

REVIEW ARTICLE

A comparative review on mucocutaneous reactions caused by Covid-19 infection versus Covid-19 vaccination

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Abstract

The prevalence and severity of mucocutaneous manifestations in Covid-19 infection are generally higher than those reported in Covid vaccines. Therefore, comparing the mucocutaneous reactions of the Covid-19 infection and vaccination is necessary to enhance our knowledge about such reactions and guide us to evaluate the risk of infection or vaccination. A thorough literature search was conducted on PubMed, Google Scholar, and EBSCO (LISTA), and 2069 articles were downloaded. After screening, 11 studies remained for the final review. The literature review revealed that the prevalence and severity of postvaccine mucocutaneous adverse reactions have been less common compared to Covid-19 infection. Postvaccine adverse reactions primarily occurred after the first dose administration and such reactions were manageable with antihistamines and corticosteroids administration. This comparative analysis highlights the frequency and potential severity of mucocutaneous reactions due to Covid-19 infection and Covid-19 vaccination. It also affirmed that potentially critical (serious) mucocutaneous reactions are more likely to occur in Covid-19 infection compared to Covid vaccination. Moreover, postvaccine reactions predominantly happened after the first dose and were reported to be non-life-threatening, self-manageable and with a lower incidence of potentially critical events. It was also concluded that the incidence of mucocutaneous reactions decreased in the following doses. Hence, given the low rate of such reactions following Covid-19 vaccination, vaccines have a lower risk of mucocutaneous reactions occurrence than Covid-19 infection. Further, due to the limited number of studies, we recommend that large-scale trials evaluate such reactions comparing various types of Covid-19 vaccines in healthy individuals and those with autoimmune skin disorders.

KEYWORDS

Covid-19, mucosa, reactions, review, skin, vaccination

Abbreviations: ACE2, Angiotensin-converting enzyme-2; HCQ, hydroxychloroquine; HSV, herpes simplex; IFN γ , interferon gamma; IL, interleukin; PLEVA, pityriasis lichenoides et varioliformis acuta; RT-PCR, reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome Coronavirus 2; SJS, Stevens-Johnson syndrome; TGF- β , transforming growth factor beta; TNF- α , tumor necrosis factor alpha; VZV, varicella zoster.

1 | INTRODUCTION

Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection, also known as Covid-19, presents predominantly as a respiratory disorder.¹ Covid-19 virus, like other coronaviruses, belongs to a RNA virus family called Coronaviridae.² It spreads through droplets, droplet nuclei and contact with contaminated surfaces and fomites.¹ The typical manifestations of Covid-19 infection include pyrexia, non-purulent cough, dyspnoea, fatigue, weakness, headache and the loss of smell or taste.^{3,4}

Although the presentations of Covid-19 infection are primarily respiratory, various extrapulmonary manifestations, including mucocutaneous signs, have also been reported.⁵ The mucocutaneous signs and symptoms of Covid-19 are highly diverse, can be resolved without any interventions, and may be unrelated to the severity of the infection.⁶ A specific classification for mucocutaneous manifestations of Covid-19 infection following six main visible patterns have been recommended: chilblain-like acral pattern, urticarial rash, livedo reticularis/racemose-like pattern, confluent erythematous/maculopapular/morbilliform rash, papulovesicular exanthem and purpuric vasculitis pattern.^{5,7,8}

Several vaccines have been developed for the prevention of severe and lethal outcomes of Covid-19 infection. Although vaccines have shown acceptable safety and efficacy profiles, they may cause few adverse reactions after administration.⁹ Vaccines reinforce the cellular immunity, especially T-helper 1 (Th₁) response by building a high level of interleukin-2 (IL-2), IL-6, tumor necrosis factor alpha (TNF α) and interferon gamma (IFN γ). Different particles of vaccines can function as haptens and induce the activity of Th₂ and increase the quantity of IL-4, IL-5 and IL-13. In addition, skin-resident memory T cells may also be activated after the injection of vaccines, which induces Th₁₇ and Th₂₂. Subsequently, Th_{17/22} trigger an inflammatory reactions cascade by transforming growth factor beta (TGF β) and IL-10. Therefore, immune-related hypersensitivity reactions seem to play a significant role in postvaccine adverse reactions.^{7,9}

