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REVIEW ARTICLE

DERMATOLOGIC THERAPY WILEY

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 to 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

This study was extracted from the entitled "Cutaneous adverse reactions of COVID-19 vaccines: a systematic review" conducted at Esfarayen University of Medical Science.

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).[1] Vaccination candidates were created by more than 100 businesses and universities throughout the world, utilizing both well-established and more experimental vaccine platforms.[2] 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.[3] 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.[4] 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.[5,6] 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.[7] 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.[8] 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]

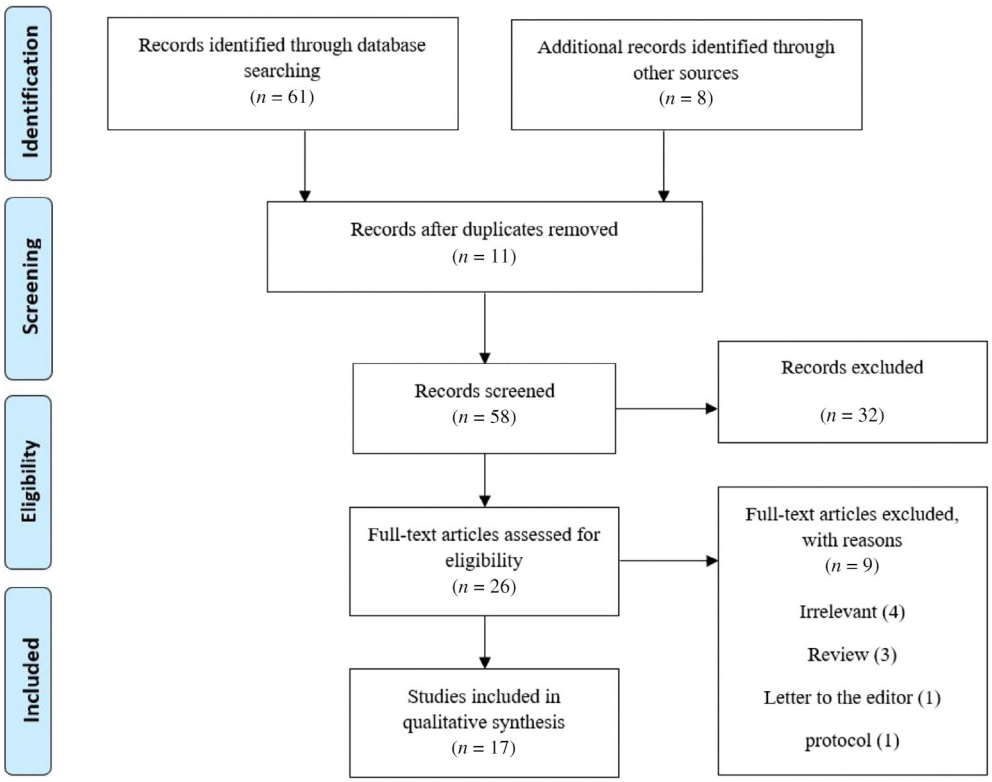

FIGURE 1 Search results from different databases

TABLE 1 Characteristics of included studies

ID	First author (reference)	Type of study	Country	Population			Past medical history	Type of vaccine (production technique)	Cutaneous manifestations	Duration of cutaneous manifestations	Mechanism of cutaneous reactions (effect factor)	Diagnostic assessment	Management	Outcomes	Other finding
				Group (*N*)	Age (M ± SD)	Sex %									
1	AL-Ansari, R. Y.[9]	Case report	2021 Saudi Arabia	1	39	Female	Allergic to a strawberry and kiwi, otherwise medically free	Pfizer-BioNTech (mRNA vaccine) first dose	Palms of the hands and soles of the feet itchiness that is associated with occasional redness	Onset: 10 days Duration: 5 days	NA	Full blood count and biochemical: unremarkable IGE level: was not available	Treated conservatively by anti-histamine	The symptoms gradually resolved within 5 days. No hospital admission was required during her course of illness	Isolated itching to palms and soles could be one of the side effects of COVID-19 vaccination (Pfizer-BioNTech)
2	Arora, P.[10]	Case report	2021 New Delhi, India	1	60	Male	Type II diabetes mellitus and hypertension	COVAXIN (inactivated)	Multiple grouped vesicles on an erythematous base, present over the knee, and anterior aspect of right thigh	Onset: 4 days Duration: 2 weeks	The combination of age and vaccination could be the plausible explanation for reactivation of VZV in patient	Tzanck smear from an intact vesicle: acantholytic cells. No multinucleated giant cells could be seen. Skin biopsy from the vesicle: intraepidermal spongiotic vesicle containing acantholytic cells with large vesicular nuclei neutrophils and dyskeratotic cells Herpes zoster involved L2 and L3 dermatome	Oral valacyclovir 1 g three times a day for 7 days along with topical fusidic acid for local application twice daily	The lesions subsided in 2 weeks without any sequelae or neuralgia. The patient received second dose of the same vaccine after 4 weeks without any adverse effects	–
