Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Funding sources: None.

IRB approval status: Not applicable.

Key words: COVID-19; diagnostic delay; melanoma diagnosis.

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Conflicts of interest

None disclosed.

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https://doi.org/10.1016/j.jaad.2022.05.018

Risk of herpes zoster reactivation after messenger RNA COVID-19 vaccination: A cohort study

To the Editor: Recent case series and media coverage suggest an association between receiving the messenger RNA (mRNA) COVID-19 vaccine and reactivation of the varicella zoster virus (VZV).[1-3] Fear of a potential adverse effect will drive vaccine refusal and subsequent preventable disease and death. The purpose of the present investigation is to evaluate the relationship between mRNA COVID-19 vaccination and VZV reactivation.

We performed a retrospective cohort study using the TriNetX Analytics Network (TriNetX, LLC), a federated health research network that aggregates health records from 63 health care organizations comprising 70 million patients. We included patients aged ≥18 years who received the mRNA COVID-19 vaccine either as the first or the second dose between December 15, 2020 and July 15, 2021 (Supplemental Material, available via Mendeley at https://data.mendeley.com//datasets/trkg3zfr5f/1). Herpes zoster reactivation (code B02; International Classification of Diseases, Tenth Edition) related to mRNA COVID-19 vaccine administration was defined as occurring within 28 days.[4]

A control population was established, comprising persons in the database diagnosed with acne, viral wart, melanocytic nevi, dry skin, lipoma, skin cysts, or seborrheic keratosis and who had no history of COVID-19 vaccination (Supplemental Material). Because persons may have received a COVID-19 vaccination at a location outside of the health care organizations participating in the database, we split our control population into 2 cohorts. The first (historical) control cohort comprised individuals

Table I. Risk of varicella zoster virus reactivation after messenger RNA COVID-19 vaccination

Cohort	Persons in cohort	Persons with VZV reactivation	Risk (per 1000 person-years)*	Risk ratio, 95% CI
mRNA COVID-19 vaccination	555,256	673	16	0.91 (0.82-1.01)
vs historical cohort†	555,256	740	17	
mRNA COVID-19 vaccination	359,789	492	18	0.98 (0.87-1.11)
vs contemporary cohort‡	359,789	501	18	

The relative risk compares the risk of VZV reactivation within 28 days after mRNA COVID-19 vaccination against persons in control cohorts after matching for age, sex, race, ethnicity, HIV, malignancy, use of antineoplastics, use of immunosuppressants, and receipt of shingles vaccine. The diagnoses in the control cohorts were determined upon by authors to be conditions that do not have a known relationship to VZV reactivation. Multiple diagnoses were included to help increase cohort size for robust propensity-matching.

HIV, Human immune deficiency virus; *mRNA*, messenger RNA; *VZV*, varicella zoster virus.

*Risk per 1000 person-years were calculated as followed: (persons with VZV reactivation)/[(Persons in cohort) × (28/365)] × 1000).

†The first (historical) control cohort comprised individuals who received a diagnosis of acne, viral wart, melanocytic nevi, dry skin, lipoma, skin cysts, or seborrheic keratosis between January 1, 2020 and December 1, 2020 and who had no history of COVID-19 vaccination to establish a cohort wherein COVID-19 vaccination was not readily available.

‡A second (contemporary) control cohort comprised of individuals diagnosed between December 15, 2020 and July 15, 2021 to account for possible seasonal variation in VZV incidence.

who received the aforementioned diagnoses between January 1, 2020 and December 1, 2020 to establish a cohort wherein COVID-19 vaccination was not readily available. A second (contemporary) control cohort comprised individuals diagnosed between December 15, 2020 and July 15, 2021, to parallel study cohort, and to account for possible seasonal variation in VZV incidence.[5] We balanced cohorts using 1:1 greedy nearest neighbor propensity score matching by age, sex, race, ethnicity, HIV status, malignancy, use of antineoplastics, use of immunosuppressants, and receipt of shingles vaccine. Using the matched cohorts, we calculated the relative risk of herpes zoster in the 28 days after index events in the respective cohorts. All statistical analyses were performed within TriNetX.

We identified 1,306,434 persons who received a dose of the mRNA COVID-19 vaccine. The mean age of patients in the mRNA COVID-19 vaccine cohort was 55.1 years (SD, 18.5), 57% were female, 14% were Black, 65% were White, 11% were Hispanic or Latino, and 6% were Asian. Prior to matching, the crude incidence of VZV reactivation within 28 days of mRNA vaccination was 0.1% (1228 of 1,306,434 patients). After 1:1 propensity-matching, demographic and clinical characteristics were balanced (SD <0.1). No difference in VZV reactivation was observed among persons receiving the mRNA COVID-19 vaccine within 28 days compared to both the historical cohort (relative risk, 0.91; 95% CI, 0.82-1.01) and the contemporary cohort (relative risk, 0.98; 95% CI, 0.87-1.11) (Table I).