Postvaccine reactions are generally short-term and disappear without any required treatment.¹⁰ Fever, fatigue, headache, chills, local reaction of the injection site, muscle pain and diarrhoea are among general postvaccine adverse effects. Further, like Covid-19 infection, Covid vaccines also seem to cause various mucocutaneous reactions. Postvaccine mucocutaneous reactions include urticaria, erythromelalgia, angioedema, delayed palm and sole itchiness, morbilliform rash, zoster lesion, papulosquamous eruption, bullous pemphigoid, erythema multiforme, Stevens-Johnson Syndrome (SJS), lichen planus-like, Perino, neutrophilic dermatosis and leukocytoclastic vasculitis.^{11,12}

To date, various types of mucocutaneous manifestations associated with Covid-19 infection and Covid-19 vaccination have been characterized and reported. Abundant evidence indicated that the reactions caused by infection were typically more lethal than post-vaccine reactions. Hence, we decided to conduct a comprehensive study to compare mucocutaneous reactions following Covid-19 infection and vaccination. The outcome of this study may imply the

similarities and differences of Covid infection and postvaccine mucocutaneous reactions. Moreover, it is likely that the findings of the study suggest that postvaccine critical adverse reactions are less extreme or have a lower incidence compared to Covid-19 infection. Thus, the results of the current work can be proof for the reduction of undesired reactions by vaccination in the dermatology field.

2 | MATERIALS AND METHODS

2.1 | Search strategy

The literature review was performed using publications on mucocutaneous adverse reactions following Covid-19 infection and post-Covid19 vaccination. A thorough search was directed on PubMed, Google Scholar and EBSCO (LISTA) utilizing a combination of the following MeSH terms: "Covid-19," "Coronavirus," "SARS-Cov-2," "Mucocutaneous," "Dermatology," "Skin," "Adverse reactions," "Vaccination," and "Post-vaccination." A total of 2069 articles were received, and 111 duplicates were excluded. Primary screening was performed on 1958 papers, and ultimately, 124 articles remained for criteria application and second screening with 11 studies being examined for the final review. Cross-checking of reference lists of articles was completed manually, and all the relevant studies were identified. The results were properly summarized and reported.

2.2 | Inclusion and exclusion criteria

The criteria for inclusion were publications reported on mucocutaneous adverse reactions following Covid-19 infection and vaccination in all age groups. The criteria for exclusion comprised all articles not meeting the inclusion criteria, publications in which no mucocutaneous manifestation was considered, animal or in vitro/ex vivo experiments, commentaries, consensus documents, non-English literature. In the end, within the published works on post-Covid infection and postvaccine mucocutaneous reactions, the most recent systematic reviews and meta-analysis with a higher level of evidence were selected. Among articles associated with the postvaccination mucocutaneous adverse events, existing executive publications, including the large-scale cohort, cross-sectional and observational studies, were selected for the review.

3 | RESULTS AND DISCUSSION

In this comparative study, we compared and summarized the recently published papers on mucocutaneous adverse reactions following Covid infection and vaccination. Therefore, authors reviewed literature to study (i) skin manifestations in Covid-19 infection (results are summarized in Table S1), (ii) skin reactions following Covid-19 vaccination (results are summarized in Table S2) and (iii) the comparison

of the mucocutaneous adverse reactions in Covid-19 patients versus postvaccination (results are summarized in Table S3).

3.1 | Skin manifestations in Covid-19 infection (Table S1)

Conforti et al.¹³ performed a systematic review on 655 patients who tested positive by reverse transcription-polymerase chain reaction (RT-PCR) coronavirus tests. All enrolled patients presented with cutaneous manifestations consisting of various types of skin rashes, including (order from the most to least prevalent) erythematous maculopapular, vascular, vesicular, urticarial, ocular/periorcular, polymorphic pattern, generalized pruritus, generalized pustular figurate erythema/erythema multiforme/SJS, atypical erythema nodosum, Kawasaki disease and atypical sweet's syndrome. The review revealed that retiform purpura and fixed livedo racemose presented more in commonly elderly individuals, and chilblain-like lesions were more frequent in younger cases and were related to a milder course of the disease. The detection of herpes simplex viruses (HSV) in the vesicle contents was determined through PCR in case of vesicular rashes considering the possibility of herpesvirus co-infections. The SJS and erythema-multiforme-like lesions were most related to Hydroxychloroquine (HCQ) consumption. The list of consumed medications in the last month is reported in the supplementary documents Table S1. It is noteworthy that mucocutaneous signs and symptoms may assist in diagnosing otherwise asymptomatic Covid-infected individuals or predict a more severe infection progression in symptomatic patients.¹³

