Cutaneous adverse reactions of COVID-19 vaccines: A systematic review

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Abstract
Numerous vaccines are under clinical development and implementation for the prevention of severe course and lethal outcomes of coronavirus disease 2019 (COVID-19). This systematic review aims to summarize and integrated the findings of studies regarding cutaneous side effects of COVID-19 vaccines. This systematic review conducted by searching the scientific databases of PubMed, Scopus, Science direct, and Web of knowledge from the beginning of the COVID-19 to May 10, 2021. Articles were reviewed and analyzed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist. Seventeen studies on cutaneous side effects of COVID-19 vaccines were included after the screening of search results based on the eligibility criteria. The results showed that the most common injection site reactions and delayed large local reactions, arising from all vaccine types, were redness/erythema (39%), followed by: itchiness (28%), urticarial rash (17%) on the neck, upper limbs, and trunk, morbilliform eruptions (6.5%), Pityriasis rosea (3%), swelling, and burning, and so forth. Most cutaneous reactions occurred in women (84%), and middle-aged people, after the first dose of vaccine, with the onset ranged from 1 to 21 days after vaccination. In addition, cutaneous reactions were generally self-limiting, and needed little or no therapeutic intervention, that were not regarded as a barrier to injecting a second dose. In conclusion, severe cutaneous side effects are very rare and approved vaccines have satisfactory safety profiles. Therefore, mild or moderate cutaneous reactions should not discourage people from vaccination. In certain groups such as patients with allergies and a history of local injection reactions, pre-vaccination counseling and assurance, also use of appropriate medications may be helpful. However, more studies are needed to investigate the side effect profile of all COVID-19 vaccines.

KEYWORDS
adverse event, COVID-19, cutaneous, dermatologic, exanthema, SARS-CoV-2, skin, vaccines

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1 | INTRODUCTION

The pandemic of coronavirus disease 2019 (COVID-19) has prompted the fast development and licensing of vaccinations against the pathogen responsible—severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Vaccination candidates were created by more than 100 businesses and universities throughout the world, utilizing both well-established and more experimental vaccine platforms. Protein subunit vaccines have not yet been included into mass immunization campaigns, although they may do so soon. Many nations lack access to COVID-19 vaccines, despite the fact that certain high-income countries have already immunized the vast majority of their citizens. Because trade names may differ locally, we will always refer to vaccinations by their generic names.

More than a year later, a range of efficacious and safe COVID-19 vaccinations are now being administered across the world. Currently licensed vaccines use nucleic acid-based vaccination platforms, such as messenger ribonucleic acid (mRNA), viral vector platforms (using various adenovirus strains), and inactivated virus.

Antiviral immunity is induced effectively by humoral and cellular immune responses. Apart from those that employ live attenuated virus, most vaccination types require many doses and/or adjuvants to effectively stimulate the innate immune system, which then elicits adaptive immunological responses. DAMPs activate pattern recognition receptors (PRRs), including toll-like receptors (TLRs), which mediate immunogenic effects. Nucleic acids (including mRNA) are danger-associated molecular patterns (DAMPs) that activate PRRs, including TLRs, which mediate immunogenic effects. As a result, the COVID-19 mRNA vaccines now available do not require adjuvants. Although induction of specific and nonspecific skin eruption due to SARS-CoV-2 infection are rare, but in a small number of individuals, SARS-CoV-2 infections can cause vesicular, urticarial, and chilblain-like eruptions. Similar pathophysiological responses might be detected after an immunogenic challenge with a comparable vaccination. Some cutaneous drug reactions, including the reaction to the vaccine, can be initial manifestation of severe drug reactions that associated with internal organs involvement. Finally, cutaneous adverse drug reactions (ADRs) appear to be common with the administration of COVID-19 vaccinations, and include erythema, swelling, itching, pernio-like lesions, and widespread rashes. Despite the fact that they might be frightening for patients and treating physicians, most clinical studies do not accurately reflect them from a dermatological standpoint.

