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# Herpesviral Keratitis Following COVID-19 Vaccination: Analysis of NHIS Database in Korea

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**Purpose:** The purpose of this study was to determine the risk of herpesviral keratitis associated with 4 coronavirus disease 2019 (COVID-19) vaccines approved in South Korea, using large-scale data from the National Health Insurance Service.

**Methods:** The study included 8,528,254 individuals, with cohorts categorized based on COVID-19 vaccination status. Two investigations were conducted: The first aimed to assess the risk of new-onset herpesviral keratitis while the second study focused on the risk of relapse in individuals with a preexisting diagnosis. Propensity score matching was used for cohort balancing, and various covariates, including vaccine types and comorbidities, were considered. Statistical analyses, including Cox proportional hazard regression, were used to calculate adjusted hazard ratio (aHR) and assess the risk of herpesviral keratitis.

**Results:** Individuals receiving COVID-19 vaccination exhibited a higher risk of new-onset herpesviral keratitis compared with the unvaccinated control group (aHR 1.43, 95% confidence interval, 1.19–1.73). Both mRNA and non-mRNA vaccines demonstrated an increased risk. Individuals with preexisting herpetic keratitis who received COVID-19 vaccination showed a higher risk of relapse herpesviral keratitis compared with the unvaccinated control group (aHR 1.98, 95% CI, 1.29–3.03). Sensitivity analyses supported the robustness of the results.

**Conclusions:** This analysis of a large national health insurance database suggests an increased risk of both new-onset and relapse of herpesviral keratitis associated with COVID-19 vaccination in South Korea. While COVID-19 vaccination is crucial for pandemic control, health care providers should be aware of potential herpesvirus reactivation and consider appropriate prophylaxis and treatment for at-risk individuals.

**Key Words:** herpesviral keratitis, COVID-19 vaccination, reactivation

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Various vaccines against coronavirus disease 2019 (COVID-19) have been developed to mitigate the spread of the pandemic. There are 4 COVID-19 vaccines available in South Korea, including the recombinant messenger RNA vaccines (Pfizer/BioNTech, BNT162b2 and Moderna, mRNA1273) and adenovirus vector-based vaccines (Oxford-AstraZeneca, ChAdOx1 nCoV-19 and Janssen Johnson & Johnson, Ad26.COV2.S). All these vaccines may cause local and systemic adverse effects, such as pain and swelling of the injection site, fever, and headache.[1]

Herpesviridae is a large group of DNA viruses responsible for causing infections and specific illnesses in humans. They are commonly known as human herpesviruses (HHVs). The family consists of herpes simplex virus (herpes simple virus [HSV]-1, HSV-2; also known as HHV-1 and HHV-2), varicella-zoster virus (varicella zoster virus [VZV] or HHV-3), Epstein–Barr virus (EBV or HHV-4), and cytomegalovirus (cytomegalovirus [CMV] or HHV-5). Human herpesviruses are mainly recognized for their ability to induce latent infections that can be reactivated by triggering factors such as physical or psychological stress, fever, exposure to sunlight, malignancy, increasing age, and immunosuppression.[2]

Several studies have reported ocular complications following COVID-19 vaccination, affecting the cornea, ocular surface, orbit, retina, uvea, and other ocular structures.[3,4] Reactivation of herpesviruses following COVID-19 infection or COVID-19 vaccination is evident in the literature.[5–9] Numerous reports highlight corneal complications, particularly herpesviral keratitis.[8,9] Information extracted from the Adverse Event Reporting System indicated that the population prevalence of ocular herpes zoster following COVID-19 vaccination was 0.5 cases per million doses while the frequency of ocular herpes simplex was reported at 0.05 cases per million doses.[4] National surveillance systems of the United States and South Korea have reported the relationship between herpes simplex or herpes zoster and COVID-19 vaccines.[10,11]

In this study, we aimed to determine the risk of herpesviral keratitis associated with the 4 COVID-19 vaccines approved in

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South Korea, using large-scale data from the National Health Insurance Service (NHIS). In addition, we categorized cases as new-onset or relapse herpesviral keratitis based on whether the patient had previously been diagnosed with herpesviral keratitis in NHIS data. Furthermore, we compared the vaccinated group with a matched unvaccinated control group.

## MATERIALS AND METHODS

### Data Source

This retrospective study used the database of the Korea Disease Control and Prevention Agency, Republic of Korea (KDCA), and the NHIS, Republic of Korea (NHIS), for policy and academic research. The research number of this study is KDCA-NHIS-2022-1-623. The K-COV-N cohort (KDCA-COVID19-NHIS cohort) consists of 8,528,254 individuals, including 566,636 COVID-19–infected patients, from October 8, 2020, to December 31, 2021. The Korean Government provided the date of COVID-19 diagnosis from October 8, 2020. Of the K-COV-N cohort, 6,053,352 individuals receiving COVID-19 vaccination were recruited as a vaccinated cohort. In addition, 2,474,902 individuals without COVID-19 vaccination were randomly recruited as the control group based on age and sex. These individuals had received insurance-eligible diagnosis at least once between

