



REVIEW ARTICLE

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

Farnoosh Seirafianpour¹ | Sogand Sodagar¹ | Arash Pour Mohammad¹  | Parsa Panahi¹ | Samaneh Mozafarpour² | Simin Almasi³ | Azadeh Goodarzi⁴ 

¹Student Research Committee, school of medicine, Iran University of Medical Sciences, Tehran, Iran

²Department of Dermatology, Skin Disease and Leishmaniasis Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

³Department of Rheumatology, Rheumatology Research Center, Firoozgar Hospital, Iran University of Medical Sciences (IUMS), Tehran, Iran

⁴Department of Dermatology, Rasoul Akram Hospital, Iran University of Medical Sciences (IUMS), Tehran, Iran

Correspondence

Azadeh Goodarzi, Department of Dermatology, Rasoul Akram Hospital, Iran University of Medical Sciences (IUMS), Tehran, Iran; Nyayesh Street, Sattarkhan Avenue, Rasoul Akram Hospital, Tehran, Iran.
Email: goodarzi.a@iums.ac.ir, azadeh_goodarzi1984@yahoo.com

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

Abbreviations: CEBD, Centre of Evidence Based Dermatology; COVID-19, "CO" stands for corona, "VI" for virus, "D" for disease, and "19" for 2019; PPE, Personal protective equipment.

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.¹

There is also dermatoses like COVID-19 treatment-related drug reactions, especially the generalized pustular rash due to hydroxychloroquine.² 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, vesiculobullous disease, autoimmune disorders, collagen vascular disease, psoriasis and so forth, could be mentioned and patients with these type of diseases considered as immunocompromised.³ 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.⁴

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.⁵

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.⁶

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.⁷

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.

2 | 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 Sciencedirect (<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.⁴⁴ 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.^{2,45} 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 condition⁹. 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 14patients, 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,

TABLE 1 Case reports of COVID-19 skin manifestations

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 ⁸	Puritic 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 ⁹	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? ¹⁰	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	Slight spongiosis, basal cell vacuolation and mild perivascular lymphocytic infiltrate	Not reported
Anwar Alramthan	A case of COVID-19 presenting in clinical picture resembling chilblains disease. First report from the Middle East ¹¹	Rash (red-purple papules)	A 27-year-old females	Asymptotic, RT-PCR confirmed COVID-19	Not reported	Acral areas (dorsal aspect of fingers bilaterally)	Not reported	Not reported
Nerea landa	Chilblain-like lesions on feet and hands during the COVID-19 Pandemic ¹²	Rash (red-purple papules) + diffused erythema	35-year-old female + subungual area of the right thumb	asymptotic RT-PCR confirmed COVID-19	Not reported	Acral areas (dorsal aspect of fingers bilaterally)	Not reported	Not reported
		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
			23 year old female	3 weeks after COVID-19 symptoms	Not reported	Toes (were a little itchy)	Not reported	Not reported
			44 year old male	10 days after COVID-19 symptoms	Not reported	Toe (slightly painful)	Not reported	Not reported
			91 year old male	3 weeks after COVID-19 confirmed by PCR	Not reported	Toe	Not reported	Not reported
			24 year old female	after COVID-19 confirmed by PCR	Not reported	Toes	Not reported	Not reported
			15 year old female	1 week after COVID-19 symptoms	Not reported	Fingers and heels (mildly painful when pressing)	Not reported	Not reported
Wu, Ping	A child confirmed COVID-19 with only symptoms of conjunctivitis and eyelid dermatitis ¹³	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 ¹⁴	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
		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

TABLE 1 (Continued)