In this systematic review, we want to draw attention to the wide range of possible cutaneous inflammatory responses that might occur during vaccination administration in order to help healthcare providers better understand these individuals. This systematic review aims to summarize and integrate the findings of studies regarding cutaneous side effects of COVID-19 vaccines.

2 | METHODS

2.1 | Study design

This study was a systematic review that was performed by searching the scientific databases of PubMed, Scopus, Science direct, and Web of knowledge for relevant English articles published from the beginning of the COVID-19 to May 10, 2021. Analysis of retrieved articles was performed in four-step selection process of identification, screening, eligibility, and inclusion criteria, based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.

2.2 | Search strategy

We conducted a comprehensive search on the scientific databases using MeSH keywords including:

- COVID-19 or SARS-CoV-2 or Coronavirus or “Corona virus” or COVID; and vaccine or vaccines or vaccination or Sputnik or Astrazeneca or Pfizer or Sinopharm or Moderna or Bharat or Johnson & Johnson; and effect or reaction or adverse or subsequence or consequence or complication or outcome or aftereffect or disorder or disturbance or sequel; and skin or cutaneous or derm or dermis or keratinocyte or dermatology (supplementary).

To find more studies, the references in the relevant papers were also followed up. The search was performed by two independent researchers.

2.3 | Study selection

In the first step, two researchers reviewed the retrieved articles and removed the duplicates. In other steps, the researchers screened the title and abstract of the records and the ineligible studies were removed. Then, the authors surveyed the full-text of the remaining studies based on inclusion and exclusion criteria and the eligible studies were identified.

We excluded the articles, which were topic to at least one of the following criteria:

- Nonoriginal articles including reviews and editorials
- Lack of full text
- Abstract papers, articles without obtainable full texts, and conference abstracts.
- Clinical trials, which were in progress without yet published results.
- COVID-19 no vaccine trials articles
- Non-English articles

2.4 | Data extraction

The following information was extracted from full-text articles by three authors: first author (reference); type of study; country of study;
population; medical history; type of vaccine; cutaneous manifestations; duration of cutaneous manifestations; mechanism of cutaneous reactions; diagnostic assessment; management; outcomes; and other findings and transferred into a data spread table. These specifications and the corresponding table were designed by three members of our team. In order to eradicate any probable duplication, the selected articles were investigated by other researchers once again.

2.5 | Quality assessment

As mentioned formerly, we utilized the PRISMA checklist for evaluation and analyze of articles. The quality and relevance of the articles were investigated by two independent and experienced members. In any case their decisions differed, a third independent researcher confirmed their disagreements.

3 | RESULTS

A total of 69 potentially relevant articles were identified through the initial searches. After removing duplicates 58 articles remained, and then 32 articles were excluded by screening titles and abstracts, and the full texts of 26 remaining articles were assessed for eligibility. Finally, 17 studies met the inclusion criteria and were included in this systematic review as Figure 1 shows.

The studies and clinical characteristics are summarized in Table 1. These studies were conducted in different countries, eight case reports from Saudi Arabia, India, Turkey, and United Kingdom, as well as seven case series from Northeast Italy, and Germany and two cross-sectional studies.

Our results showed that the most common injection site reactions and delayed large local reactions, arising from all vaccine types, were redness/erythema (39%), followed by: itchiness (28%), urticarial rash (17%) on the neck, upper limbs, and trunk, morbilliform eruptions (6.5%), Pityriasis rosea (3%), and swelling, burning, and so forth.8,12,13 (Numbers are shown in Table 2).