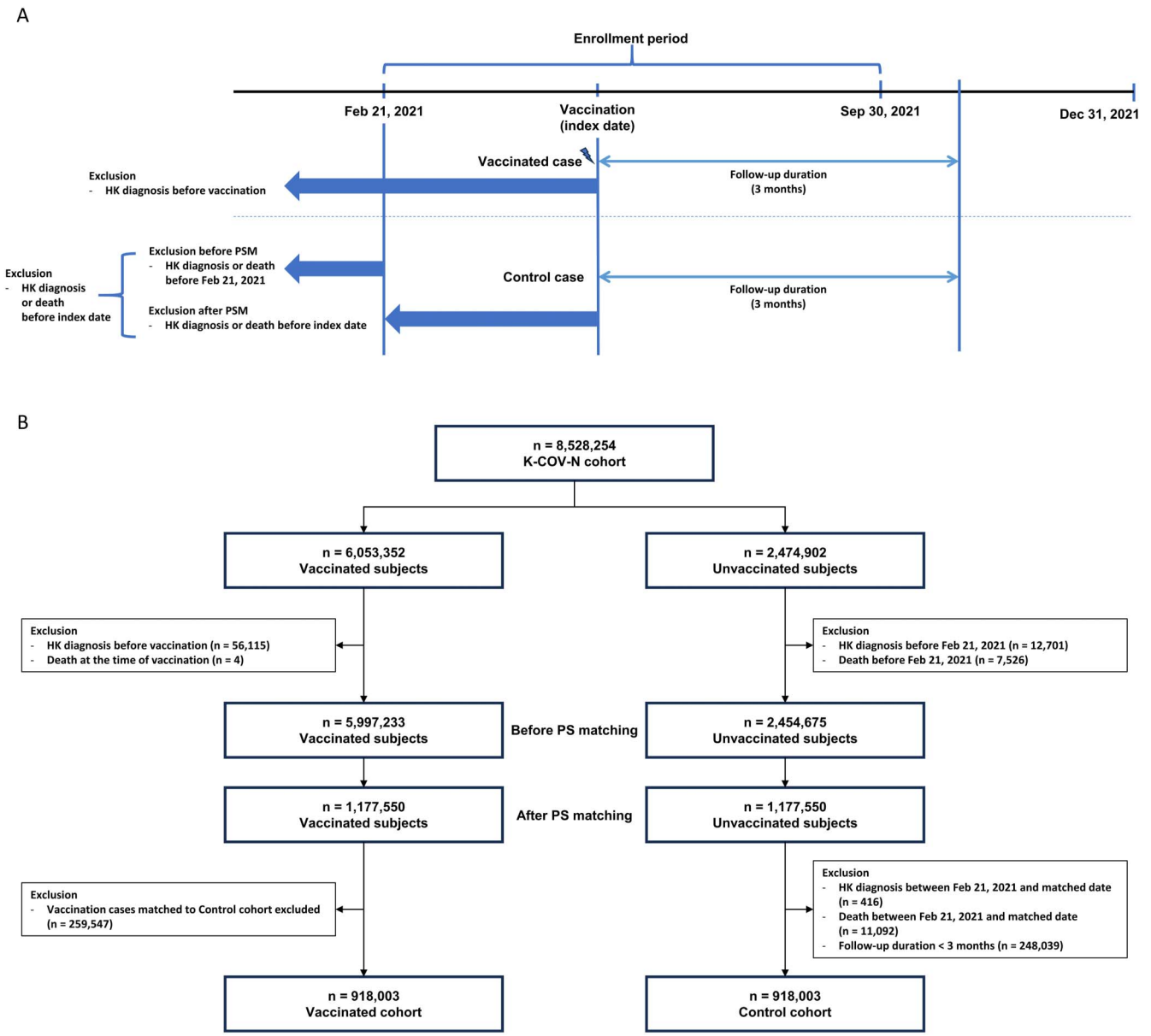


**FIGURE 1.** Flowchart of the study population of new-onset herpesviral keratitis according to COVID-19 vaccination. HK, herpesviral keratitis; K-COV-N cohort, KDCA-COVID19-NHIS cohort; PSM, propensity score matching.

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January 1, 2015, and December 31, 2021. NHIS provided information on 97% of the Korean population, including sex, age, residential area, economic status, and International Classification of Diseases, 10th revision (ICD-10) codes. KDCA provided information on COVID-19–confirmed patients, confirmed date, date of death, reporting agency area, infection route, vaccine type, dose number, and vaccination date.

## Study Design

### New-Onset Herpesviral Keratitis

This study aimed to assess whether COVID-19 vaccination is associated with an increased risk of new-onset herpesviral keratitis. The diagnosis of herpesviral keratitis was defined as the assignment of the ICD-10 code H191 (herpesviral keratitis and keratoconjunctivitis) at least once. Individuals vaccinated until September 30, 2021, were recruited as the vaccinated group since the start of vaccination in Korea on February 26, 2021. Accordingly, individuals who either received COVID-19 vaccination after October 1, 2021, or had no history of COVID-19 vaccination were considered as the control group. The index date for the vaccinated individuals was the date of their vaccination while for control individuals, it was set to the same date as the matched vaccinated individuals. Exclusion criteria for new-onset herpesviral keratitis were 1) herpesviral keratitis diagnosed before the index date and 2) follow-up duration <3 months. Both groups were followed up until the date of herpesviral keratitis diagnosis, death, or 3 months from the index date, whichever came first.

### Relapse Herpesviral Keratitis

This study aimed to assess whether COVID-19 vaccination is associated with an increased risk of relapse of herpesviral keratitis. The data were from individuals who were diagnosed with herpesviral keratitis before the index date. Exclusion criteria of relapse herpesviral keratitis were 1) herpesviral keratitis diagnosed after the index date, 2) herpesviral keratitis diagnosed within 1 year from the index date, and 3) follow-up duration <3 months. The definition of herpesviral keratitis diagnosis, vaccinated and control groups, index date, and the follow-up period are the same as in new-onset herpesviral keratitis.

## Control Group

Control groups were obtained to reduce biases affecting the study results. Propensity score matching (PSM) was performed to reduce potential bias and balance baseline characteristics between the vaccinated and control groups. The propensity score is the probability of an individual being assigned to a particular group using a logistic regression model adjusting for age, sex, residential area, economic status, hypertension (HTN), diabetes mellitus (DM), chronic kidney disease (CKD), and COVID-19. Individuals from the control group were matched with individuals from the vaccinated group based on their propensity scores using 1:1 greedy nearest-neighbor algorithm.[12,13] The adequacy of PSM was evaluated by comparing standardized mean differences (SMDs). The SMDs is better than assessing *P* values from *t* tests. To reduce immortal time bias, the index date of the control group was set to the same date as the vaccinated group.

**TABLE 1.** Baseline Characteristics of Patients With New-Onset Herpesviral Keratitis According to COVID-19 Vaccination

| | Total Cohort (n = 1,836,006) | Vaccinated Cohort (n = 918,003) | Control Cohort (n = 918,003) | SMD |
|---|---|---|---|---|
| Age (continuous) | | 42.21 (18.28) | 41.35 (20.50) | 0.012 |
| Age, yr | | | | <0.001 |
| ~19 | 215,436 (11.7) | 107,718 (11.7) | 107,718 (11.7) | |
| 20–29 | 317,019 (17.3) | 158,450 (17.3) | 158,569 (17.3) | |
| 30–39 | 426,863 (23.2) | 213,461 (23.3) | 213,402 (23.2) | |
| 40–49 | 290,647 (15.8) | 145,330 (15.8) | 145,317 (15.8) | |
| 50–59 | 205,087 (11.2) | 102,538 (11.2) | 102,549 (11.2) | |
| 60–69 | 206,456 (11.2) | 103,224 (11.2) | 103,232 (11.2) | |
| 70~ | 174,498 (9.5) | 87,282 (9.5) | 87,216 (9.5) | |
| Sex, male | 974,275 (53.1) | 479,985 (52.3) | 494,290 (53.8) | 0.031 |
| Economic status, low* | 1,282,901 (69.9) | 621,644 (67.7) | 661,257 (72.0) | 0.094 |
| Residential area | | | | 0.008 |
| Metropolitan cities | 1,311,229 (71.4) | 654,754 (71.3) | 656,475 (71.5) | |
| Mid-size and small cities | 415,951 (22.7) | 207,964 (22.7) | 207,987 (22.7) | |
| Rural areas | 108,826 (5.9) | 55,285 (6.0) | 53,541 (5.8) | |
| Comorbidities | | | | |
| Hypertension | 266,495 (14.5) | 133,208 (14.5) | 133,287 (14.5) | <0.001 |
| Diabetes mellitus | 171,563 (9.3) | 85,828 (9.3) | 85,735 (9.3) | <0.001 |
| Chronic kidney disease | 25,999 (1.4) | 12,833 (1.4) | 13,166 (1.4) | 0.003 |
| COVID-19 | 216,281 (11.8) | 93,944 (10.2) | 122,337 (13.3) | 0.096 |

Data are presented as number (%).
*Income status was divided into the highest 30% (high) and the rest (low); individuals supported by the medical aid program were classified as the low-income group.


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## Covariates

Covariates included 1) sex, male or female; 2) age: ≤ 19, every decade, or ≥ 70 years; 3) economic status, high (top 30%) or low (bottom 70%); and 4) residential area, metropolitan cities, middle and small-sized cities, and rural areas; 5) HTN (ICD-10 code; I10–13, and I15); 6) DM (ICD-10 code; E10–14); 7) CKD (ICD-10 code; N18), and 8) COVID-19 (ICD-10 code; U071) with at least 1 diagnosis during the previous 3 years. For subgroup analyses, individuals in the vaccinated group were classified into mRNA (Pfizer-BioNTech, BNT162b2 and Moderna, mRNA-1273) and non-mRNA (AstraZeneca, ChAdOx-1nCoV-19 and Janssen, Ad26.COV2.S) groups according to the type of COVID-19 vaccination.