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 ¹⁵	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 hydroptic 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 ¹⁶	Mild hemi-facial atrophy and scoliosis, generalized, pruritic rash, large, disseminated, urticarial plaques	60-year-old woman	9 days after COVID-19 symptoms	no recent changes to her medications	Trunk, head, upper and lower extremities	Not reported	1 day
Mahé, A.	A distinctive skin rash associated with Coronavirus Disease 2019 ¹⁷	transient non-pruritic blanching unilateral livedoid patch	67-year-old Caucasian male	7 days after COVID-19 symptoms	Not reported	Right anterior thigh	Not reported	1 day
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 ¹⁸	Unilateral asymptomatic rash	47-year-old Caucasian female	10 days after RT-PCR confirmed COVID-19	Not reported	Right leg	Not reported	1 day
Hunt, M.	A Case of COVID-19 Pneumonia in a Young Male with Full Body Rash as a Presenting Symptom ¹⁹	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
Magro, C.	Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases ²⁰	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 ¹⁹	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 ²⁰	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 leukocytoclasia. IHC showed striking and extensive deposition of C5b-9 within the microvasculature	Not reported

(Continues)

TABLE 1 (Continued)

First author	Title	Cutaneous manifestation	Case characteristic	Accompanied by COVID-19 symptoms	Drug history	Involvement site	Skin biopsy	Duration of skin lesion
		Dusky purpuric patches	66 years old woman	9 days after having fever, cough, diarrhea and chest pain, she became hypoxemic and after 11 days in hospital skin rash appeared	Hydroxychloroquine, enoxaparin	Palms and soles bilaterally	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
Chen, Y.	Infants Born to Mothers with a New Coronavirus (COVID-19) ²¹	Mildly purpuric reticulated eruptions, consistent with livedo racemosa	40-year-old woman	after 2 weeks of dry cough, fever, myalgias, diarrhea, and progressive dyspnea	Nothing	chest, legs and arms	. Significant vascular deposits of C5b-9 and C4d	Not reported
		Diffuse maculopapular rash and Facial skin ulceration	Above 37-week gestational age infant	edema of the lateral thigh	Nothing	Diffuse	Not reported	1 day
		First on forehead and progress to diffuse small miliary red papules	Above 37-week gestational age infant	TTN (transient tachypnea of the newborn)	Nothing	Not reported	Not reported	8-9 days
Najarian	Morbiform exanthem associated with COVID-19 ²²	Pruritic progressive erythematous macules gradually changed to patches	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
Hoenig, Leonard J.	Rash as a Clinical Manifestation of COVID-19 Photographs of a Patient ²³	Erythematous, edematous, malar eruption	26 years old man	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 ²⁴	Erythematous-purpuric, millimetric, coalescing macules	84-year-old woman	3 days after hospitalization (11 days after COVID-19 symptoms)	hydroxychloroquine and lopinavir/ritonavir	Flexural regions mainly in peri-axillary area	Not reported	Not reported
Quintana-Castaneda, Lucia	Urticarial exanthem as early diagnostic clue for COVID-19 infection ²⁵	Pruritic urticarial rash consisting of confluent, edematous and erythematous papules	61-year-old Spanish Medical Doctor	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) ²⁶	Erythematous, confluent, nonpruritic maculopapular rash	6-year old boy	2 week 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
		Acute urticaria, apparently pruritic	2-month old girl	4 days after low fever, at the same time with COVID-19 confirm	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 ²⁷	15% 3% 1%	Erythematous rash Widespread urticaria Chickenpox-like vesicles	40% had used new medicine in 15 previous days, 12% were hospitalization	Trunk	Itching was low or absent and usually lesions healed in few days	Not reported Not reported Not reported	Not reported 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 ¹	19% 9% 19% 47% 6%	Erythema with vesicles or pustules (Pseudo-chilblain) Other vesicular eruptions Urticarial lesions Maculopapular eruptions Livedo or necrosis	59% after other symptoms 15% before other symptoms Not reported Not reported Not reported	Acral areas Trunk and limbs trunk or disperse and palmar dorsum of the hands truncal or acral ischemia	Pain (32%) or itch (30%). Itching (68%) Itching (92%) Itching (57%) Not reported	younger patients middle aged patients Not reported Not reported older patients	12.7 days 10.4 days 6.8 days 8.6 days 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 ²⁸	72.0% 28.0%	Chilblain-like Erythema multiformelike	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) Acral area (21% hands and 94% feet and 27% heels or wrists)	Not reported Not reported	Mean of age were 23.4 years old Mean of age were 12.2 years old	9.2 days 7.4
Gianotti, Raffaele	Clinical and Histopathological study of skin dermatoses in patients affected by COVID-19 infection in the Northern part of Italy ²⁹	Not reported Not reported Not reported Not reported	Diffuse maculo-papulo-vesicular rash Hemorrhagic dot-like area due to extravasated erythrocytes Papular erythematous exanthema Diffuse macular livedoid hemorrhagic lesions	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 trunk trunk leg	classic dyskeratotic cells, ballooning multinucleated cells and sparse necrotic keratinocytes with lymphocytic satellitosis, perivascular spongiotic 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 Not reported	Not reported Not reported Not reported Not reported
Piccolo, V.	Chilblain-like lesions during COVID-19 epidemic: a preliminary study on 63 patients ³⁰	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 S ³¹	4.9%	Erythematous rash, urticaria	Not reported	Face, upper body	Itching	Mean age 47	Not reported