Most patients showed cutaneous reactions after the first dose of vaccination.8,12,13,16–18 Some patients had very rare adverse dermatological reactions after first and second doses.8,12,17 The majority of adverse reactions were reported after mRNA-based vaccines.9,12–14,18

The onset and duration of dermatological manifestations were ranged from 1 to 21 days after vaccination except for three reports that reactions appeared within the first hours.10,11,14 Moreover, delayed cutaneous ADRs may occur after several days, either as a primary manifestation or as a flare of a pre-existing inflammatory dermatosis.22

The cutaneous side effects of the covid-19 vaccines appear to be more common in women (84% of reported cutaneous reaction after COVID vaccination),8,9,11–16,19,21 and diverse age groups; however, most were middle-aged.8,12,13,15,16,19

None of the skin reactions after the first dose of the vaccine prohibited the administration of the second dose except for six subjects that were advised not applying the second dose.12,19 Besides, 18 individuals did not plan to receive the second dose.8,16,17 No long-term cutaneous sequelae remain in any of the affected persons.13

![Flowchart](image-url)
# TABLE 1  Characteristics of included studies

| ID  | First author (reference) | Type of study | Country       | Population | Group (N) | Age (M ± SD) | Sex %                  | Past medical history | Type of vaccine (production technique) | Cutaaneous manifestations/manifestations | Duration of cutaneous reactions (effect factor) | Mechanisms of cutaneous reactions (effect factor) | Diagnostic assessment | Management | Outcomes | Other finding |
|-----|--------------------------|---------------|---------------|------------|-----------|--------------|-----------------------|---------------------|----------------------|---------------------------------------|-------------------------------------------|-------------------------------------------|---------------------|------------|----------|--------------|
| 1   | AL-Ansari, R. Y. & al.   | Case report   | Saudi Arabia  | 1          | 60 Male   | 60 (44.39 ± 12.36) | 89%                    | Type II diabetes mellitus and hypertension | Pfizer-BioNTech mRNA (mRNA based) | Multiple grouped-vesicles on the palms and soles of the hands and feet | Onset: 10 days, Duration: 5 days | Full blood count and biochemical assessment revealed no abnormalities | Histamine and IgE level: was not available | Treated conservatively by antihistamines | No hospital admission was required during her course of illness | The symptoms gradually resolved within 5 days. No hospital admission was required during her course of illness. |  |
| 2   | Arora, P. & al.          | Case report   | India         | 1          | 60 Male   | 60 (44.39 ± 12.36) | 89%                    | Type II diabetes mellitus and hypertension | Pfizer-BioNTech mRNA (mRNA based) | Multiple grouped-vesicles on the palms and soles of the hands and feet | Onset: 4 days, Duration: 2 weeks | Full blood count and biochemical assessment revealed no abnormalities | Histamine and IgE level: was not available | Treated conservatively by antihistamines | No hospital admission was required during her course of illness. | The symptoms slowly resolved after 2 weeks. No hospital admission was required during her course of illness. |  |
| 3   | Cebeci, F. & al.         | Case report   | Turkey        | 1          | 82 Female | 82 (44.39 ± 12.36) | 97%                    | Type II diabetes mellitus and hypertension | CoronaVac (Inactivated) | Multiple grouped-vesicles on the palms and soles of the hands and feet | Onset: 1 day, Duration: 7 days | Full blood count and biochemical assessment revealed no abnormalities | Histamine and IgE level: was not available | Treated conservatively by antihistamines | No hospital admission was required during her course of illness. | The symptoms slowly resolved after 2 weeks. No hospital admission was required during her course of illness. |  |
| 4   | Paternostro, E. & al.    | Case series   | Italy         | 46         | 46 Male   | 46 (44.39 ± 12.36) | 100%                  | Type II diabetes mellitus and hypertension | Biontech/Pfizer mRNA (mRNA based) | Multiple grouped-vesicles on the palms and soles of the hands and feet | Onset: 60h, Duration: 10 days | Full blood count and biochemical assessment revealed no abnormalities | Histamine and IgE level: was not available | Treated conservatively by antihistamines | No hospital admission was required during her course of illness. | The symptoms slowly resolved after 2 weeks. No hospital admission was required during her course of illness. |  |
### TABLE 1 (Continued)

