Neuro-Ophthalmic Adverse Events of COVID-19 Infection and Vaccines: A Nationwide Cohort Study

Jae Yong Han,[1] Sunyeup Kim,[2] Jinu Han,[1] Sung Soo Kim,[1] Sueng-Han Han,[1] Seung Won Lee,[3] and Yong Joon Kim[1]

[1]Department of Ophthalmology, Institute of Vision Research, Yonsei University College of Medicine, Seoul, Republic of Korea
[2]Department of Medical AI, Sungkyunkwan University School of Medicine, Suwon, Republic of Korea
[3]Department of Precision Medicine, Sungkyunkwan University School of Medicine, Suwon, Republic of Korea

Correspondence: Seung Won Lee, Department of Precision Medicine, Sungkyunkwan University School of Medicine, Jangan-gu Seobu-ro 2066, Suwon 16419, Korea; lsw2920@gmail.com.
Yong Joon Kim, Department of Ophthalmology, Institute of Vision Research, Yonsei University College of Medicine, Seodaemungu Yonseiro 50-1, Seoul, Korea; kyjcolor@naver.com; kyjcolor@yuhs.ac.

JYH and SK equally contributed to this work as co-first authors.
SWL and YJK equally contributed to this work as co-corresponding authors.

Received: July 10, 2023
Accepted: November 3, 2023
Published: November 27, 2023

Citation: Han JY, Kim S, Han J, et al. Neuro-ophthalmic adverse events of COVID-19 infection and vaccines: A nationwide cohort study. *Invest Ophthalmol Vis Sci.* 2023;64(14):37. https://doi.org/10.1167/iovs.64.14.37

Purpose. To evaluate the association of COVID-19 infection and vaccination with neuro-ophthalmic adverse events.

Methods. In this nationwide population-based retrospective cohort study, 8,498,353 patients were classified into three groups: control, COVID-19 infection, and COVID-19 vaccination. We conducted separate analyses for the early phase (within 60 days) and late phases (61–180 days) to estimate the incidence rates and hazard ratio (HR) for each neuro-ophthalmic adverse event. The adverse events included in this analysis were optic neuritis, papilledema, ischemic optic neuropathy, third nerve palsy, fourth nerve palsy, sixth nerve palsy, facial palsy, nystagmus, ptosis, blepharospasm, anomalies of pupillary function, and Guillain-Barré syndrome/Miller Fisher syndrome (GBS/MFS).

Results. Neuro-ophthalmic adverse events other than ptosis and GBS/MFS exhibited no significant increase after COVID-19, and their incidence was extremely low. The incidence rate of ptosis in both phases was significantly higher in patients administered COVID-19 vaccination (HR = 1.65 in the early phase and HR = 2.02 in the late phase) than in the control group. Additionally, BNT162b2 conferred a lower ptosis risk than ChAdOx1. GBS/MFS had a significantly higher incidence rate in the early phase (HR = 5.97) in patients with COVID-19 infection than in the control group.

Conclusions. Ptosis was associated with COVID-19 vaccination, particularly with the ChAdOx1 vaccine, while GBS/MFS was associated with COVID-19 infection. In contrast, no association was found between other neuro-ophthalmic adverse events and COVID-19 infection or vaccination. These results may provide helpful insights for diagnosing and treating the neuro-ophthalmological adverse events after COVID-19.

Keywords: adverse events, COVID-19, COVID-19 vaccination, neuro-ophthalmology

SARS-CoV-2 caused an outbreak of an acute respiratory disease (COVID-19) in December 2019, which continues to affect people worldwide.[1,2] The World Health Organization declared the COVID-19 outbreak a global pandemic on March 11, 2020. Approximately 758 million COVID-19 cases and 6.8 million COVID-19-related deaths were globally reported as of March 2023, and at least one dose of a COVID-19 vaccine has been administered to >5.5 billion individuals worldwide. In South Korea, approximately 30 million COVID-19 cases have been confirmed, 34,000 COVID-19-related deaths have been reported, and 44.8 million people (approximately 87% of the total population) have received at least one dose of the vaccine.[3]

With the increasing number of infected individuals and vaccine recipients, a growing number of ocular adverse events, including neuro-ophthalmic adverse events, have been reported.[4–8] Multiple reports have suggested an association of COVID-19 with optic neuritis[9–11] and ophthalmoplegia related to third or sixth cranial nerve palsy.[12–18] Vaccine-related adverse events have also been reported.[19–23] However, whether COVID-19 infection and vaccination are directly related to neuro-ophthalmic adverse events is unclear.

