Mycophenolate mofetil, Azathioprine, Methotrexate                                                                                                                                                                                                                                  | Consider stopping when viral symptoms present especially with known or potential exposure                                          | Broad immunosuppression across multiple cytokine axes with immunosuppressants has the potential to increase susceptibility, persistence, and reactivation of viral infections. Immunosuppressants decrease cytokines that recruit and differentiate immune cells needed to clear the infection. In addition, inflammatory mediators can become hyperactivated, resulting in a "cytokine storm," which is the primary cause of death in severe disease. | Not reported    |
|                    |                                                                       | Psoriasis Patients treat with Infliximab, Etanercept, Certolizumab, Adalimumab, Anakinra (IL-1)                                                                                                                                                                                                                                                       | Continue if viral symptoms are mild, consider stopping if viral symptoms worsen or high fever develops                                      |                                                                                                                                                                                                                                                                          | Not reported    |
|                    |                                                                       | Psoriasis Patients treat with Dupilumab (IL-4)                                                                                                                                                                                                                                                                                                          | Continue unless severe symptoms present                                                                                               |                                                                                                                                                                                                                                                                          | Not reported    |
|                    |                                                                       | Psoriasis Patients treat with Brodalumab (IL-17), Seuculinab (IL-17a), Ixekizumab (IL-17a), Ustekinumab (IL-12/23), Gusekumab (IL-23)                                                                                                                                                                                                                          | Continue if viral symptoms are mild, consider stopping if viral symptoms worsen or high fever develops                                      |                                                                                                                                                                                                                                                                          | Not reported    |
|                    |                                                                       | Psoriasis Patients treat with Retuximab                                                                                                                                                                                                                                                                                                              | Consider stopping when viral symptoms present especially with known or potential exposure                                          |                                                                                                                                                                                                                                                                          | Not reported    |
|                    |                                                                       | Psoriasis Patients treat with Apremilast                                                                                                                                                                                                                                                                                                              | Continue unless severe symptoms present                                                                                               |                                                                                                                                                                                                                                                                          | Not reported    |
| Wang, C.           | COVID-19 and the use of immunomodulatory and biologic agents for severe cutaneous disease: An Australia/New Zealand consensus statement13 | Patients on immunomodulators, including biologic agents and new small molecular inhibitors for cutaneous disease, with suspected or confirmed COVID-19 disease                                                                                                                                                                                                 | All immunomodulators used for skin diseases should be immediately withheld, exception of systemic corticosteroid therapy, immunosuppression is thought to increase susceptibility and cause more severe infection and atypical presentations of coronavirus infections in immunocompromised hosts, including prolonged incubation periods, persistent asymptomatic viral shedding, diarrhoea, weight loss and encephalitis as primary manifestations | • Conventional immunomodulators should be withheld for 31 days from infection onset and only recommenced after complete resolution of illness and/or confirmation of negative PCR testing indicating no viral shedding | Not reported    |
|                    |                                                                       | on immunomodulators, who develop symptoms or signs of an upper respiratory tract infection, but COVID-19 is not yet confirmed                                                                                                                                                                                                                               | dose reduction or temporarily cessation for 1–2 weeks                                                                                | • Systemic corticosteroids: Reduce to 10 mg/day prednisolone or equivalent in a graduated manner.                                                                                                          |                 |
|                    |                                                                       |                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                  | • Azathioprine: Reduce to ≤0.5 mg/kg/day                                                                                               |                 |
|                    |                                                                       |                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                  | • Ciclosporin: Reduce to ≤1 mg/kg/day                                                   |                 |
|                    |                                                                       |                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                  | • Methotrexate: Reduce to ≤10 mg/week                                                   |                 |
|                    |                                                                       |                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                  | • Mycophenolate mofetil: Reduce to ≤1 g/day                                             |                 |
|                    |                                                                       |                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                  | • Systemic corticosteroids: Reduce to 10 mg/day prednisolone or equivalent in a graduated manner.                                                   |                 |
|                    |                                                                       |                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                  | • Biologics: extending the time between dosages.                                          |                 |
|                    |                                                                       |                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                  | • Retinoids: No dose adjustment required                                                 |                 |