| ID | First author (reference) | Type of study | Population | Country | Age (yr ± SD) | Sex % | Past medical history | Type of vaccine (production technique) | Cutaneous manifestations and reactions | Duration of cutaneous manifestations (days) | Mechanism of cutaneous reactions (effect factor) | Diagnostic assessment | Management | Outcomes | Other finding |
|---|--------------------------|---------------|------------|---------|---------------|-------|---------------------|----------------------------------------|------------------------------------------|------------------------------------------|---------------------------------------------|----------------|-----------|---------|-------------|
| 5 | Hoff, N.P. | Case-report | 2021 Germany | 11 | 50.09 ± 13.18 | Male: 2 (18%) | Patient no. 7 (female 44) had obesity as a comorbidity factor | Pfizer-BioNTech COVID-19 mRNA vaccine | Erythema: 62%; Induration: 62%; Soreness: 62%; Mild pruritus: 62%; Lymphadenopathy 5% | 3–12 days after vaccination | COVID-antibody reactions | Oral antihistamines (two patients) | Hospitalized with superficial and deep pericardial effusion, with Topical glucocorticoids and oral antibiotics (two patients) | Further investigations on the pathway physiological mechanisms underlying this cutaneous reaction pattern is needed to understand why and when adverse events may occur after mRNA vaccines |
| 6 | Hussain, K. | Case-report | 2021 London, UK | 62 | Female | Metastatic melanoma and relapsed CPI | Moderna (mRNA-1273) | Pityriasis rosea 4% | 2–6 days | Grade 1 eruption | Mechanical disruption | Admitted to hospital, treated with intravenous methylprednisolone 500 mg prednisone dose was increased to 80 mg | All patients were treated corticosteroids, Topical glucocorticoids, anti-myocarditis, and anti-inflammatory agents. | This case highlights the importance of sequential testing and early intervention with active irAEs in patients on CPIs, which can occur post-vaccination, especially in patients receiving CPIs following COVID-19 vaccination. |
| 7 | Catalá, A | Cross-sectional | Spain 2021 | 405 | 50.7 (17.6) | Female: 325 (80%) | Atopic dermatitis: 26.1%; Allergic rhinitis: 26.1%; Urticaria: 26.1% | M19 mRNA vaccine | Induration: 8.94 ± 6.10 days | Grade 4 reaction | Adverse immune reactions | Reported dematologistics, painless and in a predefined cutaneous reaction pattern | All patients were treated corticosteroids, Topical glucocorticoids, anti-myocarditis, and anti-inflammatory agents. | 42% of patients were treated with topical and oral corticosteroids, 15% with oral antibiotics, 39% with anti-inflammatory agents. | 8% successfully received the second dose of the vaccine and continued the booster dose, with no adverse effects. |
| 8 | Jaime-Guerrero, A | Case-report | Spain 2021 | 26 | 45 ± 4.66 | Female: 25 (96%) | Previous history of 1 or more of the following: 9 (34%) rhinocoronaviruses, 10 (46%) atopy, 5 (20%) allergic rhinitis, 3 (12%) chronic urticaria, and 1 | Pfizer-BioNTech, mRNA COVID-19 vaccine | Pityriasis rosea 14% | 1-4 days | Mechanical disruption | Patch testing was performed on all subjects, with no negative or positive results | 42% of patients were treated with topical and oral corticosteroids, 15% with oral antibiotics, and 24% with supportive care. | Patient no. 7 (female 44) had obesity as a comorbidity factor | None of the skin-reactions after the first dose of the vaccine prevented the administration of the second dose. There were no long-term cutaneous sequelae in any of the affected individuals. | Further investigations on the pathway physiological mechanisms underlying this cutaneous reaction pattern is needed to understand why and when adverse events may occur after mRNA vaccines. |
### Table 1 (Continued)