## Statistical Analysis

Descriptive statistics are presented as mean with standard deviations for continuous variables and as numbers with percentages for categorical variables. The incidence rates of herpesviral keratitis were calculated by dividing the number of incident events by the total follow-up period (10,000 person-years). A cumulative incidence plot was used to compare the incidence of herpesviral keratitis

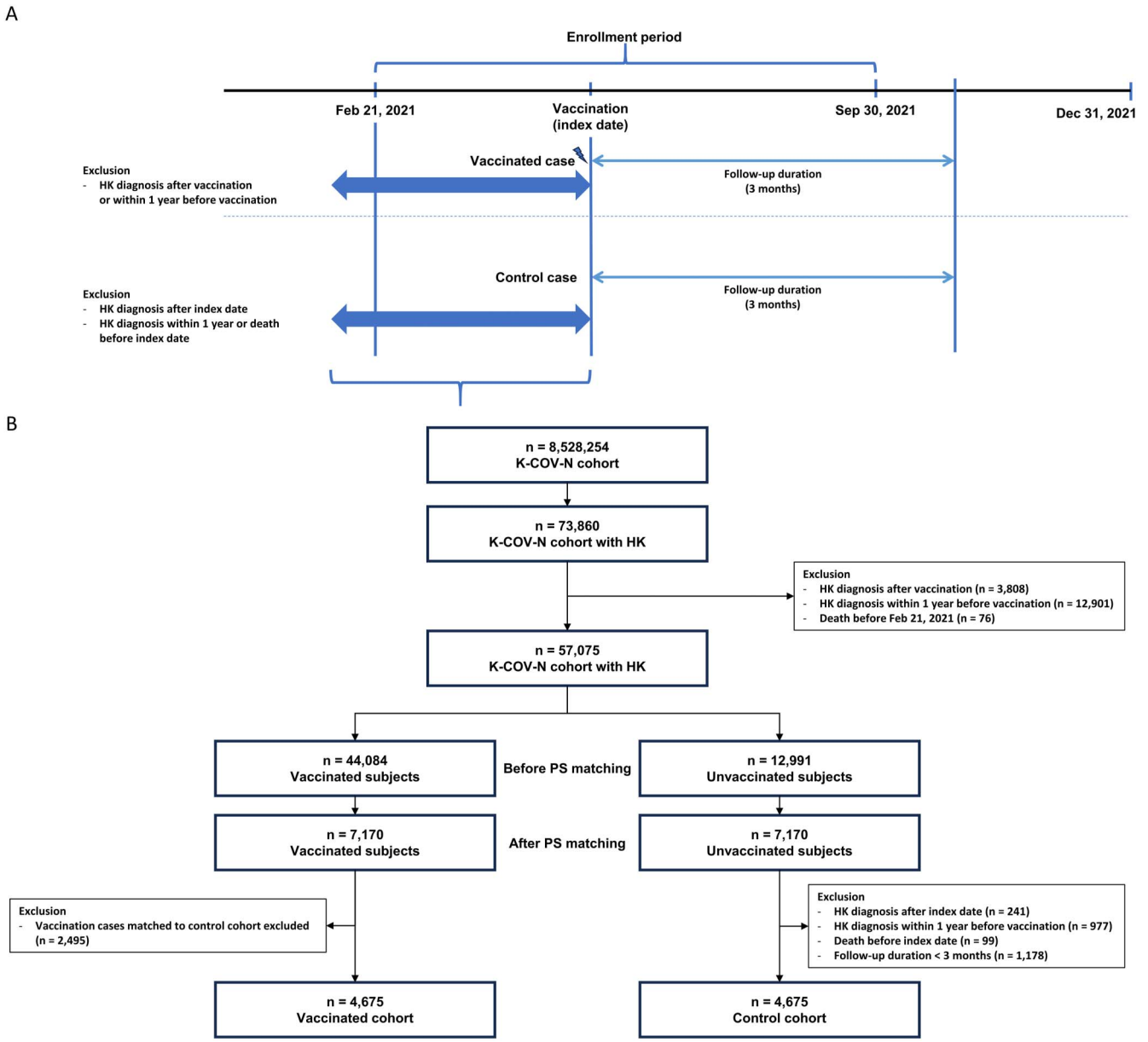


**FIGURE 2.** Flowchart of the study population of relapse herpesviral keratitis according to COVID-19 vaccination. HK, herpesviral keratitis; K-COV-N cohort, KDCA-COVID19-NHIS cohort; PSM, propensity score matching.

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**TABLE 2.** Baseline Characteristics of Patients With Relapse Herpesviral Keratitis According to COVID-19 Vaccination

| | Total Cohort (n = 9350) | Vaccinated Cohort (n = 4675) | Control Cohort (n = 4675) | SMD |
|---|---|---|---|---|
| Age (continuous) | | 48.11 (19.12) | 47.87 (20.83) | 0.012 |
| Age, yr | | | | 0.009 |
| ~19 | 626 (6.7) | 313 (6.7) | 313 (6.7) | |
| 20–29 | 1104 (11.8) | 557 (11.9) | 547 (11.7) | |
| 30–39 | 2068 (22.1) | 1032 (22.1) | 1036 (22.2) | |
| 40–49 | 1478 (15.8) | 737 (15.8) | 741 (15.9) | |
| 50–59 | 1047 (11.2) | 521 (11.1) | 526 (11.3) | |
| 60–69 | 1466 (15.7) | 731 (15.6) | 735 (15.7) | |
| 70~ | 1561 (16.7) | 784 (16.8) | 777 (16.6) | |
| Sex, male | 4599 (49.2) | 2331 (49.9) | 2268 (48.5) | 0.027 |
| Economic status, low* | 6152 (65.8) | 3004 (64.3) | 3148 (67.3) | 0.065 |
| Residential area | | | | 0.049 |
| Metropolitan cities | 6544 (70.0) | 3223 (68.9) | 3321 (71.0) | |
| Mid-size and small cities | 2235 (23.9) | 1166 (24.9) | 1069 (22.9) | |
| Rural areas | 571 (6.1) | 286 (6.1) | 285 (6.1) | |
| Comorbidities | | | | |
| Hypertension | 2278 (24.5) | 1122 (24.0) | 1156 (24.7) | 0.017 |
| Diabetes mellitus | 1598 (17.1) | 791 (16.9) | 807 (17.3) | 0.009 |
| Chronic kidney disease | 288 (3.1) | 135 (2.9) | 153 (3.3) | 0.022 |

Data are presented as number (%).
*Income status was divided into the highest 30% (high) and the rest (low); individuals supported by the medical aid program were classified as the low-income group.

between 2 groups. Cox proportional hazard regression was used to calculate the adjusted hazard ratio (aHR) and 95% confidence interval (CI) for the risk of incidence of herpesviral keratitis based on vaccination status. The control group served as the reference group, enabling the evaluation of the aHR of the vaccinated group compared with the control group. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC) and R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

## Sensitivity Analysis

To validate our results from a 3-month follow-up period, we conducted a sensitivity analysis by modifying the follow-up period to 1 and 2 months. If the results from the sensitivity analysis align with our main results, we can consider our main results to be valid.