(Continues)
| First author | Title | Patient characteristics | Recommendation | The reason | Dose adjustment |
|--------------|-------|------------------------|----------------|------------|----------------|
| Arora, G     | The COVID-19 outbreak and rheumatologic skin diseases[^55] | Well patients on immunomodulators | Immunomodulators and biologics should be continued | Discontinuation of biologic therapy may result in a loss of treatment response when rechallenged and/or development of drug antibodies | Not reported |
|             |       | Children patients on immunomodulators, biologics | Dose reduction or cessation of immunomodulators and biologics is not necessary |  | Not reported |
|             |       | Organ Transplant/Bone marrow transplant patients | Immunosuppressive treatments (eg, prednisone, ciclosporin, tacrolimus, azathioprine, mycophenolate, etc.) should not be stopped |  | Not reported |
| Kansal, NK  | COVID-19, syphilis, and biologic therapies for psoriasis and psoriatic arthritis: A word of caution[^56] | Patients on Disease-modifying antirheumatic drugs (DMARDs), biologics or other immunosuppressive medications | Required to consult their rheumatologist and stop these drugs during an infection | Because patients with rheumatologic disease are more susceptible to the COVID-19 virus either because of the rheumatologic disease itself or the medications used to treat their underlying disease. | Not reported |
|             |       | Non-infected patients | Advised to continue their medication during the epidemic |  | Not reported |
| Plachouri, KM | The management of biologics in dermatologic patients in the 2019-nCoV era[^57] | Dermatologic patients | Postpone initiation of biologic treatments in this particular period | The lack of sufficient data concerning the interaction of SARS-CoV-2 and biologics is also an important factor that should be taken into consideration when examining the option of initiating therapy with the latter. Another logistic parameter that should not be underestimated is the need of frequent careful monitoring under such treatments that includes both regular laboratory examinations as well as routine dermatologic follow-up visits, which could constitute a problem under the emerging societal circulatory restrictions that are posed in order to control the pandemic transmission | Not reported |
| Brownstone, ND | Novel Coronavirus Disease (COVID-19) and Biologic Therapy in Psoriasis: Infection Risk and Patient Counseling in Uncertain Times[^58] | Psoriatic patients with following risk factors: |  |  | Not reported |