3	Cebeci, F.[11]	Case report	2021 Istanbul, Turkey	1	82	Female	hydroxychloroquine 400 mg regularly for the last 3 years for seronegative RA, hypertension	CoronaVac (Inactive virus)	A diffuse petechial rash was observed on both lower extremities during dermatological examination. There were no symptoms other than weakness and burning in the legs	Onset: 1 day Duration: 7 days	Hypersensitivity may result either from the active vaccine component or one of the other components	A complete blood test, biochemical parameters, CRP, D-dimer, platelet, coagulation parameters: normal Urinalysis showed no signs of proteinuria or haematuria Hepatitis and HIV: negative Antinuclear antibodies, antineutrophil cytoplasmic antibodies and cardiolipin antibodies: normal Complement levels and serum proteinograms: normal. PCR and rapid IgM, IgG antibodies for SARS-COV-2: negative	Prednisolone 5 mg, which she had been using for 6 months for seronegative arthritis, was discontinued 3 weeks before the vaccine in order not to prevent the effect of the vaccine	The lesions regressed almost completely after 2 days and completely disappeared after 1 week Therefore, we decided to administer the second dose to our patient 28 days after the first dose and no skin reaction was observed after the second dose	Vaccine-associated hypersensitivity reactions are not infrequent; however, IgE or complement-mediated anaphylactic or serious delayed-onset T cell-mediated systemic reactions are extremely rare The most frequent signs of delayed-type reactions are cutaneous eruptions such as maculopapular petechial rash
4	Farinazzo, E.[12]	Case series	2021 North east Italy	46	Mean:44.39 SD: 12.36 (18–31):6 (31–44):16 (44–57]:17 (57–70):7	Female: 41 (89%) Male: 5 (11%)	–	BioNTech/Pfizer vaccine (mRNA based)	Male: itchiness 40% Diffuse urticarial 20% Pityriasis rosea-like rash on the neck, upper limbs, and trunk 20% Erythema at the inoculation site 20% Female: Itchiness 29% Urticarial rush 19% Erythema 31% Swelling 14% Morbilliform eruption 2% Fixed drug eruption 2% Chilblain-like rash 2% Pityriasis rosea-like rash 2% Malar rash 2% Painful wheals 9% Herpes Zoster 5% Chest urticarial rash with chilblain-like	60 h–10 days after injection	Regarding the urticarial manifestations, Polyethylene glycol-2000 (PEG-2000), an excipient of the vaccine, may play a role	–	For three subjects: not applying the second dose	Course was mostly mild and self-limiting. Only one patient with urticaria (nr. 45) required intravenous steroid treatment.	Cutaneous adverse reactions triggered by Comirnaty_-BioNTech/Pfizer are seldom but appear similar to those reported during SARS-CoV-2 infections

TABLE 1 (Continued)