# RESULTS

## Baseline Characteristics

As shown in Figure 1, 6,053,352 subjects were vaccinated and 2,474,902 subjects were unvaccinated among the 8,528,254 subjects. To construct the vaccination cohort, we excluded 56,115 subjects with a previous diagnosis of herpesviral keratitis before the vaccination date, along with 4 subjects who died on the day of vaccination among the vaccinated subjects. Thus, the final vaccination cohort included 5,997,233 vaccinated subjects, and after 1:1 PSM, the cohort consisted of 918,003 subjects. To construct the control cohort, we excluded herpesviral keratitis diagnosis (n = 12,701), deaths (n = 7526) before the index date, and follow-up duration <3 months (n = 248,039) among the unvaccinated subjects. Thus, the final control cohort included 918,003 unvaccinated subjects after 1:1 PSM. The vaccinated and control cohorts were 918,003 and 918,003 subjects,

**TABLE 3.** Risk of New-Onset Herpesviral Keratitis According to COVID-19 Vaccination

| | N | Incident Case of Herpesviral Keratitis | Incidence per 10,000 | Unadjusted HR (95% CI) | Adjusted HR* (95% CI) |
|---|---|---|---|---|---|
| Control cohort | 918,003 | 182 | 7.90 | Reference | Reference |
| Vaccinated cohort | 918,003 | 265 | 11.46 | 1.45 (1.20–1.75) | 1.43 (1.19–1.73) |
| Subgroup† | | | | | |
| mRNA | 655,138 | 177 | 10.72 | 1.36 (1.10–1.67) | 1.44 (1.16–1.78) |
| Non-mRNA | 169,528 | 82 | 19.21 | 2.43 (1.87–3.16) | 2.02 (1.50–2.72) |
| *P*-value‡ | | | | <0.001 | <0.001 |

Data are presented as a risk ratio (95% CI).
*Adjusted for age, sex, economic status, residential area, and comorbidities (HTN, DM, CKD, COVID-19).
†Mixed vaccination of mRNA and non-mRNA cases were excluded in this study.
‡mRNA versus non-mRNA.


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respectively (Fig. 1). The baseline characteristics of the subjects in new-onset herpesviral keratitis are shown in Table 1. Baseline characteristics between the 2 cohorts did not show any significant imbalances (all SMDs <0.15). The vaccinated and control cohorts of relapse herpesviral keratitis were 4675 and 4675 subjects, respectively (Fig. 2), and the baseline characteristics of relapse herpesviral keratitis are also summarized in Table 2.

## Does COVID-19 Vaccination Increases New-Onset Herpesviral Keratitis?

During a median 3 months of follow-up, new-onset herpesviral keratitis was diagnosed in the vaccinated cohort (265/918,003) and the control cohort (182/918,003) with an incidence of 11.46 and 7.90 per 10,000 person-years, respectively. Subjects who received COVID-19 vaccination had a higher risk of herpesviral keratitis (aHR, 1.43; 95% CI, 1.19 to 1.73) than subjects without COVID-19 vaccination (Table 3). Similarly, there was a significant difference in the cumulative incidence of new-onset herpesviral keratitis between the 2 cohorts (Fig. 3). In terms of COVID-19 vaccine types and their impact on the risk of new-onset herpesviral keratitis, mRNA vaccines (aHR, 1.44; 95% CI, 1.16–1.78) and non-mRNA vaccines (aHR, 2.02; 95% CI, 1.50–2.72) had a higher risk compared with the control cohort (Fig. 4, Table 3). The non-mRNA vaccines showed significantly higher incidence compared to the mRNA vaccines ($P < 0.001$) (Table 3).

In terms of covariates and their impact on the risk of herpesviral keratitis in new-onset herpesviral keratitis, the risk of incidence was higher in older age, male, and DM; 1) for age, the aHR in the ≥70-year group was 1.59 (95% CI, 1.09–2.32) compared with the 40 to 49-year group, 2) the aHR in male patients was 1.28 (95% CI, 1.06–1.55), and 3) the aHR in DM was 1.42 (95% CI, 1.06–1.90) (Table 4). Moreover, in subgroup analysis based on previous COVID-19 infection, the risk of herpesviral keratitis incidence was found to be higher among individuals with no history of COVID-19 infection (aHR 1.46; 95% CI, 1.19–1.77) (Table 5).

## Does COVID-19 Vaccination Increases Relapse of Herpesviral Keratitis?

During a median 3 months of follow-up, relapse of herpesviral keratitis was diagnosed in the study cohort (63/4675) and control cohort (32/4675) with an incidence of 538.74 and 274.59 per 10,000 person-years, respectively. Subjects received with COVID-19 vaccination had a higher risk of relapsed herpesviral keratitis (aHR, 1.98; 95% CI, 1.29–3.03) than subjects without COVID-19 vaccination (Table 6). Similarly, there was a significant difference in the cumulative incidence of relapse of herpesviral keratitis between the 2 cohorts (Fig. 5A). In terms of COVID-19