Seirafianpour et al.¹⁴ systematically reviewed 89 articles; they considered all primary and secondary cutaneous presentations associated with Covid-19 and listed papulovesicular rash, chilblain acral rash, urticaria, confluent erythematous/morbilliform rash/maculopapular, livedo reticularis/racemose-like rash, purpuric vasculitis pattern, varicella-like eruption, haemorrhagic lesions, pseudo-chilblain rash and erythematous pustules within the mucocutaneous manifestations of Covid-19. Multiple nails and mucocutaneous manifestations of Covid-19, including maculopapular eruptions, urticaria and the acral vasculopathy such as pseudo-chilblain/pernio-like (COVID toe) were considered as primary or evolving signs of the clinical course of the infection.¹⁴

Singh et al.¹⁵ reviewed the cutaneous manifestations of Covid-19 patients mainly from France, Spain, Italy and the United Kingdom. The systematic review and meta-analysis were performed on 56 studies related to the onset of the Covid-19 pandemic. Results showed that the cutaneous reactions of Covid-19 were age-independent and were also observed among children. The manifestations included maculopapular, chilblain-like, urticarial, vesicular, livedoid and petechial lesions. The study suggested a possible relation of Covid-19 with multisystem inflammatory syndrome manifested by rashes in paediatric patients. They also highlighted the possibility of Covid-19 infection through skin wounds caused by personal protective equipment.¹⁵ The cutaneous presentations of 507 patients with Covid-19

was reviewed by Zhao et al.¹⁶ The skin polymorphic lesions, urticaria, erythema and chilblain-like were prevalent and observed after mean of 9.92 days following the beginning of systemic symptoms. The results suggested that the receptors of SARS-Cov-2, primarily on keratinocytes, and Angiotensin-converting enzyme-2 (ACE2) in the derma might play major roles in the cutaneous adverse reactions of Covid-19 infection.¹⁶

Shams et al.¹⁷ studied 354 Covid infected patients presenting maculopapular lesions. A considerable variation of distribution and appearance within maculopapular lesions was found. The lesions appeared from diffuse maculopapular rash to scattered and generalized erythematous macules. The mean duration of skin lesions was 8 days, and which were primarily localized on trunks and extremities. However, the authors indicated that Covid-19 might not be the primary reason for the skin manifestations mentioned above, and such lesions may be the possible presentations regarding the illness, prognosis and severity.¹⁷

Sameni et al.¹⁸ systematically reviewed the skin manifestations of Covid-19 in 35 studies. Their meta-analysis revealed that from 2621 patients, 1% of patients presented with erythematous rash (59.1%) and urticaria (14.8%) as the most prevalent manifestations. Obesity, hypertension, diabetes and chronic renal failure were listed as comorbidities among the cases and there were medications that were used in the last month. The skin manifestations combined with other Covid-19 symptoms were suggested as a potential asset in the timely diagnosis of Covid-19.¹⁸

3.2 | Skin reactions following Covid-19 vaccination (Table S2)

Grieco et al.¹⁹ performed a cohort study on 2740 Italian individuals who received the Covid-19 vaccines; 60% received Pfizer, 32% AstraZeneca and 8% Moderna. They indicated that cutaneous adverse reactions to vaccines occurred in 50 cases only (28, 20 and 2 individuals after the first, second and both doses, respectively). Mucocutaneous adverse reactions were more prevalent in Pfizer recipients. The results affirmed a low chance of cutaneous reactions to Covid-19 vaccines occurring mainly after the first dose, with reactions being manageable. Oral antihistamines and corticosteroids typically resolved the issue, and lesions disappeared in 68% of patients in 0–7 days, 26% in 7–14 days and 6% in 14 days. Immediate hypersensitivity reactions such as anaphylaxis are life-threatening, and an important factor to not administering medications or vaccines to the patients; however, cutaneous adverse reactions are not contraindications for vaccination.¹⁹