ID	First author (reference)	Type of study	Country	Population			Past medical history	Type of vaccine (production technique)	Cutaneous manifestations	Duration of cutaneous manifestations	Mechanism of cutaneous reactions (effect factor)	Diagnostic assessment	Management	Outcomes	Other finding
				Group (N)	Age (M ± SD)	Sex %									
									manifestations on the first and third finger of one foot 2%. Malar erythema, an erythematous macular rash of the hands, a fixed drug eruption 10% resembling pityriasis rosea4%						
5	Hoff, N. P.[13]	Case series	2021 Germany	11	50.09 ± 13.18	Male: 2 (18%) Female: 9 (82%)	Patient no. 7 (female 44) had obesity as a comorbidity factor	Moderna (mRNA-1273) vaccine	(Painful) edema: 72%; Erythema: 63%; Induration: 27%; Soreness 18%; Mild pruritus 18%; Lymphadenopathy 18%; Urticarial plaque and cutaneous tenderness, painful burning and cutaneous tenderness: 9% All the reported lesions were near the injection site.	Onset: 3–12 days after vaccination Duration: 1–4 days	"COVID-arm"	Histology: superficial and deep perivascular dermatitis, with scattered eosinophils and intraluminal neutrophil accumulation	Oral antihistamines (two patient) Topical glucocorticoids + oral antihistamines (two patients) No treatment (seven patients)	All the cutaneous manifestations resolved within 14 days. 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 precise molecular and cellular mechanisms underlying this cutaneous pathology is needed to understand why and when rare adverse events may occur after RNA vaccines
6	Hussain, K.[14]	Case report	2021 London, UK	1	62	Female	Metastatic melanoma and related CPI therapy (Nivolumab and ipilimumab) myocarditis. New onset of symptoms consistent with Raynaud disease (RD)	Pfizer (BioNTech- 19 RNA vaccine)	COVID-Mucosal membrane involvement; rash grade 4; erythrodermia with superficial blistering noted on the patient's thigh and chest	2 days (grade 3 eruption) 3–7 days (grade 4 eruption)	Initial drug rash that resolved on cessation of the co-trimoxazole, then developed a more severe form of the rash reaction to the co-trimoxazole, during which drug-specific memory T cells were formed; COVID-19 vaccination caused a surge in the T-cell-driven response from skin-homing CD4 + T cells generated by the original delayed hypersensitivity reaction. (Recent CPI therapy, which in itself reduces the self-tolerance response of T cells and boosts effector T-cell responses)	Skin biopsy: drug-induced lichenoid dermatitis with scattered apoptotic bodies and lymphocytic infiltrate; direct immunofluorescence: negative; an infective/septic screen and a viral reactivation:(Epstein–Barr virus, human herpesvirus (HHV)-6, HHV-7, hepatitis B and C viruses, and HIV: negative	Admitted to hospital, treated with two further doses of intravenous methylprednisolone 500 mg; prednisolone dose was increased to 40 mg; lansoprazole was switched to famotidine	Systemically well, with subsequent slow improvement of the rash over a 2-week period.	This case highlights the importance of possible exacerbation of irAEs in patients on CPIs, which can occur post-vaccination, especially in the case of recent and active irAEs
7	Català, A.[15]	Cross-sectional	Spain 2021	405	50.7 (17.6)	Female: 325 (80.2%) Male: 80 (19.8%)	Atopic dermatitis 28 (6.9); Allergic asthma 24 (5.9); Allergic rhinitis 42 (10.4); Urticaria 26 (6.4); History of allergy to drugs or excipients 47 (11.6)	(Pfizer-BioNTech), mRNA-1273 (Moderna), AZD1222 (AstraZeneca)	Covid-Arm 32.1%; HSV reactivation 3.7%; VZV reactivation 10.1%; Papular vesicular 6.4%; Pityriasis rosea-like 4.9%; Morbilliform 8.9%; Urticaria or Angioedema 14.6%; Purpuric 4.0	21 days	N/A	Reporting dermatologists preclassified skin rashes in a predefined cutaneous reaction pattern	81% required treatment: Topical corticosteroids, systemic corticosteroids, topical antibiotics, NSAIDs, oral antihistamines, systemic antiviral	All patients were treated	
8	Juárez Guerrero, A.[16]	Case series	Spain 2021	26	45 ± 4.66	Female: 25 (96.2) Male: 1 (3.8)	Previous history of 1 or more of the following: 9 (60%) rhinoconjunctivitis, 10 (66.7%) asthma, 5 (33.3%) anaphylaxis (latex, kiwi, and hymenoptera, arylpropionics, contrast media), 2 (13.3%) chronic urticaria, and 1	Pfizer-BioNTech, 19 (27%) Moderna 7(73%)	DLLR occurred in 13 of 235 patients (57%). Ten of these 23 subjects (43.4%) experienced delayed skin reactions different from DLLR: 5 developed a	1.4 days when treated and 4.84 ± 0.60 days without treatment ($p = 0.83$)	Use of PEG or polyoxyethylene lipid conjugate could support type IV hypersensitivity	Patch tests, performed on all subjects, were negative in 100% of cases	42.3% were treated with topical Corticosteroids; 15.3% with oral antihistamines	22 of 23, (96%) successfully received the second dose of the vaccine. 1 refused to receive the booster dose. (DLLR reoccurred in 62% (8	