(Continues)

TABLE 2 (Continued)

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)
Marzano, Angelo Valerio	Varicella-like exanthem as a specific COVID-19-associated skin manifestation: multicenter case series of 22 patients ³²	100%	Diffuse (scatter) papulovesicular lesions	Fever (95.45%), cough (72.72%), dyspnea (36.36%), headache (50%), coryza (45.45%), weakness (50%), hypogeusia & hyposmia (18.18%), asthenia & myalgia & diarrhea & nausea (4.54%)	Trunk, limbs	itching (36.36) burning (13%) pain (9%)	Mean age 56.45	7.45
Recalcati, S.	Acral cutaneous lesions in the Time of COVID-19 ³³	100%	Acral red-purple maculopapular eruption, with possible bolous evolution or swelling, targetoid lesion	In 3 cases cough and fever 3 weeks before skin manifestation was observed	8 cases feet, 4 hand and 2 cases both area among 14 cases	Mild itching in 3 cases	11 patients with average 14.4 and 3 with average 29	2 to 4 weeks

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-19.³³ 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-2.¹¹ Digit ischemia may happen due to transient increase in antiphospholipid antibodies in severe illnesses or in viral disorders.⁶⁷ Another assumption was that this digit ischemia could be related to immunological mechanism or prothrombotic activation states.¹² Pruritic lesions in severe COVID-19-related respiratory failures revealed an inflammatory thrombogenic vasculopathy with trace amount of C5b₉ and C4d depositions.²⁰ 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.¹⁰

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.⁶⁸

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.²⁶ A 32 years old healthy female, 6 days after symptomatic current corona virus infection presented with generalized progressive maculopapular and petechial lesions in a reddish base that by the time became scaly, more itchy and less erythematous.⁶⁹

In the most cases of maculopapular lesions palmoplantar region and the mucosa were spare. A 60-year old man with a history of flu-like symptoms and positive COVID-19 infection experienced sudden disseminated red macular lesions which turned into papules on bilateral flank, groin, back and proximal lower extremities.¹⁵

In a 71-year old Caucasian woman scattered maculopapular eruption (morbilliform) with cervical lymphadenopathy, fever and cough was seen in addition to hemorrhagic macular exanthem on the legs.¹⁴ Pruritic Papulovesicular lesions was seen in a 72 years old woman who had a history of flu-like symptoms 4 days before skin rash appearance and the rash was on sub-mammary folds, hips and trunk.¹⁴ Petechial lesions have been seen in above case and another one in Thailand who misdiagnosed as dengue fever.^{68,70} Digitate papulosquamous lesions occurred in a hospitalized old man who infected with COVID-19. The initiate periumbilical scaly patches widespread rapidly toward flank and thigh and the other areas, some of them were only papular. The lesions resembled pityriasis rosea and diminished suddenly in 7 days.⁷¹ A 34 months old child with conjunctivitis and eyelid dermatitis confirmed SARS-CoV-2 in China.¹³ 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 lower limbs and trunk.²⁶ A 27 years old previously healthy