We evaluated the correlation of COVID-19 infection and vaccination with neuro-ophthalmic adverse events using the 2016–2022 data in the Korean National Health Claim Database.

Methods

Data Source, Neuro-Ophthalmic Adverse Events, and COVID-19 Vaccines

In this retrospective population-based cohort study, we used the database of the Korea Disease Control and Prevention Agency (KDCA) and the Korean National Health Insurance Service (NHIS) for policy and academic research (KDCA-NHIS approval no. KDCA-NHIS-2022-1-624). The study was

approved by the Institutional Review Board of Severance Hospital (IRB No. 4-2023-0369) and was carried out according to the tenets of the Declaration of Helsinki. The need for informed consent was waived because of the retrospective nature of the study, which was based on de-identified data.

The data that were requested encompassed all individuals diagnosed with COVID-19 in the Republic of Korea between January 1, 2020, and December 31, 2021, as well as all individuals who received COVID-19 vaccinations from January 2021 to March 31, 2022. During this timeframe, around 0.5 million people were diagnosed with COVID-19, and approximately 44 million individuals were vaccinated against COVID-19. Because of the NHISS's policy limitations, the data provided for the vaccinated population had to be restricted to roughly 8.0 million individuals through random sampling. However, data for all individuals who were infected were provided. For our study, we analyzed the requested data for these patients from January 1, 2016, to March 31, 2022.

During the pandemic, the Korean government provided obligated and fully complemented healthcare services and insurance for all COVID-19 patients. The National Health Insurance Claims–based database contains demographics and data from inpatient and outpatient healthcare and pharmaceutical visits, prescriptions, diagnoses, and procedures.[24–26] Data regarding COVID-19 and COVID-19 vaccination were provide by the KCDA for research and policy use. The date of infection and the day of the first vaccination were used as index dates. Through a literature review, we identified neuro-ophthalmic complications reported in association with COVID-19 or COVID-19 vaccination and conducted an analysis on neuro-ophthalmic complications that can be specified using ICD-10 codes. Twelve predefined neuro-ophthalmic adverse events were included in this study: optic neuritis, papilledema, ischemic optic neuropathy, third nerve palsy, fourth nerve palsy, sixth nerve palsy, facial palsy, nystagmus, ptosis, blepharospasm, pupillary function anomalies, and Guillain-Barré syndrome/Miller Fisher syndrome (GBS/MFS). Furthermore, the underlying systemic diseases in the study cohort were investigated. The ICD-10 codes used in this study are presented in Supplementary Table S1.

Four COVID-19 vaccines were included in this study: BNT162b2 (Pfizer-BioNTech), ChAdOx1 (Oxford-AstraZeneca), mRNA-1273 (Moderna), and Ad26.COV2.S (Johnson & Johnson's Janssen).