[^55]: Arora, G (2020) The COVID-19 outbreak and rheumatologic skin diseases. *Semin Arthritis Rheum* 49:174-176
[^56]: Kansal, NK (2020) COVID-19, syphilis, and biologic therapies for psoriasis and psoriatic arthritis: A word of caution. *JAMA Dermatol* 156:389-390
[^57]: Plachouri, KM (2020) The management of biologics in dermatologic patients in the 2019-nCoV era. *J Investig Dermatol Symp Proc* 25:185-186
[^58]: Brownstone, ND (2020) Novel Coronavirus Disease (COVID-19) and Biologic Therapy in Psoriasis: Infection Risk and Patient Counseling in Uncertain Times. *J Rheumatol* 47:332-333
| First author | Title | Patient characteristics | Recommendation | The reason | Dose adjustment |
|--------------|-------|-------------------------|----------------|------------|----------------|
| Villani, A   | Patients with advanced basal cell carcinomas in treatment with sonic hedgehog inhibitors during the coronavirus disease 2019 (COVID-19) period: Management and adherence to treatment | methotrexate, prednisone, cyclosporine | 4. Reduction or discontinuation of concomitant immunosuppressants (eg, methotrexate) | 4. Immunosuppressive condition (eg, HIV) | Not reported |
| Gisondi, P   | Risk of hospitalization and death from COVID-19 infection in patients with chronic plaque psoriasis receiving a biological treatment and renal transplanted recipients in maintenance immunosuppressive treatment | 4. Immunosuppressive condition (eg, HIV) | 4. Reduction or discontinuation of concomitant immunosuppressants (eg, methotrexate) | 4. Immunosuppressive condition (eg, HIV) | Not reported |
|              | Patients with chronic plaque psoriasis receiving a biological treatment and renal transplanted recipients in maintenance immunosuppressive treatment | 5. History of infections while on biologic | 5. Increase in use of topical agents, home phototherapy, or other non-immunosuppressive medications | 5. History of infections while on biologic | Not reported |
|              | | 6. Mild-to-moderate underlying psoriasis | | 6. Mild-to-moderate underlying psoriasis | Not reported |
|              | | 7. High risk of exposure to COVID-19 virus (eg, endemic area, health care worker, nursing home resident, household member or co-worker with COVID-19 infection) | | 7. High risk of exposure to COVID-19 virus (eg, endemic area, health care worker, nursing home resident, household member or co-worker with COVID-19 infection) | Not reported |
|              | | 8. Short duration of COVID-19 pandemic | | 8. Short duration of COVID-19 pandemic | Not reported |
|              | Psoriatic patients with following risk factors: | | | Psoriatic patients with following risk factors: | Not reported |
|              | 1. Young age | | | 1. Young age | Not reported |
|              | 2. No COVID-19 high risk co-morbidities | | | 2. No COVID-19 high risk co-morbidities | Not reported |
|              | 3. Biologic monotherapy | | | 3. Biologic monotherapy | Not reported |
|              | 4. Severe underlying psoriasis or psoriatic arthritis, with history of rapid flares or unstable subtypes (pustular, erythrodermic) | | | 4. Severe underlying psoriasis or psoriatic arthritis, with history of rapid flares or unstable subtypes (pustular, erythrodermic) | Not reported |
|              | 5. No concomitant immunosuppressive conditions | | | 5. No concomitant immunosuppressive conditions | Not reported |
|              | 6. Low risk of exposure to COVID-19 virus | | | 6. Low risk of exposure to COVID-19 virus | Not reported |
|              | 7. Long duration of COVID-19 pandemic | | | 7. Long duration of COVID-19 pandemic | Not reported |
|              | Patients who test positive for COVID-19 infection | Favoring biologic continuation | | Patients who test positive for COVID-19 infection | Not reported |
|              | | Advising to hold their biologic dose until their infection clears. | | | Not reported |
|              | | This requires until improvement in respiratory symptoms, and two negative COVID-19 test performed 24 hours apart. If COVID-19 retesting is not available, restarting biologic therapy until 30 days after resolution of fever and respiratory symptoms | | | Not reported |
| First author  | Title                                                                 | Patient characteristics                          | Recommendation | The reason                                                                 | Dose adjustment |
|--------------|----------------------------------------------------------------------|-------------------------------------------------|----------------|---------------------------------------------------------------------------|-----------------|
| ShakShouk, H | Treatment considerations for patients with pemphigus during the COVID-19 pandemic | Patients with pemphigus and without active infection | postponing rituximab infusions temporarily | Delaying peak patient immunosuppression during peak COVID-19 incidence to reduce the risk of adverse outcomes. | Not reported |
| Jic ZA       | United States Cutaneous Lymphoma Consortium Recommendations for Treatment of Cutaneous Lymphomas During the COVID-19 Pandemic | Low risk patients with cutaneous lymphomas      | Low-risk therapies that can be utilized at home should be continued for all patients. Home-based NBUVB and heliotherapy can be continued or initiated. | The risks of travel and exposure likely outweigh the benefit of in-office treatments such as ultraviolet light therapy and total body electron beam radiation therapy. | Not reported |
| Torres, T    | Managing Cutaneous Immune-Mediated Diseases During the COVID-19 Pandemic | Patients with cutaneous immune-mediated diseases (including psoriasis, atopic dermatitis, and hidradenitis suppurativa) and without active COVID-19 infection | Continue their treatment even during the COVID-19 outbreak | 1. Preventing disease fares 2. Immunosuppressive and immunomodulatory drugs may potentially control the "cytokine storm" | Not reported |
|              |                                                                      | Patients with cutaneous immune-mediated diseases (including psoriasis, atopic dermatitis, and hidradenitis suppurativa) and with active COVID-19 infection | Withhold immunosuppressive or biologic treatment | Not reported | Not reported |
erythematous macule appeared in upper and lower limbs, neck and shoulders and trunk which had morbilliform pattern and through the time, lesions expanded and confluent as patches more than 10 cm on the trunk.22