TABLE 3 skin care recommendations and Prevalence of secondary skin complications

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 ³⁴	Eczema	Not reported	<ul style="list-style-type: none"> • 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
		irritant	Not reported	
		contact dermatitis	Not reported	
		methicillin-resistant <i>Staphylococcus aureus</i> colonization	Not reported	
Pingping Lin	Adverse skin reactions among health care workers during the coronavirus disease 2019 Outbreak: A survey in Wuhan and Its surrounding regions ³⁵	occupational contact dermatitis	31.5%	<ul style="list-style-type: none"> • applying moisturizers/ • Using alcohol-based products instead of soaps/ • Double gloving is sufficient/
		dryness or scales	68.6%	
		papules or erythema	60.4%	
		maceration	52.9%	
Patruno, Cataldo	The role of occupational dermatology in the COVID-19 outbreak ³⁶	dryness, irritation, itching, and even fissuring and bleeding	Not reported	<ul style="list-style-type: none"> • Application of hand cream/moisturizers on intact skin after hand washing • Disposable packaging is recommended
		hand dermatitis	Not reported	
		maceration	Not reported	
Pei, S.	Occupational skin conditions on the frontline: A survey among 484 Chinese health care professionals caring for COVID-19 patients ³⁷	various degrees of pruritus	61.8%	Not reported
		Mild pruritus	45.5%	
		Moderate pruritus	15.1%	
		Severe pruritus	1.2%	
		various skin lesions	73.1%	
		erythema	38.8%	
		prurigo	22.9%	
		blisters	13.8%	
		rahagades	13.6%	
		papule/edema	12.8%	
		exudation/crust	6.8%	
lichenification	5.6%			
Scratch	11.7%			
Bin Zhang	COVID-19 epidemic: Skin protection for health care workers must not be ignored ³⁸	indentations, ecchymosis, maceration, abrasion and erosion	Not reported	<ul style="list-style-type: none"> • 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./
		blisters and itching and bleeding	Not reported	
		dermatitis and folliculitis.	Not reported	
		fungal infections	Not reported	
		desquamation, rhagades	Not reported	
		eczema-like changes	Not reported	
		ulcers followed by secondary bacterial or fungal infections	Not reported	

(Continues)

TABLE 3 (Continued)

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 Study ³⁹	Various type of Skin injury related pressure injuries moist-associated skin damage (redness, pain, itching, or prickling) skin tear related pressure injuries and moist-associated skin damage related pressure injuries and moist-associated skin damage and skin tear related pressure injuries and skin tear moist-associated skin damage and skin tear	42.8% 30% 1.8% 2% 78.8% 13.2% 7.0% 1.0%	<ul style="list-style-type: none"> 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 2019 ⁴⁰	Erythema, dryness, scale, papules, maceration, erosion, contact dermatitis	Not reported	<ul style="list-style-type: none"> 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) epidemic ⁵	Dermatitis	97.0%	<ul style="list-style-type: none"> Shorter rotating shifts in high-intensity protective gear. Latex-free gloves

TABLE 3 (Continued)

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" ⁴¹	Hand eczema, skin damage	more than 60%	<ul style="list-style-type: none"> 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 ⁴²	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 ⁴³	Hand eczema, erythema, scaling and vesiculation	Not reported	<ul style="list-style-type: none"> 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 Prevalence of skin areas affected by secondary skin complications in health care providers

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 ³⁵	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 ³⁷	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 ³⁸	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 ³⁹	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 ⁴²	Nasal bridge	83.1%

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.⁹ 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.¹⁸ Also in a 61 years old Spanish MD male patient, progressive pruritic urticarial lesions manifested which lasted about 10 days without no other symptoms.²⁵