Study Population and Exposures

The initial dataset included 8,498,353 eligible patients aged >18 years who were infected by COVID-19 or received COVID-19 vaccination between January 1, 2020, and January 31, 2022. Those without personal information (n = 945), who had been diagnosed with any neuro-ophthalmologic adverse events before the index date (n = 207,189), and whose primary vaccination date was not confirmed (n = 33,720) were excluded. Subjects with <60 days of follow-up were also excluded (n = 10,000). Finally, 8,246,499 patients were included in the analysis. Subsequently, these patients were classified into three groups: the control group included patients without any infections or vaccination (n = 2,647,634); the infection group included patients who had been infected with COVID-19 at least once during the entire period (n = 557,135); and the vaccination group included patients who had not been infected but who were administered the COVID-19 vaccination before September 2021 (n = 5,041,730) (Fig. 1). The control group comprised individuals who had neither been diagnosed with a COVID-19 infection nor received any vaccination from March 1, 2021, to August 31, 2021. However, these patients were vaccinated after September 1, 2021. Therefore the index date for the control group was set as 180 days before the day they received their first vaccine dose. The infection group consisted of patients with a history of COVID-19 infection, including those infected before (n = 192,980) or after (n = 237,020) vaccination. Furthermore, individuals infected on the same day as the vaccination day were also included (n = 5). The index date for the infection group was defined as the date of the initial confirmation of COVID-19 infection. The vaccination group comprised individuals who were vaccinated until August 31, 2021. The index date for the vaccination group was set as the date of receiving their first vaccine dose. This study exclusively analyzed data related to the initial vaccine dose. Those without a confirmed first vaccination were excluded (Fig. 1). Patients were observed from the respective index dates for up to a maximum of 180 days. Analyses were divided into an early phase with an observation period of less than 60 days and a late phase with an observation period of 61 to 180 days.

Primary and Secondary Outcomes

The primary outcome was the cumulative incidence and risks of 12 predefined neuro-ophthalmic adverse events (Supplementary Table S1). Comorbidity was confirmed when the ICD-10 code was identified more than twice during the follow-up, whereas the occurrence of adverse events was confirmed when the ICD-10 code was identified at least once during the follow-up. It is unlikely for the same code to be identified twice within a 180-day period because of the nature of adverse events.

We conducted an ad hoc analysis to explore the correlation between myasthenia gravis (MG; ICD-10: G70) and COVID-19 infection and vaccination because MG is a common cause of ptosis, which exhibited statistical significance in our study, and there have been recent reports on the association of MG with COVID-19 infection and vaccines.[18,19,27–29]

Statistical Analysis

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria). Baseline characteristics were reported as mean and standard deviation or frequency (percentage). Statistical significance was set at P value < 0.05. The cumulative incidence of neuro-ophthalmic adverse events was calculated using the Kaplan-Meier method. The hazard ratios (HRs) and 95% confidence intervals (CI) for each type of neuro-ophthalmic adverse event were calculated using Cox proportional hazards models. Cox model analysis was conducted separately for the early phase and late phase outcomes. HRs were adjusted by age, sex, presence of diabetic mellitus, hypertension, dyslipidemia, ischemic stroke, or myocardial infarction. With the control group as the reference, the adequacy of the proportional hazards assumption was confirmed using log minus-log survival plots with age, sex, diabetic mellitus, hypertension, dyslipidemia, ischemic stroke, and myocardial infarction as variables. Univariate analysis was performed for each variable to determine the risk factors related to diseases, and variables with

