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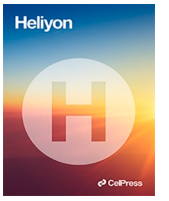

Research article

# The potential association between herpes zoster and COVID-19 vaccination

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ABSTRACT

*Objective:* Little is known about the dermatological manifestations associated with COVID-19 vaccines. The aim of the study was to determine how many cases of herpes zoster (HZ) occurred after COVID-19 vaccination and to see if there was a possible link.
*Methods:* A retrospective cohort study was performed by archive scan between 2016 and 2020, and between January 2021 and January 2022. Patients diagnosed with HZ were enrolled and their demographic and medical history including age, sex, previous systemic disease, history of COVID-19 vaccination prior to HZ symptom onset, COVID-19 vaccine type as mRNA or inactive, time to HZ onset after vaccination, and number of COVID-19 vaccines before HZ symptom onset were recorded.
*Results:* The average annual number of HZ cases from 2016 to 2020 was 271, but the number of HZ cases in 2021 was 338, reflecting an increase. The number of HZ patients with a known history of COVID-19 vaccination in 2021 was 117 and their mean age was 57.6 ± 14.2 years. Females were 59.8% (n = 70) and 28.2% (n = 33) had chronic diseases. A positive history of COVID-19 vaccination was present in 35.9% (n = 42) of HZ patients, 11.1% (n = 13) had received mRNA vaccines and 24.8% (n = 29) had received inactive COVID-19 vaccine. Mean time to HZ after COVID-19 vaccination was 24.6 ± 16.3 days.
*Conclusion:* An important finding of this study is the high rate (35.9%) of COVID-19 vaccination among people diagnosed with HZ. As COVID-19 vaccination may be associated with reactivation of varicella zoster virus, the vaccination history should be obtained in HZ patients.

## 1. Introduction

Sars-CoV-2 disease (COVID-19) is a multisystemic condition leading to severe global medical and socioeconomic consequences. Side-effects were reported in Turkey and worldwide following the introduction in 2021 of COVID-19 vaccinations aimed at reducing the morbidity and mortality of the disease and preventing viral transmission. Varicella zoster virus (VZV) infection was reported in the form of reactivation after COVID-19 vaccination or case series. Several types of COVID-19 vaccine are used across the world, and although side-effects such as vaccine site reactions, influenza-like manifestations, anemia, skin reactions, and lymphopenia have been reported in association with these, many side-effects are unclear and still the subject of research [1]. Possible cutaneous reactions, including herpes zoster (HZ), in patients with COVID-19 disease or vaccinated with COVID-19 have been reported in some literature

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reviews [2,3].

VZV infections are frequently seen worldwide. Varicella (chickenpox) is more common in childhood, while herpes zoster (HZ) developing with VZV reactivation is more frequent at later ages. HZ is localized to the dermatome and characterized by pain, rash, and vescicles and develops primarily due to secondary infection by VZV, which causes chickenpox. Although the reason for this secodnary reactivation of the virus is not fully understood, weakening of cell-mediated immunity has been implicated [4].

The purpose of this study was to investigate the possible increase of VZV cases in the COVID-19 pandemic, and whether vaccination is potentially associated with the reactivation of VZV by determining how many among all patients with HZ were diagnosed after COVID-19 vaccinations, which began being adminstered in Turkey in the early months of 2021.