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.¹⁵ 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 on 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.⁷² 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 SARSCoV-2. The lesions diminished after a week.⁷³ Morbilliform exanthema presented in a 58 years old man who complained about cough and pain in limbs, the physician prescribed Azithromycin and Benzonatate for him and after a few days, pruritic progressive

TABLE 5 expert recommendation for immunomodulators treatment and immune based dermatologic disorders

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 ⁴⁶	<p>Patient With inflammatory skin disorder being actively managed with an immunomodulator who confirmed COVID-19 Disease</p> <p>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</p>	<p>should stop the immunomodulator (s) immediately, exception of systemic corticosteroids</p> <p>Lowering the dose of immunomodulatory/ or temporarily stopping for 2 weeks.</p> <p>Exception is systemic corticosteroids.</p>	COVID-19 infection being aggravated by immunomodulators and secondary bacterial infection as part of COVID-19 complication become aggravated too	<p>Not reported</p> <ul style="list-style-type: none"> • 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 (mycophenolic acid to ≤ 720 mg/day)
Federico Bardazzi	Biologic therapy for psoriasis during the COVID-19 outbreak is not a choice ⁴⁷	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 ⁴⁸	<p>patients who are already on biological treatment and have tested positive for COVID-19</p> <p>composed of patients who are being considered for the initiation of biological therapy</p> <p>patients with severe psoriasis, those on potentially immunosuppressive therapies, and those presenting comorbid conditions might be at higher risk of infection.</p>	<p>Discontinuing or postponing the biological therapy until full recovery from the COVID-19 infection.</p> <p>avoidance of initiation of biologic therapy for high-risk patients</p> <p>all individuals stop biological treatment as soon as they are diagnosed with COVID-19 infection</p>	<p>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</p>	<p>Not reported</p> <p>Not reported</p> <p>Not reported</p>
Di Lerna, Vito	Biologics for psoriasis during COVID-19 outbreak ⁴⁹	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 ⁵⁰	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" ⁵¹	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 action ⁵²	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 dermatology ⁵³	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), Secukinumab (IL-17a), Ixekizumab (IL-17a), Ustekinumab (IL-12/23), Guselkumab (IL-23)	Continue if viral symptoms are mild, consider stopping if viral symptoms worsen or high fever develops		Not reported
		psoriasis Patients treat with Rituximab	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 statement ⁵⁴	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	<ul style="list-style-type: none"> 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 Systemic corticosteroids: Reduce to 10 mg/day prednisone or equivalent in a graduated manner.
		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	there is currently insufficient evidence to suggest that COVID-19 infection is aggravated by immunomodulators used in skin disease, however all COVID-19 infections should be considered serious	<ul style="list-style-type: none"> 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 prednisone or equivalent in a graduated manner Biologics: extending the time between dosages. Retinoids: No dose adjustment required

(Continues)

TABLE 5 (Continued)

First author	Title	Patient characteristics	Recommendation	The reason	Dose adjustment
		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,	Dose reduction or cessation of immunomodulators and biologics is not necessary	Not reported	Not reported
		Organ Transplant/Bone marrow transplant patients	Immunosuppressive treatments (eg, prednisone, ciclosporin, tacrolimus, azathioprine, mycophenolate, etc.) should not be stopped	Not reported	Not reported
Arora, G	The COVID-19 outbreak and rheumatologic skin diseases ⁵⁵	Patients on Disease-modifying antirheumatic drugs (DMARDs), biologics or other immunosuppressive medications Non-infected patients	Required to consult their rheumatologist and stop these drugs during an infection Advised to continue their medication during the epidemic	Because patients with rheumatic 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
Kansal, NK	COVID-19, syphilis, and biologic therapies for psoriasis and psoriatic arthritis: A word of caution ⁵⁶	Patients with psoriasis and psoriasis arthritis	Considering the risk to benefit ratio before discontinuing drugs and monitoring the patients who continue to receive the therapy	Because the prognosis of COVID-19 cannot be predicted in individual cases (particularly in middle aged and older patients, with comorbidities like diabetes mellitus or cardiovascular disease etc, if they are being treated with biologics).	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: 1. Any active infection, including COVID-19 2. COVID-19 risk factors including: age over 60, cardiovascular disease, hypertension, lung disease, diabetes, or cancer 3. Concomitant immunosuppression (eg,	favoring biologic discontinuation or reduction in immunomodulatory regimen, if reduction is needed option include: 1. Temporary discontinuation of the biologic 2. Reduction in biologic dose frequency 3. Transition to an alternative biologic	These recommendations are based on rate of infections in previous clinical trials studies about biologic and immunosuppressive drugs in psoriatic patients	Not reported