A 20 years old healthy male who complained of 6-day lasting fever and rash presented to emergency department and admitted in ICU. He had spreading nonpruritic maculopapular morbilliform rash on her trunk and limbs, respecting face, mucosa and the eyes. His COVID-19 confirmed in day 2.19 Skin rash in infants of positive COVID-19 mother, none of infant had positive test result among those who have been tested (3 of 4), 2 of the infant had two different patterned rashes, one of them diffuse red maculopapules and the other had ulceration on the forehead. Their rash diminished without any treatment.18 Erythematous rash appeared 4 days after fever and asthenia in a 64 years old woman used oral paracetamol, the erythematous rash extended to the both antecubital fossa, axillary area and the trunk. The rash disappeared in 5 days with no specific treatment while continuing paracetamol intake. The patient’s COVID-19 infection confirmed with positive RT-PCR.17 Malar eruption, a 26 years old man, a known case of Crohn disease, who had a history of close contact to a COVID-19 patient, developed sore throat, anosmia, ageusia, mild dry cough, malaise and chest congestion in the past 2 to 3 week, who presented with asymptomatic red and edematous malar eruption on his face with a low grade fever and mildly tender large cervical lymph node.23

C. Galván Casas summarized prevalence of different skin lesions of COVID-19 based on a study among 375 patients in Spain: maculopapular lesions 47%, urticarial eruption 19%, acral erythematous lesions with pustule or vesicle (chilblain like lesion) 19%, other vesicular lesions 9%, and livedo reticularis 6%.1

4.1.2 | Virus treatment-related

There were several drug regimens used for treatment of COVID-19 patients, some of which could result in cutaneous side effects like presence of a new dermatoses or flare/aggravation of a previous dermatologic disorder. Till to the last update of this systematic review,
generalized pustular reaction and exacerbation of psoriasis due to Hydroxychloroquine were the reported cases of cutaneous adverse reaction of COVID-19 treatment.\textsuperscript{33,74,75} (Table S7).

The following is the most common adverse reactions found in the publications irrespective of this pandemic, which could be in mind for better dermatologic disease approaching (Table S8).

**Hydroxychloroquine:** Despite the inconclusive result over the implication of Anti-Malarial drugs; it is used widely for treating COVID-19 patients. In a study by Sharma et al, a total of 21 unique dermatologic reactions were reported in 3578 patients had Hydroxychloroquine cutaneous adverse drug reactions. The most common was drug eruptions as in maculopapular eruptions, petechia, urticaria, dermatitis. Hyperpigmentation came second followed by pruritis, SJS/TEN and AGEP (Acute generalized exanthematous pustulosis).\textsuperscript{3} Dermatologists should consider the COVID-19 cutaneous manifestations such as erythematous rash, petechia, urticaria as differential diagnosis while assessing the possible Hydroxychloroquine drug reactions.\textsuperscript{27}

**Azithromycin:** Azithromycin is another drug used in combination with Hydroxychloroquine in COVID-19 treatment regimens. Skin adverse events of it may include cutaneous severe skin reaction associated with febrile reaction, generalized red or purple skin rashes, angioedema, blisters, skin peeling, burning sensation in eyes or painful skin.\textsuperscript{76}

**Antiviral drugs:** Several antiviral drugs are used for its treatment as well; including Oseltamivir which could result in SJS/TEN, angioedema and idiosyncratic cutaneous drug reactions. Ribavirin also may cause alopecia, acneiform eruptions, maculopapular eruption, and eczematous lesions, localized scleroderma, skin dryness and rash. Other antiviral drugs such as antiretrovirals are also used in some patients including Lopinavir and Ritanavir. Their adverse effects may be presented as maculopapular drug eruptions, exfoliative erythroderma, SJS/TEN, severe cutaneous drug reactions, injection site reactions.\textsuperscript{44,77}

### 4.1.3 Immunomodulators and dermatologic disorders

In overall, non-infected non-at risk patients with immune-medicated dermatologic disorders under usage of immunosuppressive immunomodulator drugs like biologic agents are not needed to be alter regimen or discontinue the therapies during pandemic, even these drugs may control the deteriorating cytokine storms also prevented disease flare-ups which both were associated with poorer outcomes and more complications in COVID-19 course, although strict adherence to quarantine and personal-social preventive hygiene performances are highly recommended especially in these groups of patients. But in patients who are living in highly prevalent disease area, showing flu like or COVID-19 specific symptoms (anosmia or asthenia) or who are highly suspected to having had any positive exposures, based on the consult with their physician and considering all circumstances, it is better to have changing in their therapeutic regimens as dose reduction, dose interval increase or temporary discontinuation. Patients with an active COVID-19 infection should hold the biologic or non-biologic immunosuppressants until the complete recovery (at least 4 weeks).