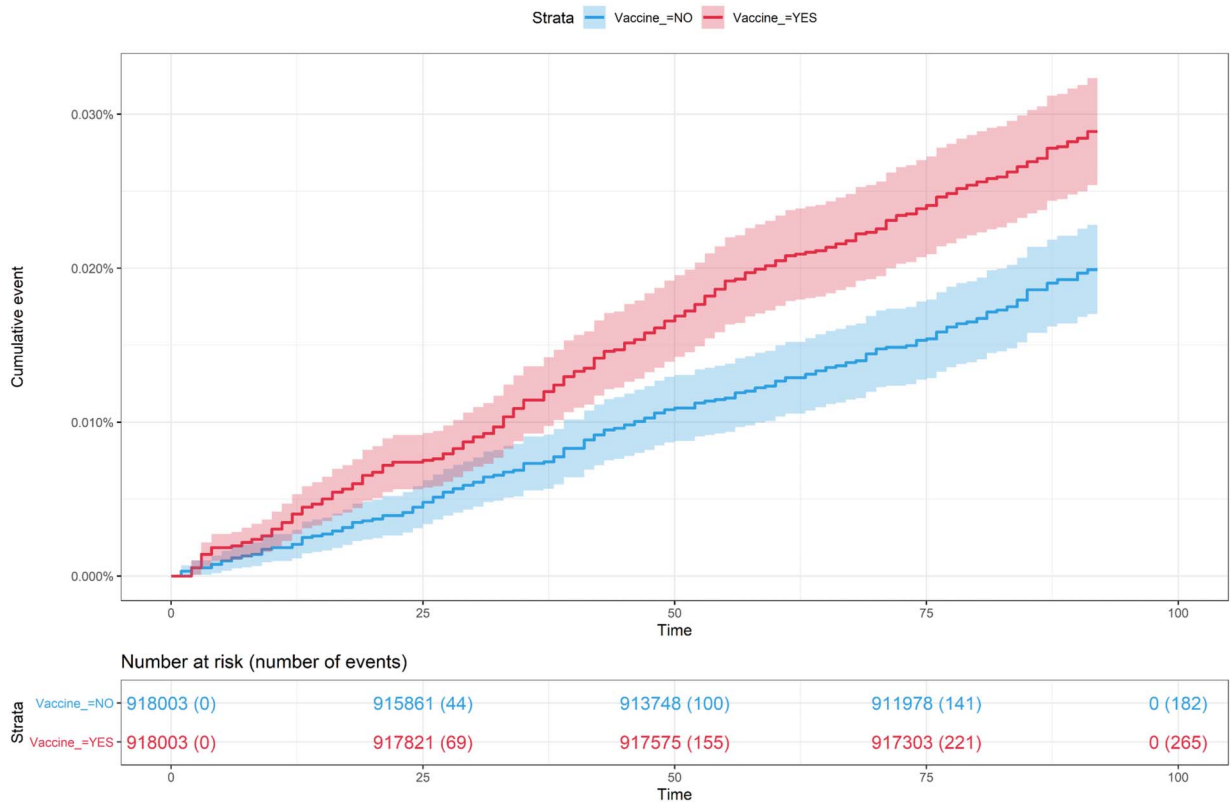


**FIGURE 3.** Cumulative incidence of new-onset herpesviral keratitis according to COVID-19 vaccination.

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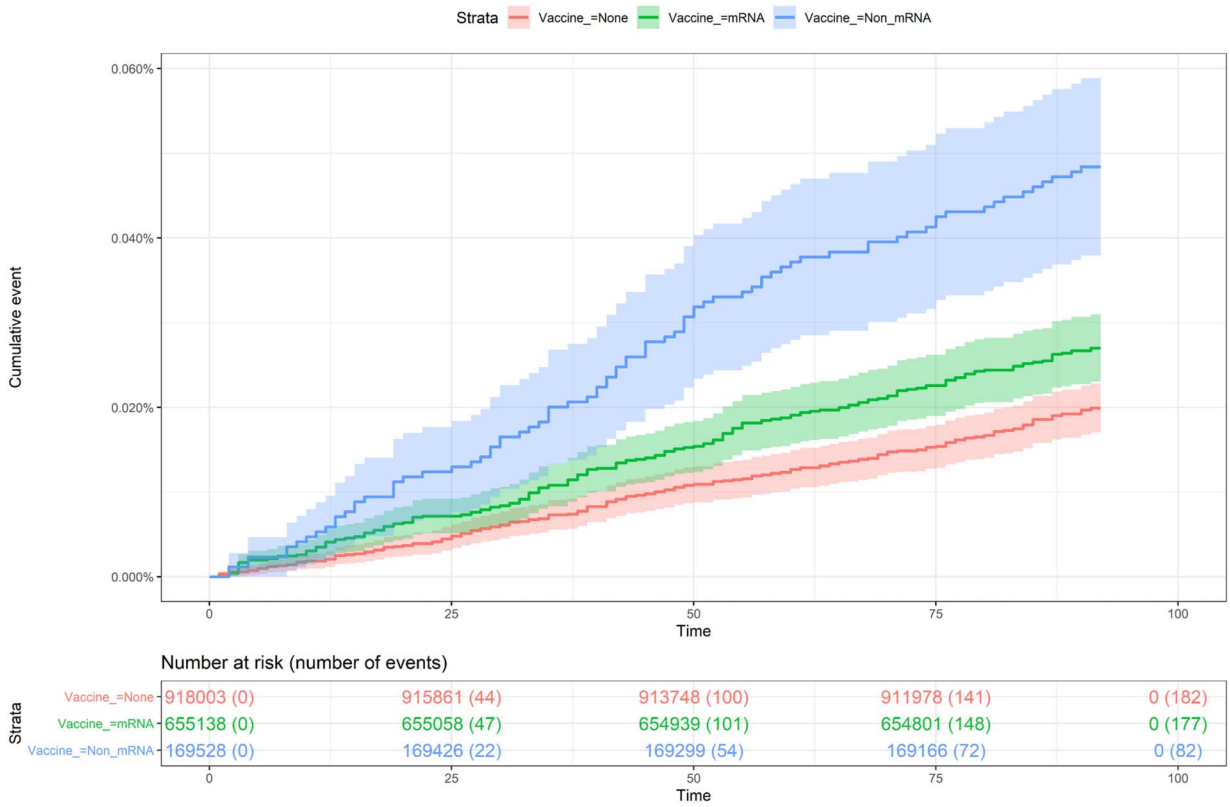


**FIGURE 4.** Cumulative incidence of new-onset herpesviral keratitis according to COVID-19 vaccine type.

vaccine types and their impact on the risk of relapsed herpesviral keratitis, mRNA vaccines (aHR, 1.91; 95% CI, 1.19–3.07) and non-mRNA vaccines (aHR, 3.21; 95% CI, 1.70–6.08) had a higher risk compared with the control cohort (Fig. 5B, Table 6). There was no significant difference between the mRNA vaccine and the non-mRNA vaccine ($P = 0.191$) (Table 6).

In terms of covariates and their impact on the risk of herpesviral keratitis in relapse herpesviral keratitis, there is no significant risk factor (Table 7).

## Sensitivity Analysis

The sensitivity analysis for new-onset herpesviral keratitis and relapse herpesviral keratitis, with different follow-up periods (1 and 2 months), showed similar results (Fig. 6).

## DISCUSSION

Globally, herpesviral keratitis is one of the leading causes of blindness. More than 90% of the adult population is infected by one of the herpesviridae family viruses at least once in early life.[5] Therefore, both new-onset and relapse herpesviral keratitis in this study represent the reactivation of the herpesvirus. The herpesviridae family is known for its capability to cause latent infection after the primary infection until reactivation due to corneal trauma, environmental stress, and immunosuppression.[14,15] There are different sites in which the viruses become latent: VZV predominantly remains dormant in neurons of the dorsal root ganglia, cranial nerve ganglia, and autonomic ganglia while HSV resides in the trigeminal ganglia for HSV-1 and sacral ganglia for HSV-2.[5,16] CMV becomes latent in myeloid cells, and EBV undergoes a latent phase in B-lymphocytes and epithelial cells.[17,18] Reactivation along the ophthalmic branch can cause herpes simplex and zoster ophthalmicus (herpes simplex ophthalmicus [HSO] and herpes zoster ophthalmicus [HZO]). Notably, viral replication appears more frequently in older individuals due to their weakened cell-mediated immunity, a condition referred to as immunosenescence.[19] This condition has been found to be associated not only with an increased susceptibility to viral infection but also with a decreased response of vaccination.[19] Consequently, advancing age is identified as a risk factor for the reactivation of HSO and HZO. In this study, the risk of new-onset herpesviral keratitis after COVID-19 vaccination was higher in individuals 70 years and older compared with the 40 to 49-year population.

Herpesvirus reactivation was reported following the administration of the influenza, hepatitis A, and rabies vaccines.[20] Little is known about the potential pathogenesis


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**TABLE 4.** Risk Factor for the Development of New-Onset Herpesviral Keratitis With or Without COVID-19 Vaccination

| | N | Incident Cases of Herpesviral Keratitis | Incidence per 10,000 | Univariable Analysis | | Multivariable Analysis | |
|---|---|---|---|---|---|---|---|
| | | | | Unadjusted HR | 95% CI | Adjusted HR* | 95% CI |
| Age, yr | | | | | | | |
| 40–49 | 290,647 | 65 | 8.88 | Reference | | Reference | |
| ~19 | 215,436 | 34 | 6.26 | 0.71 | 0.47–1.07 | 0.73 | 0.48–1.11 |
| 20–29 | 317,019 | 55 | 6.88 | 0.78 | 0.54–1.11 | 0.80 | 0.56–1.15 |
| 30–39 | 426,863 | 98 | 9.11 | 1.03 | 0.75–1.40 | 1.05 | 0.77–1.44 |
| 50–59 | 205,087 | 53 | 10.27 | 1.16 | 0.80–1.66 | 1.12 | 0.78–1.62 |
| 60–69 | 206,456 | 69 | 13.31 | 1.50 | 1.07–2.10 | 1.35 | 0.95–1.91 |
| 70~ | 174,498 | 73 | 16.87 | 1.90 | 1.36–2.65 | 1.59 | 1.09–2.32 |
| Sex | | | | | | | |
| Female | 861,731 | 191 | 8.81 | Reference | | Reference | |
| Male | 974,275 | 256 | 10.45 | 1.19 | 0.98–1.43 | 1.28 | 1.06–1.55 |
| Economic status | | | | | | | |
| High | 553,105 | 153 | 11.00 | Reference | | Reference | |
| Low | 1,282,901 | 294 | 9.11 | 0.83 | 0.68–1.01 | 0.86 | 0.71–1.05 |
| Residential area | | | | | | | |
| Middle and small cities | 415,951 | 92 | 8.80 | Reference | | Reference | |
| Metropolitan cities | 1,311,229 | 327 | 9.91 | 1.13 | 0.89–1.42 | 1.16 | 0.92–1.46 |
| Rural areas | 108,826 | 28 | 10.26 | 1.17 | 0.76–1.78 | 1.05 | 0.69–1.60 |
| Hypertension, yes | | | | | | | |
| No | 1,569,511 | 342 | 8.65 | Reference | | Reference | |
| Yes | 266,495 | 105 | 15.79 | 1.82 | 1.47–2.27 | 1.18 | 0.88–1.58 |
| Diabetes mellitus, yes | | | | | | | |
| No | 1,664,443 | 372 | 8.88 | Reference | | Reference | |
| Yes | 171,563 | 75 | 17.51 | 1.97 | 1.54–2.53 | 1.42 | 1.06–1.90 |
| Chronic kidney disease, yes | | | | | | | |
| No | 1,810,007 | 436 | 9.58 | Reference | | Reference | |
| Yes | 25,999 | 11 | 17.09 | 1.78 | 0.98–3.25 | 1.01 | 0.54–1.88 |