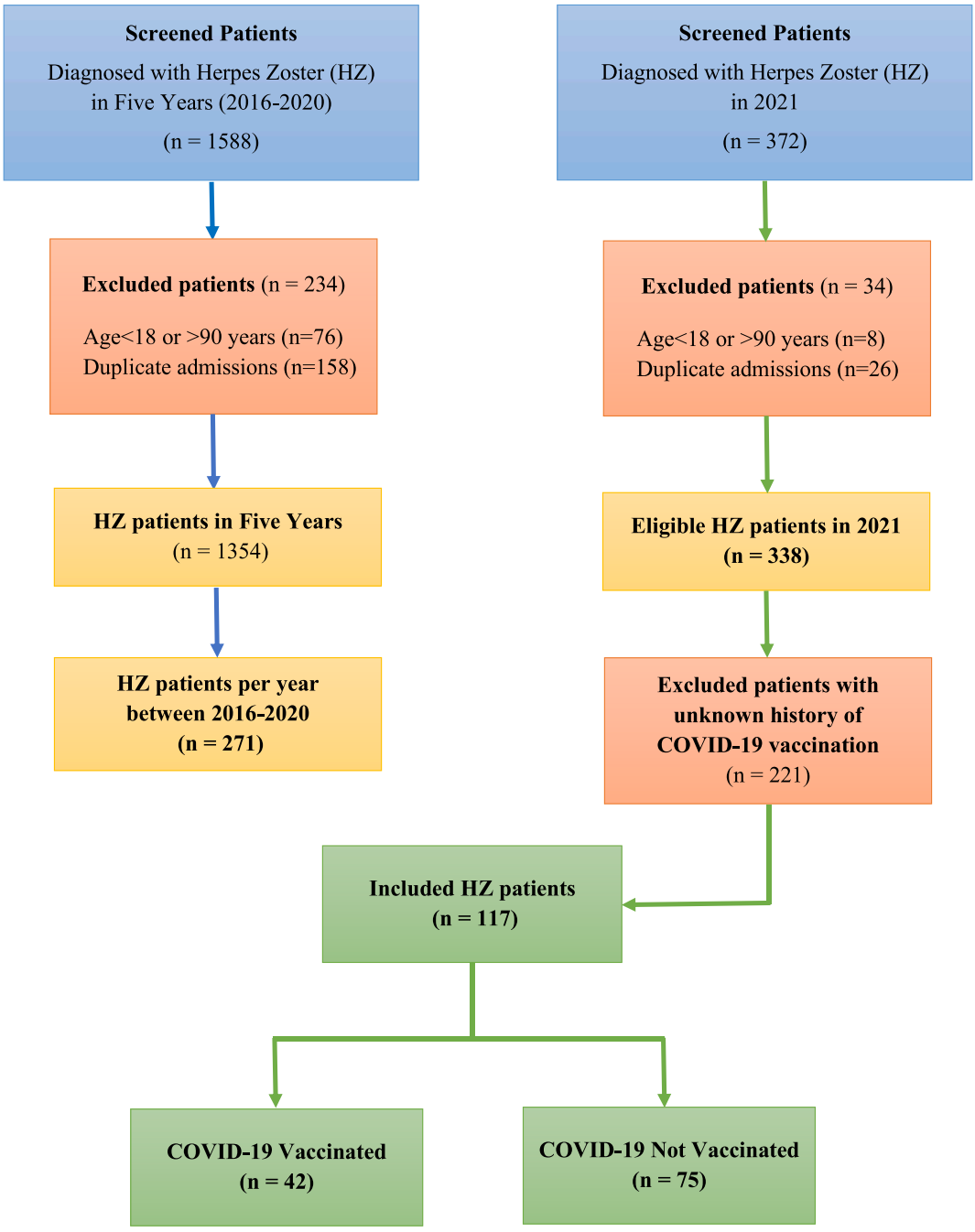


**Fig. 1.** Flow chart of the study.

## 2. Methods

### 2.1. Study design

This sudy was a single-center, retrospective cohort study.

### 2.2. Ethical approval

Prior to the study, the local ethical approval was received from the Clinical Research Ethics Committee of Medical Faculty of Ataturk University (Approval no: January 27, 2022/136). The study was conducted in compliance with the principles of the Declaration of Helsinki following receipt of approval from the local ethical committee.

### 2.3. Setting

The research was conducted in a dermatology clinic in a tertiary university hospital serving about 4.5 million people in eastern Türkiye.