A randomized, cross-sectional study by Kadali et al.²⁰ on 1271 healthcare workers studied the adverse effects of the Moderna vaccine. In this study, 38.7% of participants received Moderna and only Moderna recipients were considered for results analysis. The majority of Moderna recipients were female (89.35%). Rash was seen in 13.43% of patients and described as localized at the injection site and allergic reactions. Pruritus, accompanied with or without skin

lesions or any other skin involvement, was another post-Moderna side effect reported in 14.58% of participants. Some patients reported residual skin discolouration (3.47%), urticaria (1.62%), atopic dermatitis (0.93%), hay fever (0.69%), swelling in the mouth or throat (0.46%) and swelling of lips or tongue (0.23%) after receiving the vaccine. However, it was noted that most mucocutaneous adverse reactions were non-life-threatening and managed without medication.²⁰

Robinson et al.²¹ performed a cohort study and reported that out of 49 197 individuals who received Pfizer (25%) and Moderna (75%), 776 of first dose recipients (1.9%) experienced cutaneous symptoms, and 101 out of these 776 individuals showed cutaneous adverse reactions again after the second dose (recurrent second dose recipients). Among those without cutaneous side effects following the first dose, 765 individuals showed cutaneous reactions with the second dose. The most common mucocutaneous adverse reactions after Covid-19 vaccines administration were as follows (i) the first dose recipients: itching or rash (1.5%), urticaria (0.4%) and angioedema (0.3%), (ii) the recurrent second dose recipients: itching (13%), urticaria (3.3%) and angioedema (2.6%), and (iii) in the new second dose recipients: itching and rash (2.3%), urticaria (0.6%) and angioedema (0.4%). It is noteworthy that such reactions were significantly more common in females (85%) and Caucasians (62%).²¹

Catala et al.²² performed a cross-sectional study among 391 Spanish individuals (405 reactions) who received Pfizer (40.2%), Moderna (36.3%) and AstraZeneca (23.5%). Besides injection site reactions, known as Covid arm (32.1%), the rest of the cutaneous reactions were classified as urticaria (14.6%), morbilliform (8.9%), papulovesicular (6.4%), pityriasis rosea-like (4.9%), purpuric eruption (4%), varicella and herpetic-like lesions (13.8%). Covid arm was predominantly reported in females (95.4%) and primarily seen in Moderna recipients (61.9%). Moreover, varicella-like reactions were more related to the Pfizer vaccine (17.2%), and urticaria lesions were reported in 21.1% of AstraZeneca recipients. All mucocutaneous adverse reactions were more prevalent in females, and lesions appeared within 21 days of vaccination. Though most reactions were mild-to-moderate and self-manageable, 21% were severe-to-very severe and needed treatment.²²

McMahon et al.¹¹ conducted a registry-based study investigating the association between cutaneous reactions in Moderna and Pfizer. Moderna (83%) and Pfizer (17%) vaccines were administered to 414 healthcare workers (90% female). The most prevalent mucocutaneous adverse effect was the injection site reactions after the first and second shot in 331 and 119 individuals, respectively. Recipients reported that they had experienced less mucocutaneous adverse reactions after the second doses.¹¹

3.3 | Mucocutaneous adverse reactions in Covid-19 infection versus post-Covid vaccination (Table S3)

Although Covid-19 infection and vaccination may cause unique sets of reactions, they can have mucocutaneous manifestations in

common. We categorized the mucocutaneous manifestations that were common in Covid-19 and vaccination into two groups: non-critical and critical. The non-critical reactions were (i) generalized pruritus, (ii) erythematous rash such as maculopapular, morbilliform and papulovesicular eruption, (iii) minor vasculopathies such as chilblain-like and livedoid purpura, (iv) viral exanthem including localized HSV and varicella zoster (VZV) reactivation, (v) erythema nodosum and (vi) urticarial lesions.^{13,15,18} Further, the common critical adverse reactions in both groups that require immediate medical attention were (i) angioedema, (ii) erythema multiforme and SJS; however, the severity and incidence of such reactions were greater after Covid infection.¹⁶ On the other hand, most of the patients in the vaccination group with the reactions mentioned above did not require hospitalization, and their conditions were managed with short-term antihistamines and corticosteroids treatment.¹²