Data are presented as HR (95% CIs).
*Adjusted for age, sex, economic status, residential area, and comorbidities (HTN, DM, CKD, COVID-19).

of herpesvirus reactivation following COVID-19 vaccination, and it is unclear what role the vaccines may have on relapse or new-onset herpesviral keratitis. Vaccine administration can cause hyperthermia, tissue injury, an immunocompromised state, and cytokines.[5] Maybe, the administration of the COVID-19 vaccine can elicit an immunomodulatory reaction that leads to the reactivation of latent herpesvirus. The vaccine-induced immune system activation induces a strong T-cell response. Vaccines produce a cellular response with increased spike-specific T-helper type 1 $CD4^+$ T cells and $CD8^+$ cells.[16] This stimulation in cellular immunity may cause a massive shift of naive $CD8^+$ cells in the setting of SARS-CoV-2 vaccination, resulting in a temporary loss of the ability of virus-specific $CD8^+$ cells to regulate dormant virus.[16,21] In this study, the vaccinated group, regardless of whether they had a history of herpetic keratitis, had a higher risk of herpesviral keratitis compared with the unvaccinated control group. In addition, patients with a history of herpetic eye disease had a slightly higher hazard ratio (HR) of herpesviral keratitis after COVID-19 vaccination compared with patients with new-onset

**TABLE 5.** Subgroup Analysis of Incidence Rate and Risk of New-Onset Herpesviral Keratitis According to the COVID-19 Infection

| Group | Vaccination | N | Incident Case of Herpesviral Keratitis | Incidence per 10,000 | Unadjusted HR (95% CI) | Adjusted HR* (95% CI) |
|---|---|---|---|---|---|---|
| No previous COVID-19 infection | No | 795,666 | 165 | 8.26 | Reference | Reference |
| | Yes | 824,059 | 248 | 11.95 | 1.45 (1.19–1.76) | 1.46 (1.19–1.77) |
| Previous COVID-19 infection | No | 122,337 | 17 | 5.52 | Reference | Reference |
| | Yes | 93,944 | 17 | 7.18 | 1.30 (0.66–2.54) | 1.18 (0.59–2.34) |

Data are presented as a risk ratio (95% CI).
*Adjusted for age, sex, economic status, residential area, and comorbidities (HTN, DM, CKD).

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**TABLE 6.** Risk of Relapse Herpesviral Keratitis According to COVID-19 Vaccination

| | N | Incident Case of Herpesviral Keratitis | Incidence per 10,000 | Unadjusted HR (95% CI) | Adjusted HR* (95% CI) |
|---|---|---|---|---|---|
| Control cohort | 4675 | 32 | 274.59 | Reference | Reference |
| Vaccinated cohort | 4675 | 63 | 538.74 | 1.96 (1.28–3.00) | 1.98 (1.29–3.03) |
| Subgroup† | | | | | |
| mRNA | 3014 | 40 | 530.61 | 1.93 (1.21–3.08) | 1.87 (1.16–3.01) |
| Non-mRNA | 1171 | 22 | 753.30 | 2.74 (1.59–4.72) | 3.21 (1.70–6.08) |
| *P* value‡ | | | | 0.005 | 0.191 |

Data are presented as a risk ratio (95% CI).
*Adjusted for age, sex, economic status, residential area, and comorbidities (HTN, DM, CKD).
†Mixed vaccination of mRNA and non-mRNA cases were excluded in this study.
‡mRNA versus non-mRNA.

herpesviral keratitis. Moreover, in subgroup analysis based on previous COVID-19 infection, the risk of herpesviral keratitis incidence was found to be higher among individuals with no history of COVID-19 infection.

Recently, in the matched case-control analysis of the NHIS database of Korea, BNT162b2 was associated with an increased risk of herpes zoster reactivation.[11] However, the risk did not increase in the analysis of ChAdOx-1nCoV-19 vaccination.[11] In this study, in terms of COVID-19 vaccine types, both the mRNA vaccine (BNT162b2, mRNA-1273) and non-mRNA vaccine (ChAdOx-1nCoV-19, Ad26.COV2.S) groups had a higher risk of herpesviral keratitis compared with the unvaccinated control group.

In a recent systematic review conducted by Shafiee et al,[5] the possible association between COVID-19 vaccination and the reactivation of herpesvirus was explored through observational studies. According to their meta-analysis findings, individuals who received the COVID-19 vaccine exhibited a VZV reactivation rate of 14 persons per 1000 doses and HSV reactivation rate of 16 persons per 1000 doses. Various vaccines, including Pfizer/BioNTech (n = 76), Oxford-AstraZeneca (n = 22), Moderna (n = 17), and Johnson and Johnson (n = 1), were associated with reactivation. Many reported cases involved patients having comorbidities, with common conditions including HTN, DM, dyslipidemia, chicken pox, and atrial fibrillation. In this study, both mRNA and non-mRNA vaccines exhibited a similar increasing tendency in the reactivation of herpesviral keratitis. The non-mRNA vaccines showed significantly higher incidence compared with the mRNA vaccines in new-onset herpesviral keratitis. However, there was no significant difference observed between the mRNA and non-mRNA vaccines in relapse herpesviral keratitis. Furthermore, no statistically significant comorbidities were identified.

Many studies reported herpetic eye disease occurring most frequently with 1 to 2 weeks following COVID-19 vaccination. Singh et al[8] reported that 60% of cases of HSO and HZO were diagnosed within the first 2 weeks of vaccination, whereas 4 of the 5 cases of Cohen et al[22] presented with symptoms with the first week of vaccination. A recent study by Liu et al[23] involved the pathophysiological alterations after the COVID-19 vaccine in which $CD8^+$ T cells reduction, increase in classic monocyte contents, increased NF-κB signaling, and reduced type I interferon responses were reported; they have admitted that in the first 28 days after vaccine injection; the immune system is in the vulnerable state. Therefore, they postulated that it is imperative to consider the potential long-term impact of vaccination to certain medical conditions[24] or to general human health. Furthermore, pandemic-related psychological stress has been noted to potentially play a causal role, too. It is possible that the vaccinated group may have experienced a higher level of mental stress. In this study, there was an increasing tendency to a 3-month follow-up period in the cumulative incidence of new-onset and relapse herpesviral keratitis following both mRNA and non-mRNA type vaccines.

Our study has a strength in that we had a relative risk analysis through the comparison with the unvaccinated control group in a large population.

This study has a number of limitations. First, the analysis relied solely on a single disease code (H191), raising the potential for an overestimation of herpes keratitis. Second, our study was limited by the inability to differentiate herpesvirus subtypes (HSV, VZV, EBV, and CMV). Third, the cases reported to NHIS data are limited to South Korea where 4 vaccines, BNT162b2, mRNA-1273, ChAdOx-1nCoV-19, and Ad26.COV2.S, are approved for use. Therefore, herpesviral keratitis after vaccination with Convidecia, Sputnik, Sinopharm, Zifivax, and Novavax could not be evaluated. Fourth, the severity and complication of herpesviral keratitis could not be identified in the study. Finally, unfortunately, the database we used did not contain detailed clinical information; therefore, we were not able to use other lifestyle factors for analysis in this study.