| ID | First author (reference) | Type of study | Country | Group (N) | Age (M ± SD) | Sex % | Past medical history | Type of vaccine (production technique) | Cutaneous manifestations (effect factor) | Duration of cutaneous manifestations | Mechanisms of cutaneous reactions (effect factor) | Diagnostic assessment | Management | Outcomes | Other finding |
|----|---------------------------|---------------|---------|-----------|--------------|-------|----------------------|---------------------------------------|----------------------------------------|--------------------------------------|------------------------------------------|-------------------------------|------------|----------|--------------|
| 9  | Larson, V.                | Case series   | USA 2021 | 12        | 69.25 ± 19.5 | Female: 50% Male: 50% | All items are 8.3% lichen simplex chronicus, inflammatory bowel disease (Crohn’s, ulcerative colitis), chronic eczema, acne vulgaris and herpes simplex virus, and allergic rhinitis, childhood atopic dermatitis | Pfizer-BioNTech: 5 Moderna: 7 | COVID-19: 16% moderate reaction: 35% maculopapular exanthema 16.0%; pruritic urticarial papules 8.3%; erythematous plaques 8.3%; DRESS 16.0% | 1–25 days | Use of PEG could support type IV hypersensitivity. Mixed-cell infiltrates, epidermal spongiosis, and interface changes. Eosinophils are a common finding but are not always present | Skin biopsies, microscopic examination and histopathologic diagnosis. | DIF was performed in four patients. | Topical corticosteroids and antihistamines, oral antibiotics were used | of 13 who had developed them after the first dose of a similar DHP or smaller size (50%): They resolved earlier (mean: 1.7 days) than the first dose (mean: 4.4 days, p < 0.005). 30% had no recurrence of DLR. One developed the same reaction after the second dose; MFDE also reoccurred after the second dose |
| 10 | Lopatynsky-Reyes, E. Z.   | Case series   | Mexico 2021 | 2 International Healthcare Workers 31, 28 | Female: 50% Male: 50% | N/A | | Pfizer-BioNTech, Moderna (both second dose) | | Onset: 24 h | Dermatologist report: urticarial rash and contact dermatitis | | | | Cutaneous reactions were resolved in 12 (91.7%) patients. 10 patients completed their vaccination series. Follow-up informed on five patients. It could not be obtained and patient refused her second vaccine dose because of persistent symptoms |
| 11 | McMahan, D. K.            | Cross-sectional registry-based study | USA 2021 | 454 | 44(SD: 59) | Female: 65% Male: 35% | Chronic obstructive pulmonary disease 8.6%; contact dermatitis 6.2%; 3.9% psoriasis 2.2%; urticaria 1.7% | Pfizer: 83%; Moderna: 17% | | | | | | | | | | | |
TABLE 1  (Continued)