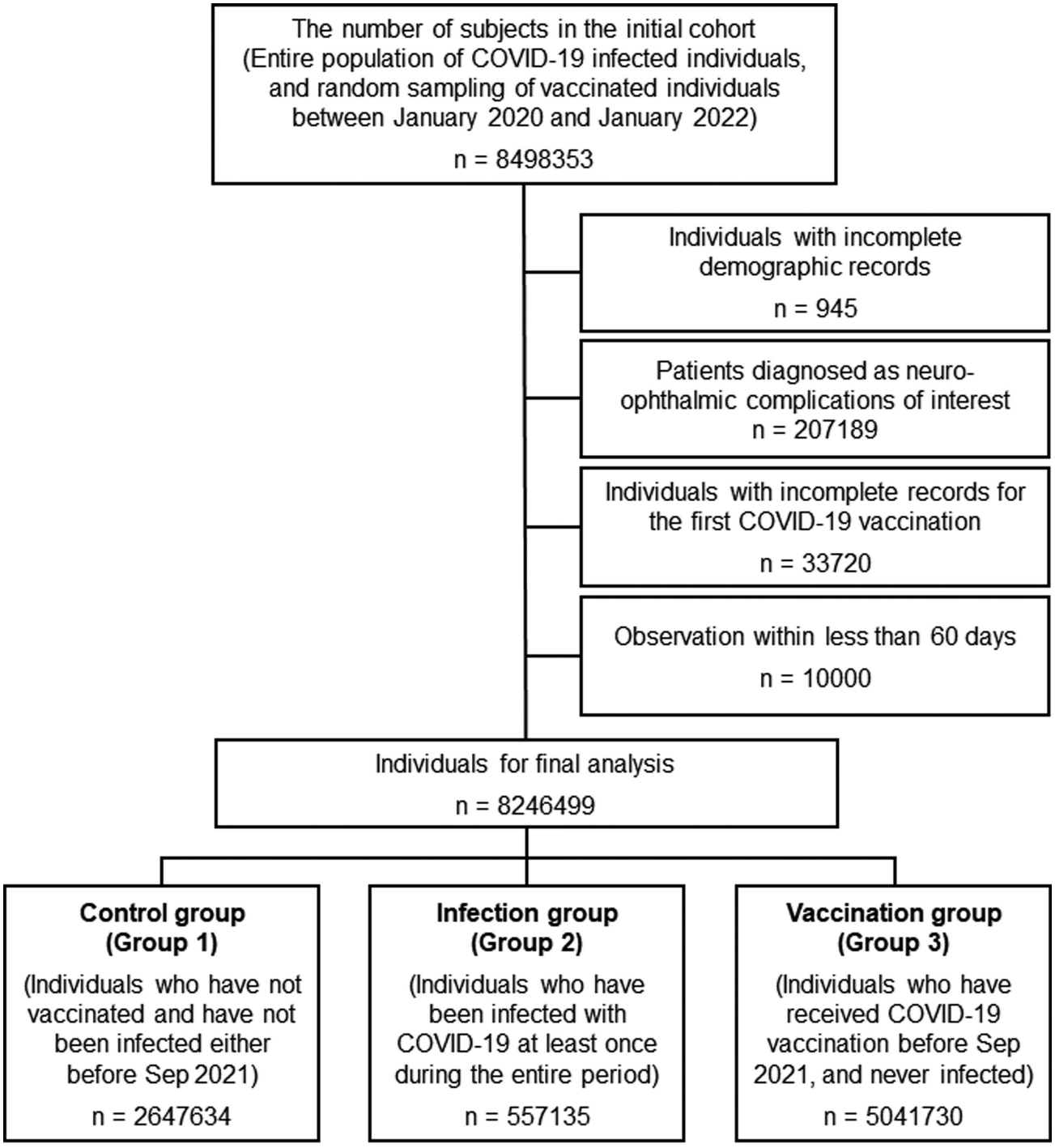

Figure 1. Diagram showing the flow of subjects in the current study.

P value < 0.1 in univariate analysis were included in the multivariate analysis.

Results

Demographics and Baseline Characteristics

The demographics and baseline characteristics of the study cohort are presented in the Table. The mean age of participants in the control, infection, and vaccination groups was 33.41 ± 13.32, 41.02 ± 21.24, and 54.03 ± 17.10 years, respectively. The proportion of men was the highest in the control group (53.1% vs. 51.6% vs. 48.5%). The socioeconomic status increased significantly from the control to the vaccination group, and the residential area differed significantly among the three groups. Furthermore, the proportion of participants with comorbidities increased significantly from the control to the vaccination group. The demographics of the vaccination group are presented according to the vaccine type in Supplementary Table S2. Among the