In patients who were symptomatic but were no definite cases, therapies should stop for at least 2 weeks. Most of skin diseases which were treated with systemic immunomodulators were usually associated with more severe COVID-19 morbidity. Dermatologic disorders which were associated with metabolic syndrome, older age or vital organ comorbidities in particular respiratory disorders like patients with psoriasis, hidradenitis suppurativa and atopic tendencies may have poorer prognosis if become infected. Patients with more severe skin disorders (eg, severe psoriasis) were in higher risk for developing pneumonias by any cause that is of great importance in this pandemic. In overall these group of patients may benefit more from future SARS-Cov-2 vaccination. Since the chronic nature of this pandemic, specialists should decide based on recent evidence with regard to case-by-case variations considering cost-benefit ratio and also disease psychological burden.\textsuperscript{46,54,63,78,79}

Biologic immunomodulators especially TNF-a inhibitors, janus kinase (JAK) inhibitors, anti-IL 6 (Tocilizumab) may capable to control cytokine storms and it was systemic consequences like ARDS and etc in COVID-19 course and some trials were conducted to evaluate their efficacy in disease management, so patients who are using these drugs do not be needed to disrupt.\textsuperscript{80}

Here in we discuss about experts' recommendations of management of specific cutaneous diseases during pandemic:

#### 4.1.4 Immunobullous disorders

- Virus could act as target mimicry in immunobullous disorders and may trigger or aggravate disease course but it is not recommended to do not treat properly, since poor disease control have its own consequences; even probable more severe and complicated COVID-19 infection; due to deregulated inflammatory storms.\textsuperscript{61,81-83}
- If possible, postpone rituximab infusions temporarily in management of pemphigus, especially in the case of time approximation regarding peak of drug immunosuppression and peak of society COVID-19 burden.
- Consume the lowest effective dose of corticosteroids and non-biologic immunosuppressants.
- Discontinue steroid sparing agents during active COVID-19 infection although complete cessation of steroids is not usually possible due to probable adrenal crises.
- Consider hydroxychloroquine in elderly patients with pemphigus.
- In overall, in the case of urgent needs, IVIG could be a proper rapid response adjuvant immunomodulator therapy (immunenehancing in a positive way or minimal immunosuppressive prosperities) for management of non-infected pemphigus or pemphigoid patients or in patients with active COVID-19 infection (it is effective for both conditions).
- Mycophenolate mofetil was not associated with outcome worsening in pemphigus patient affected by COVID-19 (case report).
• Brutton Tyrosine Kinase inhibitor, Ofatumumab and Tocilizumab which act more selectively may be an option in the certain infected cases of pemphigus.

4.1.5 | Psoriasis

• There were not exact data about incidence of COVID-19 in psoriatic patients who are under treatment.47-50,52,60,64,65,84,87
• Risk of hospitalization or death is not higher than normal population in psoriasis patients under treatment with immunomodulators by itself, but psoriasis may be associated with comorbidities like metabolic syndrome especially in elderly people that is associated with higher mortality rate of COVID-19 infection.
• Monotherapy with immunosuppressives, targeted therapies and lack of comorbidities predict the lower associated risk of COVID-19 complications in psoriatic patients.
• There were not enough evidence regarding superiority of any biologic therapies for psoriasis in the SARS-CoV-2 outbreak.
• Known case of COVID-19 or patients with confirmed risky exposures, should discontinue biologics but non-infected non at-risk patients could continue the treatment as previous.
• Preventive cessation of biologic or undertreatment of severe cases are not logical strategies, since resultant disease flare up and higher pro-inflammatory state of patients (other than the significant cost, burden and impaired life quality) prone them to poorer outcomes in the case of possible infection occurrence also initiation of a biologic agent after discontinuation of another one usually accompanies by lesser response.
• Initiation of a biologic therapy needed to consider all circumstances and if decided to start, psoriatic patients who have other concomitant comorbidities should have more closed and frequent visits also further monitoring.
• There were some case reports regarding management of complicated psoriatic cases who were also affected by COVID-19, like successful treatment with Guselkumab.86

4.1.6 | Atopic dermatitis

• JAK inhibitors like baricitinib and upatcitinib should not be stopped in the setting of COVID-19 pandemic.80,88
• In the case of Dupilumab used, there was no any risk of COVID-19 infection even in highly contagious area.