A number of lesions were primarily observed in Covid-19 infection but were not reported after vaccination. The critical categories of such reactions were (i) major vasculopathies including dry gangrene, necrotic and retiform purpura, (ii) multisystem inflammatory syndromes such as Kawasaki syndrome and Kawasaki-like disease and (iii) generalized viral exanthema following HSV and VZV reactivation. Additionally, the non-critical mucocutaneous reactions that were only seen in Covid-19 infection included (i) minor vasculopathies such as petechia, eruptive cherry angioma and porcelain-like purpura, (ii) ocular and preocular involvement including conjunctivitis and eyelid dermatitis, (iii) generalized pustular figurate erythema and (iv) Sweet's syndrome.^{13,15,17}

The most common skin manifestations in Covid-19 infection were maculopapular rashes and urticaria,¹⁸ and maculopapular lesions were frequently related to the severe form of the disease (2% mortality rate).¹⁷ However, maculopapular eruption could be related to certain medications. Therefore, severely ill patients may require a higher number of medications, and this could be the reason for frequently seen maculopapular rashes in severe Covid infection. Chilblain-like, vesicular, urticarial, maculopapular, livedoid and necrotic lesions are associated with the progressively severe disease.¹⁶

The most prevalent mucocutaneous adverse effects following Covid-19 vaccination and specific to vaccination were Covid arm, urticaria and morbilliform eruptions,¹¹ with several reactions exclusively associated with vaccination. The most critical reaction is (i) anaphylaxis (0.23% in 1116 patients reported in the study carried by Kadali et al.²⁰), (ii) angioedema and (iii) erythema multiforme and SJS. The other types of vaccine-exclusive adverse effects are non-critical reactions, including (i) Covid arm and erythematous plaque in the injection site, (ii) erythromelalgia, (iii) pityriasis rosea-like rashes, (iv) swollen injection site of the cosmetic fillers and (v) pityriasis lichenoides et varioliformis acuta (PLEVA).^{19,20,22}

4 | CONCLUSION

Dermatological manifestations might be the primary signs of Covid-19 infection even in asymptomatic carriers. Moreover,

potentially critical mucocutaneous reactions are more likely to be seen in Covid-19 infection than vaccination; the critical (serious) reactions might require multidisciplinary medical approaches and treatments. It is also suggested that the severity of such reactions is comparable with the severity of the infection and prognosis.

Current data affirmed a lower rate of mucocutaneous adverse reactions following Covid-19 vaccination compared to the infection. Such reactions occurred mainly after the first dose of vaccines, with a higher prevalence in female and Caucasian patients. Further, most of the first dose reactions did not recur following the second dose, and the incidence of mucocutaneous reactions decreased after the second dose. Postvaccine reactions were observed to be self-limited, non-life-threatening, manageable and with a lower incidence of potentially critical conditions.

5 | LIMITATION AND RECOMMENDATION

There were limited studies focused on post-Covid vaccines mucocutaneous adverse reactions. Therefore, it is recommended that large-scale clinical trials evaluate mucocutaneous adverse reactions comparing various types of Covid-19 vaccines to see which vaccines trigger autoimmune reactions in the mucosa and skin more than others. Furthermore, it would be valuable to assess the incidence of mucocutaneous adverse reactions to Covid vaccines in patients with underlying autoimmune diseases of the skin and mucosa.

AUTHOR CONTRIBUTIONS

Contributions to the current study are SS in the design, database search, screening publications, literature review and drafting the manuscript, ZA in the screening publications, literature review, and drafting the manuscript, and AG in drafting and revising the manuscript critically for important intellectual content. All authors have read and approved the final version to be published and agreed to be accountable for all aspects of the work. All authors agreed on the order in which their names are listed in the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Table S3 Specifications of the mucocutaneous adverse reactions in Covid-19 patients versus post-vaccination vaccination

SUPPORTING INFORMATION

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

Table S1 The latest updates on the mucocutaneous manifestations following Covid-19 infection

Table S2 The latest updates on the mucocutaneous adverse reactions following Covid-19 vaccination in patients with CARs

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