### 2.4. Participants

The patients, aged between 18 and 90 years, attended a dermatology outpatient or inpatient clinic over a five-year period between January 2016 and 2020, and during the pandemic between January 2021 and January 2022. Patients with a diagnosis of HZ from the hospital database with an ICD-10 code (B02: Herpes Zoster) were included in the study.

Patients' records and epicrisis notes were scanned retrospectively in the hospital archive. Since the design of the study was a retrospective archive scan, informed consent was not obtained from the patients.

Age and sex of the HZ patients were recorded, as well as information on previous systemic diseases, medications, history of COVID-19 vaccination before the onset of symptoms, whether the vaccine administered was mRNA (BioNTech®) or inactive (Coronovac®) COVID-19 vaccine, time to onset of HZ after vaccination and number of vaccinations before onset of symptoms. Patients under 18 years of age or over 90 years of age, cases with an unknown COVID-19 vaccination history, missing or duplicate data, and patients diagnosed in other clinics (other than dermatology) were excluded from the study. The diagnosis needs to be made by a dermatologist, and therefore patients with ICD-10 codes who did not attend a dermatology outpatient or inpatient clinic were not considered to have

**Table 1**
The patients' demographic characteristics.

| | | HZ Patients in 2021 |
|---|---|---|
| **Age** | Mean | 57.61 |
| | Standard Deviation | 14.21 |
| | Minimum | 20 |
| | Maximum | 89 |
| | Median | 60.0 |
| | Interquartile Range | 18.0 |
| **Sex (n %)** | Female | 70 (59.8%) |
| | Male | 47 (40.2%) |
| | Total | 117 (100%) |
| **Chronic disease (n %)** | No | 84 (71.8%) |
| | Yes | 33 (28.2%) |
| | Hypertension | 14 (12%) |
| | Diabetes Mellitus | 10 (8.5%) |
| | Coronary Artery Disease | 6 (5.1%) |
| | Malignancy | 2 (1.7%) |
| | Malignancy + Diabetes | 1 (0.9%) |
| **COVID-19 vaccination history (n %)** | No | 75 (64.1%) |
| | Yes | 42 (35.9%) |
| | Total | 117 (100%) |
| **Number of COVID–19 vaccine administrations after which HZ* developed (n %)** | 1st | 13 (11.1%) |
| | 2nd | 23 (19.7%) |
| | 3rd | 6 (5.1%) |
| **Type of COVID-19 vaccine (n %)** | Inactive | 29 (24.8%) |
| | mRNA | 13 (11.1%) |
| **COVID-19 vaccine administered how many days prior to eruption?** | Mean | 24.64 |
| | Standard Deviation | 16.29 |
| | Minimum | 1 |
| | Maximum | 50 |
| | Median | 23.0 |
| | Interquartile Range | 30.0 |

HZ: Herpes Zoster.

definite HZ and were therefore excluded. Chronic illnesses were identified through a chronic illness record, which was entered into the hospital system by a designated expert, and these records were reviewed to identify chronic illnesses. Patients with chronic diseases were included in the study because this situation should be associated with possible immunosuppression or complications due to the chronic disease and therefore increased susceptibility to HZ. The inclusion and exclusion criteria were presented in Fig. 1.

### 2.5. Statistical analysis

The study data were analyzed on SPSS 23.0 software (IBM, USA). Categorical data were expressed as frequency and percentage, and numerical data as mean and standard deviation. Normality of distribution was evaluated using the Shapiro Wilk test. The Mann–Whitney *U* test was applied in the analysis of two non-normally distributed independent data. The chi-square test was employed in the analysis of categorical data. P values lower than 0.05 were regarded as statistically significant.

## 3. Results

The total number of patients over a five-year period between 2016 and 2020 was 1588. These patients were diagnosed with HZ by a dermatologist in a dermatology outpatient or inpatient clinic. Using the exclusion criteria, 234 patients were excluded, leaving 1354 patients. The annual incidence rate for HZ was determined to be 271 (Fig. 1).