(Continues)

TABLE 1 (Continued)

ID	First author (reference)	Type of study	Country	Population			Past medical history	Type of vaccine (production technique)	Cutaneous manifestations	Duration of cutaneous manifestations	Mechanism of cutaneous reactions (effect factor)	Diagnostic assessment	Management	Outcomes	Other finding
				Group (N)	Age (M ± SD)	Sex %									
							(6.7%) nickel and methylchloroisothiazolinone/ methylisothiazolinone allergic contact dermatitis		generalized maculopapular exanthema, 2 exfoliations of the skin of the palms, 1 acute generalized exanthematous pustulosis (AGEP), 1 generalized micropapular exanthema accompanied by a 7-cm blister on the shoulder, and 1 multiple fixed drug eruptions (MFDE)					of 13) who had developed them after the first dose, of a similar (38%) or smaller size (63%). They resolved earlier (mean: 1.7 days) than the first dose (mean: 4.4 days) ($p < 0.05$). 38% had no recurrence of DLLR. One developed the same reaction after the second dose; MFDE also reoccurred after the second dose	
9	Larson, V.[17]	Case series	USA 2021	12	69.25 ± 19.5	Female: 50% Male: 50%	All items are 8.3% lichen simplex chronicus, inflammatory bowel disease (on mesalamine, vedolizumab) eczema, acne vulgaris and herpes simplex virus, and allergic rhinitis, psoriasis, childhood atopic dermatitis	Pfizer BioNTech = 5 Moderna = 7	COVID arm: 16.6%; eruption 25%; eczematous patches 16.6%; pityriasis-rosea-like eruption 8.3%; palpable purpuric papules 8.3%; erythematous and edematous plaques 8.3%; Bullous pemphigoid 16.6%	1–21 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[9] and antihistamines,[5] oral prednisone[4] and oral antibiotics[2] were used	Cutaneous reactions were resolved in 11(91.7%) patients At least 10 patients completed their vaccination series. Follow-up information for patient 1 could not be obtained; and patient 9 declined her second vaccine dose because of persistent symptoms	
10	Lopatynsky-Reyes, E. Z.[18]	Case series	Mexico 2021	2 International Healthcare Workers	31, 28	Female: 50% Male: 50%	N/A	Pfizer-(BioNTech), Moderna (both second dose)	inflammation on the BCG scar, erythematous reaction, induration, mild edema	Onset: 24 h Duration: 4 days	NA	Dermatologist report: arborizing and comma-shaped vessels	NA	Signs of reaction on the injection site were resolved within 4 days	
11	McMahon, D. E.[8]	Cross-sectional (registry-based study)	USA 2021	414	44 (36–59)	Female 90% Male:10%	Atopic dermatitis 84%; contact dermatitis 2.9%; psoriasis 2.2%; urticaria 1.7%; acne vulgaris 1.4%; hypertension15%; obstructive lung disease 4.8%; morbid obesity 4.1%; cardiovascular disease 2.4%; diabetes mellitus 3.6%; rheumatologic disease 2.4%; malignancy 1.9%	Moderna 83% Pfizer 17%	(Mo1, Mo2, Pf1, PF2) Delayed large local reaction (66, 30, 15, 18%) local injection site reaction (54, 70, 24, 25%) swelling (44, 68, 18, 15%) erythema (49, 67, 18, 20%) pain (35, 59, 24, 18%) urticaria within 24 h (0, 2, 0, 2.5%) urticaria after 24 h (4.8, 4.9, 26, 18%) urticaria unknown timing (1.1, 0, 0, 0%) morbilliform (4.1, 6.9, 18, 7.5%) erythromelalgia (1.9, 5.9, 2.9, 5%) flare of existing dermatologic conditions (1.1, 1, 24, 7.5%) vesicular (1.5, 1, 8.8, 5%) pemio/ chilblains (1.1, 0, 3, 8.8, 5%) zoster (VZV) (1.9, 0, 2.9, 10%) angioedema 5 (1.9, 0, 0, 2.5%) pityriasis rosea (0.4, 0, 5.9, 2.5%) erythema multiforme	Onset: First-dose: 7 (2–8) Second-dose: 1 (1–2) days	T cells mediated reactions, neomycin, or thimersol and PEG may be as potential etiologies	Dermal examination	Responded well to topical corticosteroids; oral antihistamines; and/or painrelieving medications	16 individuals did not plan to receive the second dose. The second no severe sequelae after the second dose in patients experiencing a delayed large reaction after the first dose; reactions resolved after a median of 3–4 days	