Investigative Ophthalmology & Visual Science

Table. Baseline Characteristics and Demographics of the Study Population

Demographic	Group 1 N = 2,647,634	Group 2 N = 577,135	Group 3 N = 5,041,730	*P* Value Group 1 Vs 2	*P* Value Group 1 Vs 3	*P* Value Group 2 Vs 3
Age (yr)	33.34 ± 13.26	41.02 ± 21.24	54.03 ± 17.10	<0.0001	<0.0001	<0.0001
<40	1,724,022 (65.12%)	263,216 (47.24%)	1,082,299 (21.47%)			
40–64	876,975 (33.12%)	211,421 (37.95%)	2,585,131 (51.27%)			
65–74	26,386 (1.00%)	55,773 (10.01%)	809,811 (16.06%)			
≥75	20,251 (0.76%)	26,725 (4.80%)	564,489 (11.20%)			
Sex				<0.0001	<0.0001	<0.0001
Male	1,405,924 (53.10%)	287,700 (51.64%)	2,443,542 (48.47%)			
Female	1,241,710 (46.90%)	269,435 (48.36%)	2,598,188 (51.53%)			
Socioeconomic status				<0.0001	<0.0001	<0.0001
High	1,020,600 (38.55%)	227,354 (40.81%)	2,213,813 (43.91%)			
Middle	898,258 (33.93%)	176,130 (31.61%)	1,446,352 (28.69%)			
Low	728,776 (27.53%)	153,651 (27.58%)	1,381,565 (27.40%)			
Residence				<0.0001	<0.0001	<0.0001
Urban	1,163,375 (43.94%)	296,637 (53.24%)	2,202,165 (43.68%)			
Rural	1,484,259 (56.06%)	260,498 (46.76%)	2,839,565 (56.32%)			
Systemic diseases						
Hypertension	192,229 (7.26%)	117,177 (21.03%)	1,683,638 (33.39%)	<0.0001	<0.0001	<0.0001
Diabetes	164,239 (6.20%)	95,030 (17.06%)	1,239,751 (24.59%)	<0.0001	<0.0001	<0.0001
Dyslipidemia	422,509 (15.96%)	182,172 (32.70%)	2,342,384 (46.46%)	<0.0001	<0.0001	<0.0001
Ischemic stroke	13,452 (0.51%)	12,622 (2.27%)	175,321 (3.48%)	<0.0001	<0.0001	<0.0001
Transient ischemic attack	5597 (0.21%)	4504 (0.81%)	67,347 (1.34%)	<0.0001	<0.0001	<0.0001
Hemorrhagic stroke	4093 (0.15%)	2631 (0.47%)	26,819 (0.53%)	<0.0001	<0.0001	<0.0001
Myocardial infarction	6761 (0.26%)	4826 (0.87%)	60,704 (1.20%)	<0.0001	<0.0001	<0.0001
Chronic kidney disease	11,786 (0.45%)	7891 (1.42%)	99,357 (1.97%)	<0.0001	<0.0001	<0.0001
Malignancy	72,091 (2.72%)	34,752 (6.24%)	458,332 (9.09%)	<0.0001	<0.0001	<0.0001
Hyperthyroidism	33,059 (1.25%)	9410 (1.69%)	115,574 (2.29%)	<0.0001	<0.0001	<0.0001
Hypothyroidism	78,612 (2.97%)	29,925 (5.37%)	336,590 (6.68%)	<0.0001	<0.0001	<0.0001
Chronic liver disease	121,130 (4.58%)	47,154 (8.46%)	564,063 (11.19%)	<0.0001	<0.0001	<0.0001
COPD	12,231 (0.46%)	8625 (1.55%)	124,486 (2.47%)	<0.0001	<0.0001	<0.0001

N, numbers; yr, years; SD, standard deviation; COPD, chronic obstructive pulmonary disease.
Data are presented as mean ± standard deviation or frequency (percent).

5,041,730 individuals in the vaccination group, 1,887,870 (37.4%), 2,534,990 (50.3%), 413,862 (8.2%), and 205,008 (4.1%) had been administered the ChAdOx1, BNT162b2, mRNA-1273, and Ad26.COV2.S vaccines, respectively. The number of people vaccinated with each vaccine type varied because of the timing of vaccine development and issues related to supply and distribution in South Korea. Additionally, ChAdOx1 and BNT162b2 vaccines, whose supply was initiated relatively early, were more often administered to older individuals because of the policy of initiating vaccine administration for older individuals. These differences in age distribution were also reflected in the comorbidity ratio (Supplementary Table S2).