| ID  | First author (references) | Type of study | Country | Population | Age (M ± SD) | Sex % | Past medical history | Type of vaccine (production technique) | Type of cutaneous manifestations | Question of cutaneous reactions (effect factor) | Mechanism of cutaneous reactions (effect factor) | Diagnostic assessment | Management | Outcomes | Other finding |
|-----|---------------------------|----------------|---------|------------|--------------|-------|----------------------|---------------------------------------|----------------------------------------|------------------------------------------|-------------------------------------------|---------------------|------------|----------|--------------|
| 12  | Negash M, F. 11           | Case series    | Italy   | 2021       | 9            | 46 ± 9.26 | Female: 88.9%        | Pfizer (Biontech)                       | Widespread pruritus; redness; 1-2 days facial erythema; maculopapular rash; Glandular secretions; erythematous edema; itching; nasal popular lesions; Ulceration with ortheliosis. | N/A                                      | Dermatologist report | For three subjects not applying the second dose; antihistamine; short course steroids | Cutaneous adverse reactions were resolved |
| 13  | Sprute, R. 11             | Case report    | Canada  | 2021       | 1            | 42         | Female               | Vaxzevria (viral vector vaccine)       | The delayed reaction as erythema (50 mm), in the axilla and near the injection site. | The earlier reactions: day 2-6 | Polysorbate 80 is the excipient in Vaxzevria and Olmesartan contains PEG 400, amplification of hypersensitivity reaction due to concomitant drug intake is unlikely | Dermal examination; A biopsy was not performed | Continuously 6 weeks after the second vaccination. The second vaccination was well tolerated. | The symptoms cleared up after 15 days and fully resolved over the following 3 days. No systemic symptoms occurred with delayed local reaction |
| 14  | Thiy, M. 11               | Case report    | Switzerland | 2021 | 11           | 70 ± 17.8   | Female: 63.6%        | Pfizer – B Modern – 3 (BNT162b2) mRNA-1273 | Erythematous 54% (purpura: 33.1%; urticula: 9%; prurigo-like: 9%; physiologic rash: 11%) | Onset: mean 4-5 days (range 1-16) after the first and 11.5 days (range 2-21) after the second injection | Laborotary tests results: elevated white blood cell count reflecting absolute neutrophil and eosinophil (tripled); hepatic function panel: normal; creatine clearance elevated | A biopsy from the shoulder; epidermal spongiosis with focal, occasional; subcorneal dermal neutrophilic inflammation; with eosinophils; direct immunofluorescence; study negative | The patient did not require treatment | For all the patients, the lesions decreased in size, number or disappeared completely during the 2 weeks after the first consultation. No systemic symptoms occurred with delayed local reaction |
| 15  | Lopiono, A. K. 11         | Case report    | USA     | 2021       | 1            | 74         | Male                 | Janssen Ad26.COV2.S vaccine | New onset rash with edema; amnioscaph and widespread erythematous plaques; studded with numerous red nodules; non-fallacular pustules; The rash spared the face, genitals, and mucosae; significant acral swelling in the absence of palpable lymphadenopathy | Based on the clinical findings and work-up; the differential diagnosis included acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms, and AGEP-DRESS overlap | Laboratory tests results: elevated white blood cell count reflecting absolute neutrophilia and eosinophilia (tripled); hepatic function panel: normal; creatinine clearance elevated | A biopsy from the shoulder; epidermal spongiosis with focal, occasional; subcorneal dermal neutrophilic inflammation; with eosinophils; direct immunofluorescence; study negative | Prednisone daily and topical steroids | Responded to oral pranlukast 20 mg PO daily and topical steroids; the acral swelling was also reduced | (Continues) |
| ID | First author (reference) | Type of study | Country | Group/N | Age (M ± SD) | Sex % | Past medical history | Type of vaccine (production technique) | Cutaneous manifestations/manifestations | Duration of cutaneous reactions (effect factor) | Mechanism of cutaneous reactions (effect factor) | Diagnostic assessment | Management | Outcomes | Other finding |
|----|--------------------------|---------------|---------|---------|--------------|-------|---------------------|------------------------------------|----------------------------------|----------------------------------|---------------------------------------------|---------------------------------|-------------|----------|---------------|
| 16 | Eid, Edward 3            | Case report   | Lebanon | 1       | 79           | Male  | Hypertension, coronary artery disease, and antineutrophil cytoplasmic antibodiedemal glomerulonephritis | mRNA COVID-19 vaccine. Itchy and tender lesions over the right thigh | On dermatologic examination, a confluent of vesicles, scattered and overlapping on erythematous base were appreciated scattered over the right thigh | Onset: 6 days Duration: 1 day | A definitive theoretical elucidation of the underlying cause for the VZV reactivation seen in our case remains elusive | Based on the clinical findings, a diagnosis of herpes zoster infection was made | Systemic antiviral treatment | Resolution of the condition |
| 17 | Chopra, S. 5,12          | Case report   | USA     | 1       | 56           | Female| Intensely pruritic rash on the left hand and spread to the left elbow, both hands and both feet, dusky violaceous papule on the small finger of her hand, edematous, violaceous papule on the palms of the hands and dorsal feet, and urticarial lesions on the dorsal aspect of the hands, elbows, and upper portion of thighs. Occasional chills 1 day after the vaccination | Moderna | Histologic findings/CHRR: | Punch biopsy on edematous dusky pink papule of the dorsal aspect of the foot. Histopathologic examination: ulceration and an underlying perivascular and periadnexal mixed inflammatory infiltrate with lymphocytes and scattered eosinophils within the papillary, mid, and reticular dermis | Prednisone taper triamcinolone 0.1% cream | Rash was controlled with the treatment | Rash was controlled with the treatment | Other finding |

Table 1 (Continued)
A systematic review reported that the cutaneous side effects of COVID-19 vaccines are relatively uncommon and self-limiting. According to our review findings, the cutaneous side effects are more frequent after the second dose of the vaccine. However, the high prevalence of side effects of COVID-19 vaccines is a key factor for giving proper guidance for the healthcare workforce.