TABLE 1 (Continued)

ID	First author (reference)	Type of study	Country	Population			Past medical history	Type of vaccine (production technique)	Cutaneous manifestations	Duration of cutaneous manifestations	Mechanism of cutaneous reactions (effect factor)	Diagnostic assessment	Management	Outcomes	Other finding
				Group (N)	Age (M ± SD)	Sex %									
									(1.1, 0, 0, 0%) filler reaction (1.1, 4.9, 0, 2.5%) vasculitis (0.7, 0, 2.9, 0%) contact dermatitis 3 (1.1, 1, 0, 5%) reaction in breastfed infant (0, 1, 5.9, 2.5%) onset of new dermatologic conditionx (0.7, 0, 0, 5%) petechiae (0.4, 2, 2.9, 0%)						
12	Peigottu, M. F.[19]	Case series	Italy 2021	9	46 ± 9.26	Female: 88.9% Male: 11.1%	Significant allergology history 100%; Atopy, drug allergy: 88.8%;previous angioedema: 11.2%	Pfizer (BioNTech)	Widespread pruritus:3, mild facial erythema:1, maculopapular rash:3, Glottisedema:1 erythematous edema, itching maculo-papular lesions:5 Urticarial rash with arthralgias:1	Onset: 1–2 day	N/A	Dermatologist report	For three subjects: not applying the second dose; antihistamine; short-course steroids	Cutaneous adverse reactions were resolved	
13	Sprute, R.[20]	Case report	Germany 2021	1	62	Female	Cat allergy; taking 5 mg olmesartan (ALIUD Pharma GmbH) once daily	Vaxzevria (viral vector vaccine)	The delayed reaction as erythema (10 mm), in duration and pain near the injection site. The earlier reactions: soreness, erythema (5 mm), warmth, swelling near injection site	Earlier reactions: day 2–6 Delayed reactions: day 10–15	Polysorbate 80 is the excipient in Vaxzevria vaccine and Olmesartan contains PEG 400, amplifcation of hypersensitivity reaction due to concomitant drug intake is unlikely	Dermal examination; A biopsy was not performed	Did not require treatment; heterologous boost with Comirnaty 6 weeks after the Vaxzevria 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	Tihy, M.[21]	Case series	Switzerland 2021	11	70 ± 17.8	Female: 63.6% Male: 36.4%	Not reported	Pfizer = 8 Modern = 3 (BNT162b2/mRNA-1273)	Erythematous 54.5%; purpuric 18.1%; urticaria l9%; prurigo-like 9%; pityriasis rosea-like 9%	Onset: mean 4.5 days (range 1–8) after the first and 11.5 days (range: 2–21) after the second injection	N/A	Histological findings: Drug-reaction-like, Early leucocytoclastic Vasculitis, Acantholytic dermatosis, AGEP pattern/ blood PCR test for HHV6 and HHV7: 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	Erythematous rash or purpura was the most common clinical demonstration, and drug-reaction-like pattern was the most common histological finding
15	Lospinoso, K.[22]	Case report	2021 USA	1	74	Male	Panhypopituitarism secondary to craniopharyngioma resection, vision loss of the left eye, neurogenic bladder, and obstructive sleep apnea. Allergies to Sulfa drugs and amoxicillin-clavulanic acid; no prior vaccination-related reaction	Janssen Ad26.COV2.S vaccine	New-onset rash ipsilateral arm discomfort, generalized distribution of erythematous plaques, studded with numerous small, non-follicular pustules. The rash spared the face, genitals, and mucosae; significant acral swelling in the absence of palpable lymphadenopathy	Onset: 3 days Duration: less than 20 days	Based on the clinical findings and workup, the differential diagnosis included acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms, and AGEP-DRESS overlap	Laboratory test results: elevated white blood cell count reflecting absolute neutrophilia and an elevated eosinophil (tripled); hepatic function panel: normal; creatinine: elevated A biopsy from the shoulder: epidermal spongiosis with focal, occasional; subcorneal neutrophilic pustules and dermal neutrophilic inflammation with eosinophils, direct immunofluorescence study: negative	Prednisone daily and topical steroids	Responded to oral prednisone 20 mg PO daily and topical steroids; the acral swelling was also reduced	–