4.1.7 | Acne

• Systemic retinoids were area of some controversies in the pandemic since mucosal fragility and the altered mucosal thickness, resultant from the isotretinoine may be a susceptibility factor for coronavirus infection or even have higher viral load in mucosal surfaces, on the other hand isotretinoine can help to have better olfactory function. So low-dose isotretinoin with folic acid supplementation in association with proper nasal mucosal care is recommended for indicated acne management.89

4.1.8 | Future perspective of dermatology during pandemic

Of course we will encounter large volume of reported primary and secondary skin manifestations of COVID-19 (like new skin presentations, related to virus itself or its treatment) also more exact recommendations for controlling dermatologic disorders during pandemic especially with further reported cases of patients with an evident dermatologic morbidity that are affected by new corona virus and the manner of controlling their underlying skin disease and concomitant infection. Also with increase of global knowledge about basic personal and social preventive health care and hygiene, it may be expected lesser prevalence of cutaneous contagious disorders like warts, bacterial and pathogenic fungal infections, scabies, pediculosis, sexually transmitted disease and so forth. Also a tremendous progression in teledermatology could be another significant outcome.

5 | CONCLUSION

In this systematic review, we focused on various aspects of dermatologic fields and COVID-19 infection. These entities classified as primary specific virus-induced or virus associated drug-induced dermatoses and the secondary cutaneous involvements due to circumstances during pandemic. We also discussed on expert recommendations about immune-mediated dermatologic disorders which were under treatment with immunomodulators.

Erythematous rash or patchy exanthematous red rash, Morbilliform exanthema, Maculopapular rash, urticaria and acute urticaria, Acro-ischemic lesions (Psuedo-chilblain or Pernio-like lesion or "COVID toe"), Digital ischemia, Digital papulosquamous lesions, Chickenpox-like blisters, Varicella-like exanthema, Pruritic Papulovesicular, Petechial skin rash, Acute hemorrhagic edema, livedo-reticularis (LR), Symmetrical pruritic papules, Conjunctivitis and eyelid dermatitis. Skin rash in infants of positive COVID-19 mother and Malar eruption were the reported terms for primary skin manifestations of COVID-19 up to now. Generalized pustular reaction and exacerbation of psoriasis due to Hydroxychloroquine were the reported cases of cutaneous adverse reaction of COVID-19 treatment.

In overall, non-infected non-at risk patients with immune-mediated dermatologic disorders under usage of immunosuppressive immunomodulator drugs like biologic agents are not needed to alter regimen or discontinue the therapies during pandemic, even these drugs may control the deteriorating cytokine storms also prevent disease flare-ups which both are associated with poorer outcomes and more complications in COVID-19 course. Patients with an active COVID-19 infection should hold the biologic or non-biologic immunosuppressants until the complete recovery (at least 4 weeks). In
patients who are symptomatic but are no definite cases, therapies should stop for at least 2 weeks.

Dermatologic disorders which were associated with metabolic syndrome, older age or vital organ comorbidities in particular respiratory disorders like patients with psoriasis, hidradenitis suppurativa and atopic tendencies had poorer prognosis if become infected. Patients with more severe skin disorders (eg, severe psoriasis) were in higher risk for developing pneumonias by any cause that was of great importance in this pandemic. In overall these group of patients may benefit more from future SARS-Cov-2 vaccination.

Of course we will encounter large volume of reported primary and secondary skin manifestations of COVID-19 (like new skin presentations, related to virus itself or its treatment) also more exact recommendations for controlling dermatologic disorders during pandemic especially with increase our knowledge about management of patients with an especial dermatologic disorder who are affected by new corona virus. High adherence to protective health care strategies and social isolation or distance is the mainstay of better controlling the disease during pandemic and the role of teledermatology is really significant in this area.

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CONFLICT OF INTEREST
The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS
The authors contribute equally to all stages of this study. The team has reviewed the manuscript and the data, and all contributors were in full agreement. Azadeh Goodarzi wrote the initial draft, Azadeh Goodarzi, Farnoosh Seirafianpour, Sogand Sodagar, Arash Pour Mohammad, Parsa Panahi, and Samaneh Mozafarpour wrote the final manuscript and, all the authors made extensive contributions to the final draft of this manuscript. Azadeh Goodarzi edited the document.

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