The current systematic review included studies both from vaccines trial and real-world settings. Moreover, according to our findings, the onset of cutaneous manifestations was 1–21 days after vaccination. Because it is currently unclear whether it should be regarded as a risk factor for anaphylaxis, although the timing of onset after exposure is not consistent with a type I IgE-mediated reaction. A systematic review reported that the most frequent adverse cutaneous reactions occurred within 7 days after injection.

Our review focused only on cutaneous side effects of COVID-19 vaccines in real-world settings, but the mentioned systematic review included studies both from vaccines trial and real-world settings that may explain this inconsistent finding.

The current review showed that the cutaneous side effects of the COVID-19 vaccines appear to be more common in women. The cause is due to several probable factors. Women show more vigorous immune responses to external antigens than men. Accordingly, numerous researches have been shown that women have more immune responses to vaccines and also experience more side effects. However, the high prevalence of side effects of COVID-19 vaccines among women may reflect reporting bias. Because women constitute the vast majority of the healthcare workforce who were the first group to be vaccinated against COVID-19. In addition, the healthcare workforce is more likely to be visited by physicians. Another justification is that females are sensitive to health situations and skin problems.

### 4 | DISCUSSION

We entered a new stage of the COVID-19 pandemic in 2021. Given that mass vaccinations are administering across the world and more vaccines have been approved, diagnose the cutaneous side effects of those is important. Understanding the cutaneous demonstrations of COVID-19 vaccines is a key factor for giving proper guidance for the vaccine. The current systematic review summarized and integrated the findings of studies regarding cutaneous side effects due to COVID-19 vaccines.

First, according to our findings, it is noteworthy to note that severe cutaneous side effects are very rare and approved vaccines have satisfactory safety profiles. Our findings are in consistency with a prospective observational study on a sample of 2740 Italian subjects, which showed that cutaneous adverse reactions after COVID-19 vaccination are uncommon. Most cutaneous reactions are self-limiting and need little or no treatment. In addition, the findings of this review showed injection site reactions are prevalent cutaneous side effects due to COVID-19 vaccines. COVID-19 vaccines like other vaccines such as the combined pneumococcal vaccine often cause cutaneous reactions near the injection site including erythema, swelling, and induration. Consistent with our findings, Sun et al.’s study found that early-onset local injection reactions including erythema, pruritus, swelling, and induration are the most frequent cutaneous side effects with COVID-19 vaccines.

Another study reported that pain and erythema are the most frequent cutaneous side effects of all COVID-19 vaccines. Furthermore, a delayed large local reaction also referred to as “COVID arm,” which is characterized by erythematous and edematous patch at the local of injection onset at least 4 days or more after vaccination, was reported mainly in mRNA-based vaccines. Although these reactions are self-limiting, topical steroids or oral medications can be applied to alleviate these reactions. Clinicopathological classification can be helpful in the early diagnosis and management of the dermal reactions to mRNA COVID-19 vaccines.

**TABLE 2** The number of cases and percentage of the common reported cutaneous reactions

| Cutaneous reactions | N = 944 | % |
|---------------------|--------|---|
| Redness/erythema    | 389    | 39% |
| Itchiness           | 279    | 28% |
| Urticarial rash     | 172    | 17% |
| Morbilliform eruption| 64    | 6.5% |
| Pityriasis rosea    | 30     | 3% |

Most of the encountered skin reactions were self-limiting, and need little or no therapeutic intervention. Some patients treated conservatively by anti-histamine, topical glucocorticoids, prednisolone, antibiotic, systemic antiviral, and intravenous methylprednisolone.