If we look at the rates of HZ during the pandemic in 2021, the total number of patients diagnosed with HZ was found to be 419, which included all patients diagnosed with HZ, even those not from the dermatology clinic. Of these, 47 were not enrolled because they were considered potentially misdiagnosed and we chose not to enroll them. As our study focused on COVID-19 vaccination of HZ patients, patients with unknown vaccination history were excluded. After applying the other exclusion criteria, 117 patients were finally included in the study.

The participants' demographic characteristics are shown in Table 1. The mean age of the patients was 57.6 ± 14.2 years. Women represented 59.8% (n = 70) of the patients and men 40.2% (n = 47). Chronic disease was present in 28.2% (n = 33) of the participants, the most common being hypertension (n = 14, 12%). Only one patient (0.8%) was receiving immunosuppressive therapy.

A previous history of COVID-19 vaccination was present in 35.9% (n = 42) of the patients with HZ; 11.1% (n = 13) had received mRNA vaccine and 24.8% (n = 29) inactive COVID-19 vaccine. Analysis showed that 11.1% of these patients had received a first dose of COVID-19 vaccine, 19.7% a second, and 5.1% a third. Mean time to development of HZ after COVID-19 vaccination was 24.6 ± 16.3 days.

Analysis of the relationship between gender and HZ development following COVID-19 vaccination showed a history of vaccination in 34.3% of women and 38.3% of men. The difference was not statistically significant ($p > 0.05$). Histories of COVID-199 vaccination were present in 36.4% of the patients with chronic disease and in 35.7% of those without. The difference was not statistically significant ($p > 0.05$). No difference in terms of age was determined between the patients with and without histories of vaccination ($p > 0.05$) (Table 2).

Analysis of the association between the type of COVID-19 vaccine (inactive or mRNA) and gender revealed higher levels of inactive vaccine receipt among both women (75%) and men (61.1%), although no statistically significant difference was observed ($p > 0.05$). In terms of the relationship between type of vaccine and chronic disease, a history of inactive vaccine was present in 83.3% of the patients with chronic diseases and a history of mRNA vaccine in 16.7%. However, no statistically significant association was found between type of vaccine and presence of chronic disease ($p > 0.05$). Patients receiving mRNA vaccine were younger (46.6 ± 13.2 years), while those receiving inactive COVID-19 vaccine were older (62.2 ± 9.1 years), and the difference was statistically significant ($p < 0.001$).

Time elapsing to the development of HZ according to COVID-19 vaccine types was 22.8 ± 25.5 days for mRNA vaccine and 17.6 ± 15.9 days for inactive COVID-19 vaccine, and the difference was not statistically significant ($p > 0.05$).

**Table 2**
Relationships between history of COVID-19 vaccination and the type of COVID-19 vaccine and chronic disease, age, and time to development of eruption.

| | | History of COVID-19 Vaccination | | | Type of COVID-19 Vaccine | | |
|---|---|---|---|---|---|---|---|
| | | Yes | No | P | mRNA | Inactive | P |
| Sex | Female (n, %) | 24 (34.3%) | 46 (65.7%) | 0.657[a] | 6 (25%) | 18 (75%) | 0.531[a] |
| | Male (n, %) | 18 (38.3%) | 29 (61.7%) | | 7 (38.9%) | 11 (61.1%) | |
| Chronic disease | No (n, %) | 30 (35.7%) | 54 (64.3%) | 0.947[a] | 11 (36.7%) | 19 (63.3%) | 0.282[a] |
| | Yes (n, %) | 12 (36.4%) | 21 (63.6%) | | 2 (16.7%) | 10 (83.3%) | |
| Age **(Years: mean ± Std. Dev)** | | 57.4 ± 12.7 | 57.7 ± 15.1 | 0.971[b] | 46.6 ± 13.2 | 62.2 ± 9.1 | **<0.001**[b] |
| Time to development of eruption after vaccination **(Days: mean ± Std. Dev)** | | 24.6 ± 16.3 | – | – | 22.8 ± 25.5 | 17.6 ± 15.9 | 0.629[b] |

Std. Dev: Standard Deviation.
[a] Chi–square test.
[b] Mann–Whitney *U* test.