TABLE 5 (Continued)

First author	Title	Patient characteristics	Recommendation	The reason	Dose adjustment
		<p>methotrexate, prednisone, cyclosporine)</p> <p>4. Immunosuppressive condition (eg, HIV)</p> <p>5. History of infections while on biologic</p> <p>6. Mild-to-moderate underlying psoriasis</p> <p>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)</p> <p>8. Short duration of COVID-19 pandemic</p>	<p>4. Reduction or discontinuation of concomitant immunosuppressants (eg, methotrexate)</p> <p>5. Increase in use of topical agents, home phototherapy, or other non-immunosuppressive medications</p>		
		<p>Psoriatic patients with following risk factors:</p> <p>1. Young age</p> <p>2. No COVID-19 high risk comorbidities</p> <p>3. Biologic monotherapy</p> <p>4. Severe underlying psoriasis or psoriatic arthritis, with history of rapid flares or unstable subtypes (pustular, erythrodermic)</p> <p>5. No concomitant immunosuppressive conditions</p> <p>6. Low risk of exposure to COVID-19 virus</p> <p>7. Long duration of COVID-19 pandemic</p>	favoring biologic continuation		Not reported
		Patients who test positive for COVID-19 infection	Advising to hold their biologic dose until their infection clears.		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
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 ⁵⁹	Patients with advanced basal cell carcinoma receiving treatment with the hedgehog pathway inhibitors sonidegib and vismodegib during the COVID-19 period	Continuing therapy. Dose adjustment to prolong treatment duration, when possible.	Based on their analysis on 37 patients at Italian referral center for skin cancer diagnosis and management	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 ⁶⁰	Patients with chronic plaque psoriasis receiving a biological treatment and renal transplanted recipients in maintenance immunosuppressive treatment	There is no need to discontinue their therapies	There is no early signal of an increased hospitalization or death from COVID-19. Based on retrospective observational study in verona	Not reported

(Continues)

TABLE 5 (Continued)

First author	Title	Patient characteristics	Recommendation	The reason	Dose adjustment
ShakShouk, H	Treatment considerations for patients with pemphigus during the COVID-19 pandemic ⁶¹	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
			glucocorticoids and steroid-sparing immunosuppressive agents, such as azathioprine and mycophenolate mofetil, should be tapered to the lowest effective dose	Their nonspecific immunosuppressive effects increase infection risk, among other complications, in a dose-dependent manner.	Not reported
		Patients with pemphigus and active COVID-19 infection	postponing rituximab infusions temporarily	Delaying peak patient immunosuppression during peak COVID-19 incidence to reduce the risk of adverse outcomes.	Not reported
			In active COVID-19 infection, immunosuppressive steroid-sparing medications should be discontinued when possible	Their nonspecific immunosuppressive effects increase infection risk, among other complications, in a dose-dependent manner.	Not reported
Jic ZA	United States Cutaneous Lymphoma Consortium Recommendations for Treatment of Cutaneous Lymphomas During the COVID-19 Pandemic ⁶²	Low risk patients with cutaneous lymphomas	Low-risk therapies that can be utilized at home should be continued for all patients. Home-based NBUBV 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
		Intermediate low risk patients with cutaneous lymphomas	Therapies may be continued, but dose adjustments may be advised on an individual basis. Initiation of these therapies may be postponed using low-risk bridge therapies short term. Increasing or initiation of a retinoid or interferon should be considered in cases that necessitate the removal of other high-risk therapies.	Not reported	Not reported
		Intermediate high risk patients with cutaneous lymphomas			Not reported
		High risk patients with cutaneous lymphomas	May require travel to the clinic or hospital. These should only be utilized in the highest risk patients and the additional risks of therapy-related travel should be considered. Infusion regimens may be adjusted to increase treatment intervals. Allogeneic stem cell transplant and treatment with CHOP, alemtuzumab, fludarabine are strongly discouraged, Consider alternative lower risk therapies whenever possible.	Allogeneic stem cell transplant and treatment with CHOP, alemtuzumab, fludarabine are strongly discouraged during the pandemic because they often lead to significant cytopenias that are known risk factors for COVID-19 complications.	Romidepsin and mogamulizumab may be considered on individual basis with extended intervals and lower doses.
Torres, T	Managing Cutaneous Immune-Mediated Diseases During the COVID-19 Pandemic ⁶³	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