Investigating mechanisms of adverse cutaneous reactions, it was suggested that type I allergic reactions occur due to dimerization of high-affinity IgE receptors in sensitized individuals after contact with an allergen (e.g., PEGs such as Polyethylene glycol-2000 (PEG-2000), an excipient of the vaccine, may play a role in the allergic reactions after vaccination. Reactivation of VZV and herpes zoster infection have been reported in some patients. The combination of age and vaccination have been suggested as the plausible explanation for reactivation of VZV in patients.

Cutaneous allergic reactions to COVID-19 can be immediate-type reactions and delayed reactions. Immediate-type reactions such as itching and urticaria occur due to the release of mediators from mast cell granules and most of these reactions are immunoglobulin E-
mediated and initiate within minutes to an hour of vaccination. Delayed cutaneous reactions are typically seen several days after the vaccination. Delayed large local reaction also referred to as “COVID arm,” which is characterized by erythematous and edematous patch at the local of injection onset at least 4 days or more after vaccination, was reported mainly in mRNA-based vaccines. The research suggests that T-cell-mediated hypersensitivity reactions have the main role in the onset of these skin lesions. However, the mechanism of possible cutaneous reactions related to COVID-19 vaccines has not yet been elucidated, and any possible allergens have not yet been recognized. However, our review showed that the majority of cutaneous adverse reactions are associated with mRNA-based vaccines, which is consistent with a previous study. Among the various excipients in COVID-19 vaccines, it seems that PEG in mRNA vaccines is one of the suspected causes of allergic reactions. Nevertheless, additional work is required to further dissect the phenomenon and reveal the underlying immunologic mechanism and determine the best suitable vaccine type for individual groups of patients. Herpes zoster infection (VZV reactivation) has been experienced by some patients. COVID vaccination in old patients could lead to VZV reactivation.

5 | LIMITATIONS

The current review presents findings on an evolving universal phenomenon and some limitations should be considered. The studies included in this review were mainly case reports and case series, which can make their results challenging. Therefore, future studies with robust designs such as cohorts in this field are needed to provide more accurate findings with more details. In addition, due to potential underreporting of complications, side effects such as cutaneous reactions following COVID-19 vaccination may be more than reported. More clinical trials still are needed to investigate the side effect profile of all COVID-19 vaccines.

6 | CONCLUSIONS

Cutaneous side effects and allergic reaction is one of the expected complications after any COVID-19 or non-COVID-19 vaccination. Recognizing these reactions can have a key role in vaccine strategy because anxieties about developing reactions can considerably influence people’s willingness to receive the first dose or return for a second dose. Injection site reactions are one of the most common cutaneous side effects after COVID-19 vaccines, which most of these reactions are mild or moderate, have no serious consequences, and are usually self-limiting without any interventions. Therefore, these reactions should not discourage people from vaccination.

It seems that cutaneous side effects with mRNA-based COVID-19 vaccines are more common; however, the COVID-19 vaccine boundary is growing rapidly and future research results may provide more detailed information. In certain groups such as patients with allergies and a history of local injection reactions, it seems that pre-vaccination counseling and giving guidance and use of antihistamines and topical medications may benefit.

CONFLICT OF INTEREST

The all authors declare that there is no conflict of interest regarding the publication of this article.

AUTHOR CONTRIBUTIONS

The conception and design of the study was contributed by Ahmadreza Shamsabadi and Kowsar Qaderi. Acquisition of data was contributed by Mohammad Hossein Golezar and Bagher Moradi. Analysis and interpretation of data was contributed by Abbas Mardani. Manthar Ali Mallah drafted the article. Important intellectual content was critically revised by Hossein Kavoussi and Samira Golezar. All authors contributed to the final approval of the version submitted.

ETHICS STATEMENT

This article is based on published data, and hence ethical approval is not required.

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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