Association of COVID-19 Infection and Vaccination With Neuro-Ophthalmic Adverse Events

The cumulative incidence rates of each neuro-ophthalmic adverse event from the index date to 180 days of follow-up are presented in Supplementary Table S3. The Kaplan—Meier curves of each event are provided in Supplementary Figure S1. The HR of each adverse event was analyzed using a multivariable Cox proportional hazards model, based on the follow-up duration (early and late phases). Several conditions showed an increased incidence rate in the infection and vaccination groups compared to the control group during the early phase. However, only ptosis in the vaccination group (HR = 1.65 [95% CI, 1.23–2.21]; $P < 0.001$) and GBS/MFS in the infection group (HR = 5.97 [95% CI, 2.17–16.43]; $P < 0.001$) demonstrated a statistically significant increase (Fig. 2). In the late phase, as in the early phase, the vaccination group showed a significant increase in the ptosis incidence rate (HR = 2.02 [95% CI, 1.63–2.49], $P < 0.001$), whereas for GBS/MFS, no significant differences were seen among groups. Additionally, in the late phase, the infection group showed a significantly higher facial palsy incidence rate (HR = 0.61 [95% CI, 0.48–0.77]; $P < 0.001$) (Supplementary Fig. S2).

We further incorporated all the demographic variables in an analysis. Although minor numerical differences were found as compared to the above analysis, the statistically significant results remained (Supplementary Figures S3 and S4).

Multivariable Cox proportional hazards models revealed differences in the incidence rates and HRs between men and women. In the infection group, during the early phase, only GBS/MFS showed a significantly increased HR relative to the control group for both men (HR = 5.63 [95% CI, 1.62–19.55]) and women (HR = 6.53 [95% CI, 1.14–37.42]). In the late phase, only facial palsy showed a significant decrease in HR for both men (HR = 0.58 [95% CI, 0.42–0.81]) and women (HR = 0.63 [95% CI, 0.45–0.87]). In the vaccination group, during the early phase, the ptosis HR was significantly increased compared to the control group in both men (HR = 1.58 [95% CI: 1.04–2.42]) and women (HR = 1.68 [95% CI, 1.12–2.53]), whereas papilledema showed a signifi-