TABLE 5 (Continued)

First author	Title	Patient characteristics	Recommendation	The reason	Dose adjustment
Megna, M	Biologics for psoriasis in COVID-19 era: what do we know? ⁶⁴	Psoriatic patients without COVID-19 infection	Treatment discontinuation should be avoided	Unnecessary biologic discontinuation would lead to a worsening of psoriasis and psoriatic arthritis in a high percentage of the cases. As a consequence, there may be higher disease burden, destructive impact on quality of life, as well as increased health care costs due to the augmented number of consultations and recovery. Furthermore, the unavoidable subsequent return to biologic therapy could be associated with switching toward higher cost drugs, due to the well-known lower efficacy of biologics in the same patient after their interruption	Not reported
		Psoriatic patients with COVID-19 infection	Treatment discontinuation		Not reported
Amerio, P	COVID-19 and psoriasis: should we fear for patients treated with biologics ⁶⁵	Psoriatic patients	The treatment of psoriatic patients with biologicals should not be discontinued during the time of this pandemic	Based on literature review	Not reported
		elderly patients with coexisting morbidities such as hypertension, diabetes and obesity that enhance their chance of developing, if ever infected, a more severe disease; when patients develop flu like or COVID-19 specific (anosmia, asthenia) symptoms and if are exposed to high risk contact with infected people	Suspend the treatment should be made		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^{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, erythematous, and urticarial dermatosis. Hyperpigmentation came second followed by pruritis, SJS/TEN and AGEP (Acute generalized exanthematous pustulosis).² Dermatologists should consider the COVID-19 cutaneous manifestations such as erythematous rash, petechia, urticaria as differential diagnosis while assessing the possible Hydroxychloroquine drug reactions.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 fever, generalized red or purple skin rashes, angioedema, blisters, skin peeling, burning sensation in eyes or painful skin.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 and eczematous lesions, localized scleroderma, skin dryness and rash. Other antiviral drugs such as antiretrovirals are also used in some patient 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.^{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 altered regimen or discontinued 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.^{46,54,63,78,79}

Biologic immunomodulators especially TNF- α inhibitors, janus kinase (JAK) inhibitors, anti-IL 6 (Tocilizumab) may be capable to control cytokine storms and its 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 be disrupted.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.^{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 (immuneenhancing in a positive way or minimal immunosuppressive properties) 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).

- Bruton 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 were 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 upatacinib 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 tele dermatology 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 (Pseudo-chilblain or Pernio-like lesion or "COVID toe"), Digital ischemia, Digitate papulosquamous lesions, Chickenpox-like blisters, Varicella-like exanthema, Pruritic Papulovesicular, Petechial skin rash, Acute hemorrhagic edema, livedoreticularis (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 manifestation 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.

ORCID

Arash Pour Mohammad  <https://orcid.org/0000-0003-3064-4299>

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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