(Continues)

TABLE 1 (Continued)

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				Group (*N*)	Age (M ± SD)	Sex %									
16	Eid, Edward[23]	Case report	2021 Lebanon	1	79	Male	Hypertension, coronary artery disease, and antineutrophilic cytoplasmic antibodyrelated glomerulonephritis	mRNA COVID-19 vaccine.	Itchy and tender lesions over the right thigh On dermatologic examination, a confluence of vesicles, some excoriated and overlying an erythematous base were appreciated scattered over the right thigh	Onset: 6 days Duration: 1 day	A definitive theoretical elucidation of the underlying causes 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.[24]	Case report	2021 USA	1	56	Female	–	Moderna	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 papules 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	Onset: 9 days	Histologic findings: DHR, cutaneous acral eruptions	Punch biopsy: an 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 triamcinolone cream. She declined her second vaccination dose at the time of conversation	

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

Cutaneous reactions	$N = 944$	%
Redness/erythem	389	39%
Itchiness	279	28%
Urticarial rash	172	17%
Morbilliform eruption	64	6.5%
Pityriasis rosae	30	3%

Most of the encountered skin reactions were self-limiting, and need little or no therapeutic intervention.[20,21,25] Some patients treated conservatively by anti-histamine,[8,9,13,15–17,19] topical glucocorticoids,[8,13,15–17,22,24] prednisolone,[15,17,19,22] antibiotic,[15,17] systemic antiviral,[15,23] and intravenous methylprednisolone.[14]

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.[8,12,17,20] Reactivation of VZV and herpes zoster infection have been reported in some patients,[8,10,12,23,26] that The combination of age and vaccination have been suggested as the plausible explanation for reactivation of VZV in patients.[10]

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 consistence with a prospective observational study on a sample of 2740 Italian subjects, which showed that cutaneous adverse reactions after COVID-19 vaccination are uncommon.[27] 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 and swelling[28] and are because of nonspecific stimulation of inflammation.[29] 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.[30] Another study reported that pain and erythema are the most frequent cutaneous side effects of all COVID-19 vaccines.[31] 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.[8,32,33] Although these reactions are self-limiting, topical steroids or oral medications can be applied to alleviate these reactions.[30] Clinicopathological classification can be helpful in the early diagnosis and management of the dermal reactions to mRNA COVID-19 vaccines.[22]

Our review findings revealed the cutaneous side effects of COVID-19 vaccines were mostly affected middle-age populations. Similarly, current evidence shows that local injection site reactions are more seen in the younger population compared the older people.[34,35] Moreover, according to our findings, the most onset of cutaneous manifestation 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 Ig-E mediated reaction.[12] A systematic review reported that the most frequent adverse cutaneous reactions occurred within 7 days after injection.[30] 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 may 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.[36,37] 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.[8,30] Another justification is that females are sensitive to health situations and skin problems.[38] However, there is no definite identified reason for this issue and requires to be addressed in forthcoming studies.

Cutaneous reactions of COVID-19 vaccine most often occur after the first dose[12,13,16,17,19] which is consistent with Grieco et al.' findings.[28] According to our review findings, recurring infrequently after administering the second dose of the COVID-19 vaccine and only six persons were given the advice do not to apply the second dose due to diffuse urticaria and maculopapular rash. It is currently unclear whether these after the first dose of the COVID-19 vaccine should be considered as a potential risk factor for anaphylaxis reactions.[39] However, it seems that people who have presented potentially anaphylactic reactions such as diffuse urticaria to the first dose of a COVID-19 vaccine require to be referred to an allergist for accurate assessment.[40]

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.[13] 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.[7,13,34] The research suggests that T-cell-mediated hypersensitivity reactions have the main role in the onset of these skin lesions.[32,33] 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.[30] Among the various excipients in COVID-19 vaccines, it seems that PEG in mRNA vaccines is one of the suspected causes of allergic reactions.[29] 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.[10,12,19,24,27] COVID vaccination in old patients could lead to VZV reactivation.[10]

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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SUPPORTING INFORMATION

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

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