Herein our data suggest mRNA COVID-19 vaccination is not associated with increased rates of VZV reactivation. We hope this reassures patients and the providers caring for them. Our analysis is limited by potential misclassification bias, which is inherent in the use of diagnostic codes. In addition, persons may have developed herpes zoster, but did not seek care. Lastly, we cannot ascertain the completeness of records, particularly the rates of shingles vaccination.

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Funding sources: This work was supported by grants from the NIH (San Diego Center for AIDS Research, CFAR, AI036214). Funders had no role in the design and conduct of study; collection, management, analysis, and interpretation of the datal preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

IRB approval status: All data is deidentified and provided in aggregate, no protected health information or personal data are available to users.

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Conflicts of interest

None declared.

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Histologic subtype of cutaneous immune-related adverse events predicts overall survival in patients receiving immune checkpoint inhibitors

To the Editor: Immune-related adverse events due to immune checkpoint inhibitors can lead to treatment interruption or cessation, increasing cancer-related mortality.[1] Cutaneous immune-related adverse events (cIRAEs) typically precede noncutaneous immune-related adverse events (ncIRAEs) and may serve as a clinical indicator for further immune-related adverse event development and overall survival.[1,2] Histopathologic classification is especially critical for cIRAEs because clinical morphology and histopathologic pattern often do not correlate with each other in patients with cIRAEs.[2-5] The goal of our study was to identify associations between histopathologic patterns of cIRAEs with the development of ncIRAEs and patient outcomes.

We performed a 9-year retrospective chart review of patients on immune checkpoint inhibitors at our oncodermatology clinic who underwent a skin biopsy for drug eruption. The skin biopsy's histologic findings were classified based on dominant patterns as follows: bullous (based on positive direct immunofluorescence), granulomatous, vacuolar interface, lichenoid interface, psoriasiform, superficial perivascular dermatitis, and spongiotic. The histology of superficial perivascular dermatitis lacked an epidermal change, and the inflammatory infiltrate was predominantly lymphocytic or lymphohistiocytic, with or without eosinophils. Logistic regression was used to evaluate associations between the histologic subtypes and other clinical parameters. The Cox proportional hazards analysis was used to calculate progression-free and overall survival hazard ratios (HRs). To address multiple hypothesis testing, only results with a false discovery rate (FDR) of less than 0.15 were considered significant.

Of 95 patients with biopsy-proven cIRAEs (Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/6cvsg3zvg4/1), at least 1 ncIRAE developed in 48 patients (51%). Forty patients experienced a cIRAE before an ncIRAE developed. The vacuolar interface histology was significantly associated with pneumonitis ($P = .01$). The psoriasiform histology was significantly associated with musculoskeletal ncIRAEs ($P = .002$). Other significant associations included associations between the psoriasiform histology and multiple ncIRAEs ($P = .02$) as well as between ipilimumab/nivolumab combination therapy and the bullous histology ($P = .03$). Majority of ncIRAEs occurred within months of cIRAE onset (Supplementary Fig 1, available via Mendeley at https://data.mendeley.com/datasets/6cvsg3zvg4/1.)

The spongiotic and lichenoid interface histologic patterns were associated with improved progression-free survival (Fig 1, *A*), although no subtype reached statistical significance. For overall survival (Fig 1, *B*), both the spongiotic (HR = 0.28 [0.09-0.82], FDR = 0.07) and lichenoid interface (HR = 0.41 [0.17-1.01], FDR = 0.09) subtypes were significantly associated with a decreased mortality risk. In contrast, the vacuolar interface (HR = 3.64 [1.83-7.21], FDR < 0.001) and superficial perivascular dermatitis (HR = 3.07 [0.99-9.43], FDR = 0.09) subtypes were significantly associated with an increased mortality risk.

cIRAEs may serve as an informative and actionable clinical biomarker for the development of ncIRAEs and patient prognosis. In our cohort examining the associations between the biopsy-proven cIRAE histologic subtypes and ncIRAEs, of particular interest was the association of the vacuolar interface histology with pneumonitis because pneumonitis can rapidly progress and increase patient morbidity and mortality. Regarding a significant association between the psoriasiform histology and musculoskeletal ncIRAEs, only 1 of 9 patients with the psoriasiform histology had a prior diagnosis of psoriasis; therefore, exposure to immunotherapy might unmask a predisposition to psoriasis and psoriatic arthritis. The limitations included the fact that this was a single-institution, retrospective, chart-review study; therefore, rarer histologies might not