## 4. Discussion

The emergence of new variants due to mutation of the virus in the SARS-CoV-2 pandemic shows that the disease will remain a matter of concern and that vaccines will be needed for a long time to keep it under control. Information about side-effects associated with vaccines is also increasing as global vaccination rates rise [5].

Reactivation of VZV after vaccinations has rarely been reported. However, especially after vaccination against influenza, hepatitis A, Japanese encephalitis and rabies, reactivated VZV infections have been reported [6]. With this in mind, in our study, the annual number of HZ cases was found to be 271 between 2016 and 2020, but there was an increase in 2021, when the number of HZ cases was 338. This increase may reflect the possible association of COVID-19 vaccination with the HZ cases, as vaccination started in 2021.

While VZV reactivation may occur spontaneously, it can also emerge due to adaptive immune aging in the elderly, and in situations such as immunosuppressive drug use, trauma, x-rays, malignancy, infections, and physical and mental stress [7]. In this regard, it is thought that more susceptible individuals with chronic diseases, who are prone to complications and immunosuppression, will reactivate VZV. Considering this, the annual number of HZ incidence was found 271 between 2016 and 2020, but it was found to be increased in 2021 as 338. This reflects the possible association of COVID-19 vaccination with the HZ cases. However, when we look at the patients with chronic diseases in our study, no significance was found between the patients with and without chronic diseases, which gives us an important result, the COVID-19 vaccination has the main stimulator for the HZ.

The incidence of VZV reactivation following COVID-19 vaccination is uncertain, and the likely pathogenesis is also unclear. Various hypotheses have been proposed. A $CD8^+$ T cell and $CD4^+$ T-helper response is normally triggered after vaccination. Paradoxically, it has also been suggested that the virus becomes temporarily uncontrollable due to the alteration of VZV-specific naive B cells after SARS-COV-2 vaccination [8].

Another hypothesis focuses on the toll-like receptor (TLR) signals implicated in the reactivation of herpes viruses. Researchers have suggested that an increase in type 1 interferon and pro-inflammatory cytokines, which produce a decrease in antigen expression, together with the decrease in TLR expression after vaccination, may contribute to VZV reactivation [9].

The present study investigated patients diagnosed with HZ from January 2021, when COVID–19 vaccination commenced in Turkey, in order to determine the potential association with such vaccination. A history of COVID-19 vaccination was determined in 42 (35.9%) of the 117 patients diagnosed with HZ. This finding is notably high.

Adverse effects following vaccination may occur incidentally, or else within a causal relationship. In particular, it is important that there should be a chronological and plausible biological relationship between adverse events occurring after vaccination [10].

HZ was reported to appear in a mean nine days after COVID-19 vaccination in one case study [11]. In another study, HZ occurred within a minimum of one day and a maximum of 24 days after vaccination [12]. In the present study, the meantime elapsing to the development of HZ after COVID–19 vaccinations were $24.6 \pm 16.3$ days. Mean times were $22.8 \pm 25.5$ days after mRNA vaccines and $17.6 \pm 15.9$ days after inactive vaccines. In a multicenter prospective study, HZ was the most common non-local cutaneous reaction, with an incidence of 0.7% ($n = 17$) in 2290 patients hospitalized for adverse reactions to COVID-19 vaccination [13]. When compared with our data, this rate is quite low, and this would be evaluated that, HZ reactivations were not thought to be related to previous vaccinations with COVID-19, and therefore it would be kept in mind and ask the vaccination history.

The incidence of side-effects with mRNA vaccines is generally low [14]. In the present study, 11.1% ($n = 13$) of the HZ patients with histories of vaccination had received an mRNA vaccine, based on the most recent vaccination, and 24.8% ($n = 29$) had received inactive COVID–19 vaccines. HZ cases following inactive vaccination are rarer in the literature [12]. The greater frequency of HZ following inactive vaccines in the present study may be due to mRNA vaccines beginning to be administered later than inactive vaccines in Turkey.