In conclusion, based on the extensive NHIS database analysis, it is indicated that all authorized COVID-19 vaccines in South Korea may lead to the reactivation of herpesviruses when compared with the control group. While vaccination plays a crucial role in managing the COVID-19 pandemic, ophthalmologists should be aware of the potential for herpesvirus reactivation following vaccination. Providing patients at risk with the optimal prophylaxis and treatment is essential.


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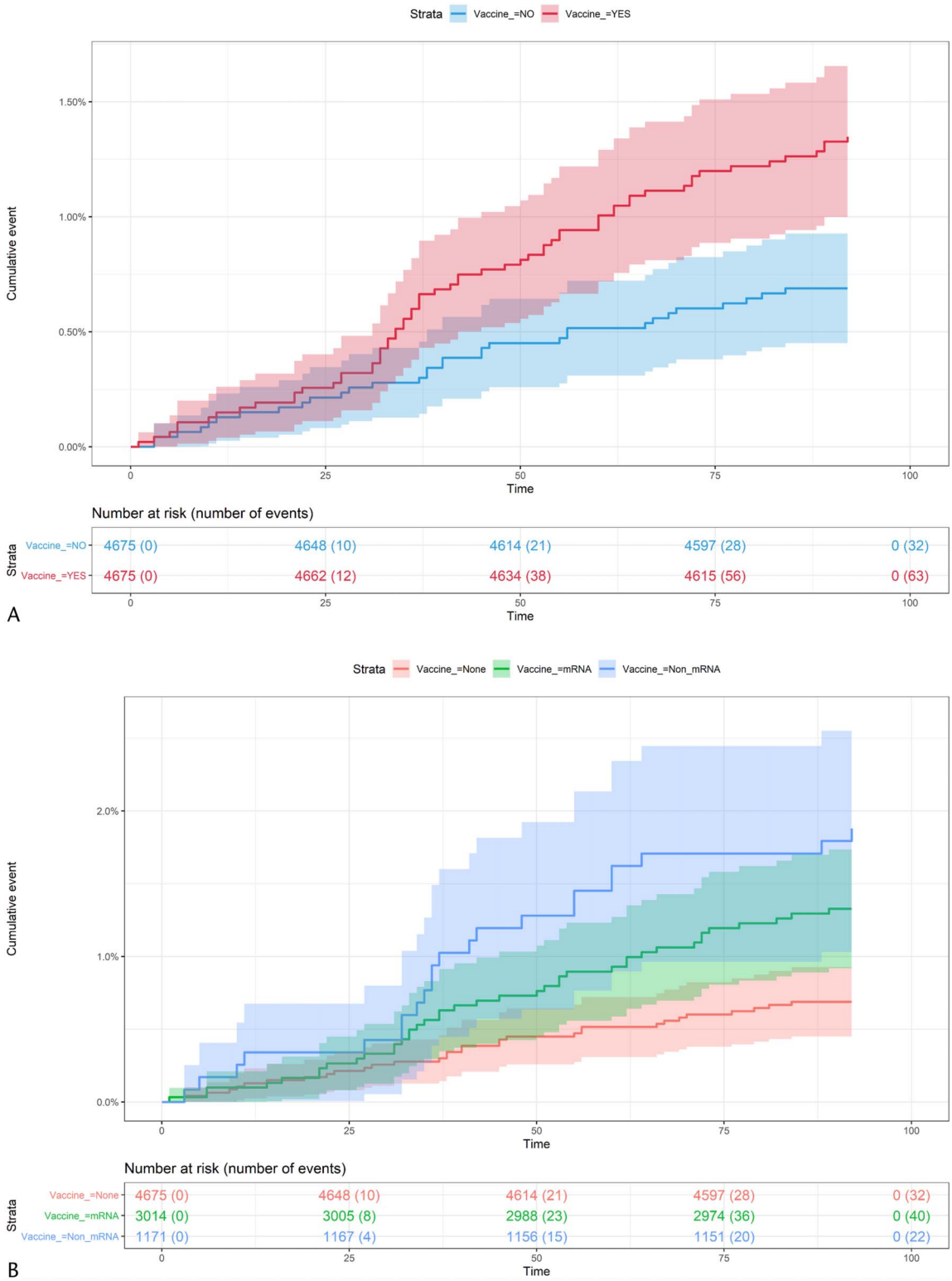


**FIGURE 5.** A, Cumulative incidence of relapse herpesviral keratitis according to COVID-19 vaccination. B, Cumulative incidence of relapse herpesviral keratitis according to COVID-19 vaccine type.

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**TABLE 7.** Risk Factor for the Development of Relapse Herpesviral Keratitis With or Without COVID-19 Vaccination

| | N | Incident Cases of Herpesviral Keratitis | Incidence per 10,000 | Univariable Analysis | | Multivariable Analysis | |
|---|---|---|---|---|---|---|---|
| | | | | Unadjusted HR | 95% CI | Adjusted HR* | 95% CI |
| Age, yr | | | | | | | |
| 40–49 | 1478 | 16 | 431.77 | Reference | | Reference | |
| ~19 | 626 | 8 | 510.67 | 1.18 | 0.51–2.76 | 1.20 | 0.51–2.81 |
| 20–29 | 1104 | 12 | 434.03 | 1.01 | 0.48–2.13 | 1.02 | 0.48–2.16 |
| 30–39 | 2068 | 18 | 347.48 | 0.81 | 0.41–1.58 | 0.81 | 0.41–1.59 |
| 50–59 | 1047 | 11 | 419.80 | 0.97 | 0.45–2.10 | 0.94 | 0.43–2.04 |
| 60–69 | 1466 | 18 | 491.88 | 1.14 | 0.58–2.23 | 1.07 | 0.52–2.16 |
| 70~ | 1561 | 12 | 311.60 | 0.72 | 0.34–1.52 | 0.65 | 0.28–1.48 |
| Sex | | | | | | | |
| Female | 4751 | 43 | 361.74 | Reference | | Reference | |
| Male | 4599 | 52 | 453.72 | 1.25 | 0.84–1.88 | 1.23 | 0.82–1.85 |
| Economic status | | | | | | | |
| High | 3198 | 33 | 413.79 | Reference | | Reference | |
| Low | 6152 | 62 | 403.31 | 0.97 | 0.64–1.49 | 0.99 | 0.65–1.51 |
| Residential area | | | | | | | |
| Middle and small cities | 2235 | 18 | 322.23 | Reference | | Reference | |
| Metropolitan cities | 6544 | 72 | 440.67 | 1.37 | 0.82–2.29 | 1.41 | 0.84–2.36 |
| Rural areas | 571 | 5 | 351.36 | 1.09 | 0.40–2.94 | 1.11 | 0.41–3.00 |
| Hypertension, yes | | | | | | | |
| No | 7072 | 72 | 407.01 | Reference | | Reference | |
| Yes | 2278 | 23 | 406.51 | 1.00 | 0.62–1.60 | 0.93 | 0.50–1.70 |
| Diabetes mellitus, yes | | | | | | | |
| No | 7752 | 76 | 391.85 | Reference | | Reference | |
| Yes | 1598 | 19 | 480.71 | 1.23 | 0.74–2.03 | 1.32 | 0.72–2.40 |
| Chronic kidney disease, yes | | | | | | | |
| No | 9062 | 91 | 402.08 | Reference | | Reference | |
| Yes | 288 | 4 | 558.96 | 1.39 | 0.51–3.78 | 1.36 | 0.47–3.95 |

Data are presented as HR (95% CIs).
*Adjusted for age, sex, economic status, residential area, and comorbidities (HTN, DM, CKD).