Investigative Ophthalmology & Visual Science

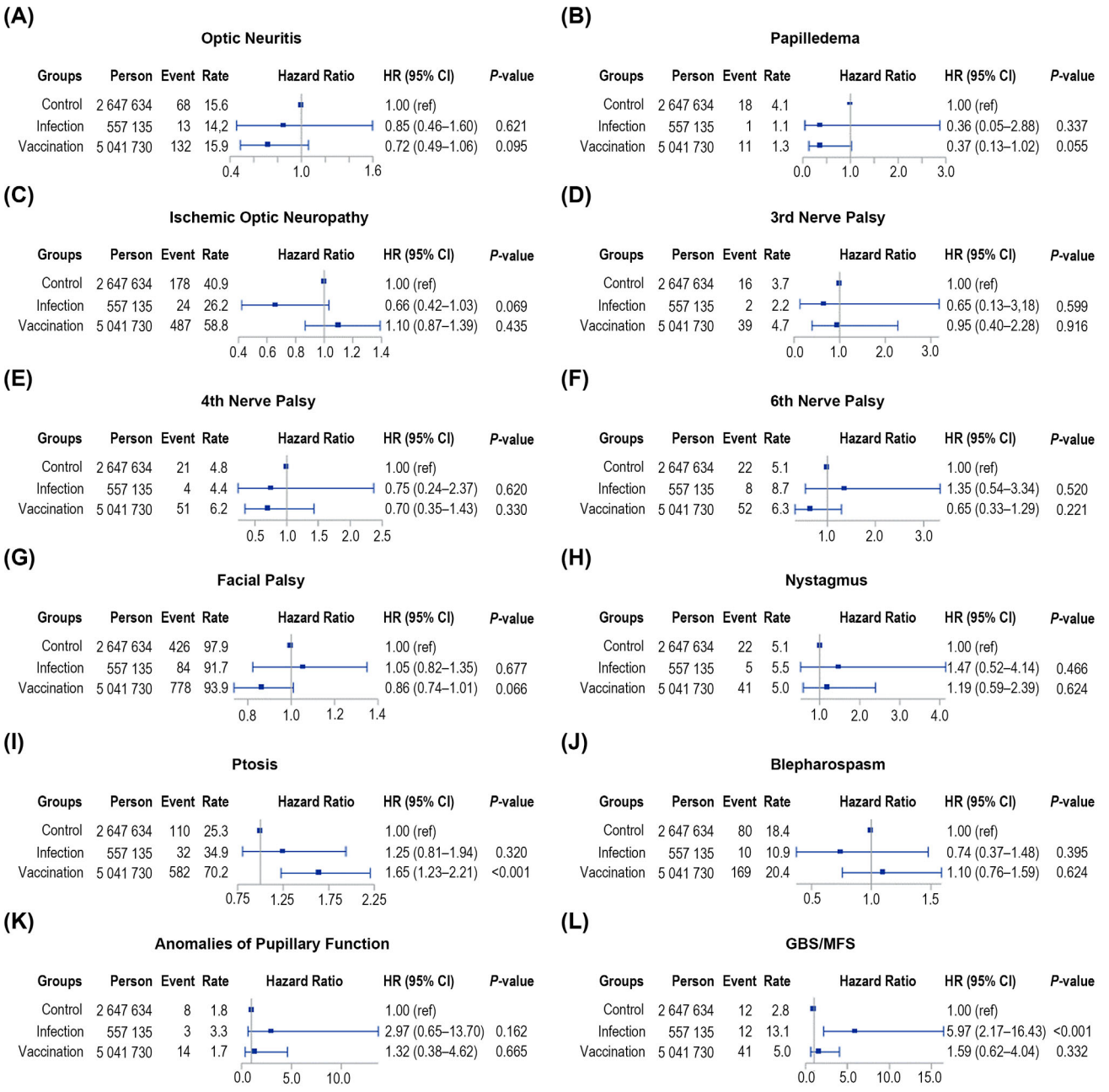

Figure 2. Risks of neuro-ophthalmic complications within 60 days of follow-up in the study groups. The Cox model was adjusted for age, sex, presence of diabetic mellitus, hypertension, dyslipidemia, ischemic stroke, or myocardial infarction. Rate, incidence rate per 100,000 person-years; ref, reference.

cant decrease in HR (HR = 0.20 [95% CI, 0.06–0.69]). In the late phase, ptosis still showed a significant increase in HR in both men (HR = 2.05 [95% CI, 1.48–2.84]) and women (HR = 1.93 [95% CI, 1.47–2.55]), whereas the HR for third nerve palsy was significantly decreased in women (HR = 0.37 [95% CI, 0.14–0.99]).

Association of Ptosis, Myasthenia Gravis, and Guillain-Barré Syndrome/Miller Fisher Syndrome With COVID-19

In the previous analyses, three conditions showed significantly increased HRs and incidence rates in the infection and vaccination groups compared to that in the control group. Considering the number of actual events, only ptosis and GBS/MFS were significantly increased in the COVID-19 vaccinated group (Fig. 2 and Supplementary Fig. S2). Therefore the association between the increased incidence of these two diseases and the vaccine type was evaluated. Multivariable Cox proportional hazards models indicated that the ChAdOx1 vaccine was strongly associated with ptosis: the incidence rate was 97.00 (HR = 1.71 [95%CI, 1.26–2.32]) in the early phase and 113.6 (HR = 2.55 [95% CI, 2.05–3.17]) in the late phase (Fig. 3). Throughout the entire follow-up period, the ptosis incidence rate was higher for all vaccine groups except the Ad26.COV2.S group than in the control group. Unlike ptosis, only individuals who