The incidence of reactivation of VZV infection increases in elderly individuals in association with adaptive immune aging. More than 1000 HZ cases were identified after mRNA vaccination in the Vaccine Adverse Event Reporting System, the majority of which consisted of individuals over 60 [15].

Underlying chronic diseases may also be involved in the reactivation of VZV infection. Histories of vaccination were present in only 12 (36.4%) of the 33 patients with chronic disease among the 117 HZ patients, the other 21 (63.6%) having no history of vaccination. When we look at the vaccinated group ($n = 42$), we see that only 28.6% ($n = 12$) had a chronic disease and most of the vaccinated patients (71.4%) did not have a chronic disease. The fact that the percentage of chronic disease in the vaccinated patients is so low reduces the expectation that HZ develops due to chronic disease rather than vaccination.

HZ development has been reported to be more widespread after first dose vaccination than after the second [12]. In the present study, however, HZ emerged after the first dose in 11.1% ($n = 13$) of the 42 patients with histories of vaccination, in 19.7% ($n = 23$) after the second dose, and in 5.1% ($n = 6$) after the third.

Although inactive vaccines were given more than mRNA vaccines to both sexes and to patients with and without chronic disease, no significant difference was observed between the vaccine types in terms of sex or chronic disease. The only significant finding was that mRNA vaccine was administered significantly more frequently to very young individuals. Mean age at receipt of mRNA vaccine was $46.6 \pm 13.2$ years, compared to $62.2 \pm 9.1$ years for inactive vaccine ($p < 0.001$). We attributed this to the fact that COVID-19 vaccines first began being administered to the elderly in Turkey, and that inactive COVID-19 vaccines were produced first.

## 5. Limitations

There are some limitations. First, the diagnosis of HZ was made clinically, without histological or molecular confirmation. Second, the study was a single center study and therefore the results could not be generalized. Third, the VZV immunization history of the

patients was not known, which could influence reactivation. Fourth, COVID-19 vaccination coverage in the study area was not known and was not assessed, so the prevalence of HZ in the vaccine group in the population is unknown. Fifth, some patients developed a history of HZ development after the first dose of COVID-19 vaccine, some after the second, and others after the third. In addition, from the perspective the type of the latest COVID-19 vaccine administered was considered, and previous COVID-19 vaccine types and the type of vaccine most frequently administered to patients with HZ were not investigated. We also did not evaluate whether repeat doses of the same type of COVID-19 vaccine increased the tendency to HZ. A final limitation is that patients with a recent history of active SARS-CoV-2 infection could not be identified. However, this study was a relatively comprehensive study including a one-year period.

## 6. Conclusion

In contrast to previous studies, the number of HZ cases due to inactivate vaccines in the present study was proportionally higher than that of HZ cases due to mRNA vaccines. There have been several case reports of HZ development following receipt of COVID–19 vaccines. However, this study yielded an important finding in terms of showing the high proportion of COVID-19 vaccination among individuals diagnosed with HZ. In this era of widespread global vaccination, it is crucially important to recognize and understand the side-effects of these new vaccines. Although not recommended at present, as the relationship between COVID-19 vaccines and HZ becomes clearer, elderly and at-risk patients who may develop serious complications may require HZ vaccination or prophylaxis with antivirals before receiving COVID-19 vaccines. Although placebo-controlled studies are needed to confirm this, we think that there may be a link between COVID-19 vaccines and the emergence of HZ.

## Ethics statement

The local ethical approval was received from the Clinical Research Ethics Committee of Medical Faculty of Ataturk University (Approval no: January 27, 2022/136).

## Financial Support

None.

## Data availability statement

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

## CRediT authorship contribution statement

**Erdal Pala:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Mustafa Bayraktar:** Writing – review & editing, Writing – original draft, Validation, Software, Methodology, Formal analysis. **Rümeysa Calp:** Resources, Methodology, Investigation, Data curation.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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