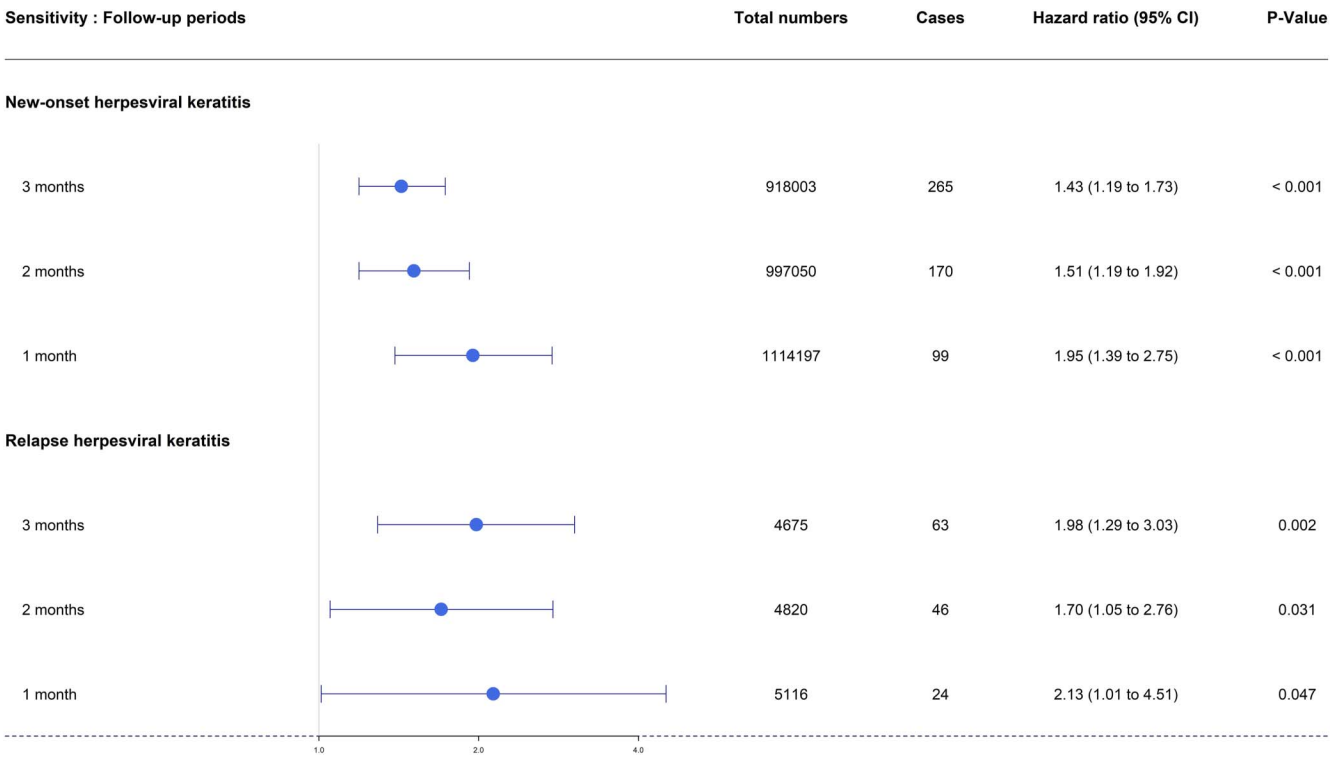


**FIGURE 6.** Sensitivity analysis.


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## REFERENCES


1. Pormohammad A, Zarei M, Ghorbani S, et al. Efficacy and safety of COVID-19 vaccines: a systematic review and meta-analysis of randomized clinical trials. *Vaccines (Basel)*. 2021;9:467.
2. Huang LY, Chiang CC, Li YL, et al. Corneal complications after COVID-19 vaccination: a systemic review. *J Clin Med*. 2022;11:6828.
3. Haseeb AA, Solyman O, Abushanab MM, et al. Ocular complications following vaccination for COVID-19: a one-year retrospective. *Vaccines (Basel)*. 2022;10:342.
4. Wang MT, Niederer RL, McGhee CN, et al. COVID-19 vaccination and the eye. *Am J Ophthalmol*. 2022;240:79–98.
5. Shafiee A, Amini MJ, Arabzadeh Bahri R, et al. Herpesviruses reactivation following COVID-19 vaccination: a systematic review and meta-analysis. *Eur J Med Res*. 2023;28:278.
6. Navarro-Bielsa A, Gracia-Cazaña T, Aldea-Manrique B, et al. COVID-19 infection and vaccines: potential triggers of Herpesviridae reactivation. *An Bras Dermatol*. 2023;98:347–354.
7. Shafiee A, Teymouri Athar MM, Amini MJ, et al. Reactivation of herpesviruses during COVID-19: a systematic review and meta-analysis. *Rev Med Virol*. 2023;33:e2437.
8. Singh RB, Parmar UPS, Ichhpujani P, et al. Herpetic eye disease after SARS-CoV-2 vaccination: a CDC-VAERS database analysis. *Cornea*. 2023;42:731–738.
9. Kuziez L, Eleiwa TK, Chauhan MZ, et al. Corneal adverse events associated with SARS-CoV-2/COVID-19 vaccination: a systematic review. *Vaccines (Basel)*. 2023;11:166.
10. Gringeri M, Battini V, Cammarata G, et al. Herpes zoster and simplex reactivation following COVID-19 vaccination: new insights from a vaccine adverse event reporting system (VAERS) database analysis. *Expert Rev Vaccines*. 2022;21:675–684.
11. Yoon JG, Kim YE, Choi MJ, et al. Herpes zoster reactivation after mRNA and adenovirus-vectored coronavirus disease 2019 vaccination: analysis of national health insurance database. *J Infect Dis*. 2023;228:1326–1335.
12. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70:41–55.
13. Gu XS, Rosenbaum PR. Comparison of multivariate matching methods: structures, distances, and algorithms. *J Comput Graph Stat*. 1993;2:405–420.
14. Whitley RJ, Roizman B. Herpes simplex virus infections. *Lancet*. 2001; 357:1513–1518.
15. Liesegang TJ. Herpes zoster ophthalmicus. Natural history, risk factors, clinical presentation, and morbidity. *Ophthalmology*. 2008;115:S3–S12.
16. Katsikas Triantafyllidis K, Giannos P, Mian IT, et al. Varicella zoster virus reactivation following COVID-19 vaccination: a systematic review of case reports. *Vaccines (Basel)*. 2021;9:1013.
17. Amon W, Farrell PJ. Reactivation of Epstein-Barr virus from latency. *Rev Med Virol*. 2005;15:149–156.
18. Mendelson M, Monard S, Sissons P, et al. Detection of endogenous human cytomegalovirus in CD34+ bone marrow progenitors. *J Gen Virol*. 1996;77(Pt 12):3099–3102.
19. Crooke SN, Ovsyannikova IG, Poland GA, et al. Immunosenescence and human vaccine immune responses. *Immun Ageing*. 2019;16:25.
20. Bostan E, Yalici-Armagan B. Herpes zoster following inactivated COVID-19 vaccine: a coexistence or coincidence? *J Cosmet Dermatol*. 2021;20:1566–1567.
21. Sahin U, Muik A, Vogler I, et al. BNT162b2 vaccine induces neutralizing antibodies and poly-specific T cells in humans. *Nature*. 2021;595:572–577.
22. Cohen S, Olshaker H, Fischer N, et al. Herpetic eye disease following the SARS-CoV-2 vaccinations. *Ocul Immunol Inflamm*. 2023;31:1151–1162.
23. Liu J, Wang J, Xu J, et al. Comprehensive investigations revealed consistent pathophysiological alterations after vaccination with COVID-19 vaccines. *Cell Discov*. 2021;7:99.
24. Hviid A, Hansen JV, Frisch M, et al. Measles, mumps, rubella vaccination and autism. *Ann Intern Med*. 2019;171:388.


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