Investigative Ophthalmology & Visual Science

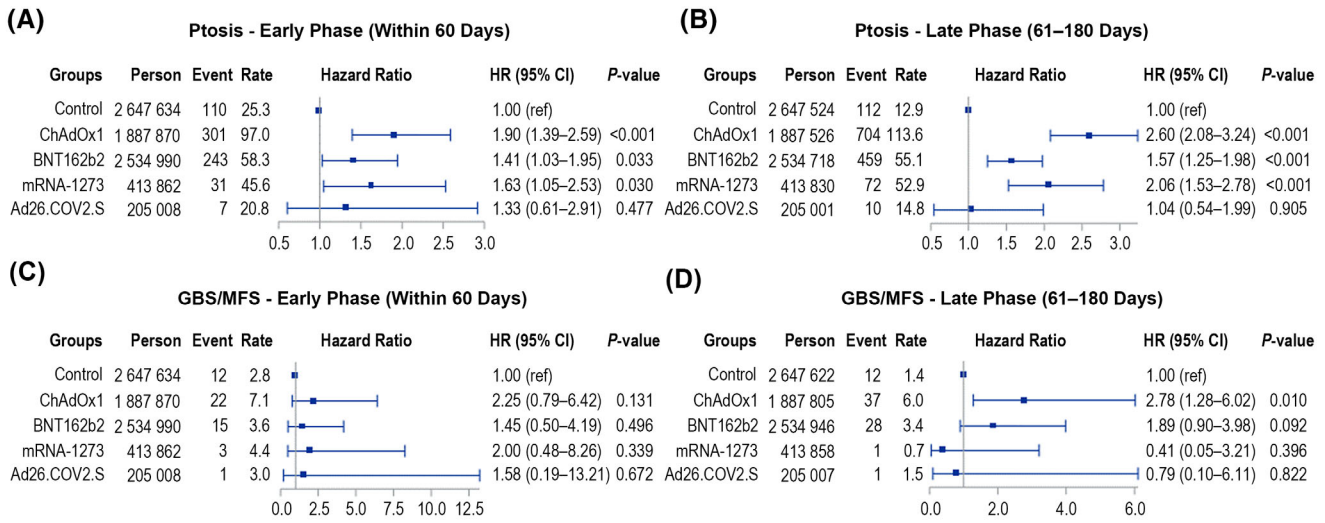

Figure 3. Risks of ptosis and GBS/MFS in patients with COVID-19 vaccination according to the vaccine type. Risk of ptosis in the (**A**) early phase and (**B**) late phase. Risk of GBS/MFS in the (**C**) early phase and (**D**) late phase. Rate, incidence rate per 100,000 person-years; ref, reference.

received the ChAdOx1 vaccine showed a statistically significant increase in GBS/MFS in the late phase (Fig. 3).

Furthermore, the ptosis risk factors were additionally analyzed by multivariate analysis (Supplementary Table S4). Before 60 days, age, socioeconomic status, residence, and history of diabetic mellitus and dyslipidemia showed a significant association with ptosis. The risk increased with age (HR = 1.04 [95% CI, 1.03–1.05]; $P < 0.001$) and was higher for individuals with middle (HR = 1.26 [95% CI, 1.03–1.55]; $P = 0.022$) and low (HR = 1.23 [95% CI, 1.01–1.50]; $P = 0.036$) socioeconomic status than for those with a high income. The risk was higher for those living in urban areas than for those living in rural areas (HR = 0.81 [95% CI, 0.69–0.95]; $P = 0.011$) and for those with underlying diabetes (HR = 1.30 [95% CI, 1.07–1.57]; $P = 0.008$) and dyslipidemia (HR = 1.41 [95% CI, 1.13–1.76]; $P = 0.003$). The risk associated with different vaccine types was also assessed using the ChAdOx1 vaccine as reference. BNT162b2 posed a significantly lower risk of ptosis than did ChAdOx1 (HR = 0.75 [95% CI, 0.63–0.89]; $P = 0.001$).

Although age (HR = 1.04 [95% CI, 1.03–1.04]; $P < 0.001$), residence (HR = 0.86 [95% CI, 0.77–0.96]; $P = 0.009$), dyslipidemia history (HR = 1.41 [95% CI, 1.21–1.63]; $P < 0.001$), and BNT162b2 vaccination (HR = 0.61 [95% CI, 0.54–0.68]; $P < 0.001$) were associated similarly with ptosis in the early phase, the increased risk in socioeconomic status and history of diabetes mellitus was not. Furthermore, Ad26.COV2.S showed a significant association with ptosis (HR = 0.41 [95% CI, 0.22–0.77]; $P = 0.006$). Additionally, women had a significantly higher risk (1.24 times) than men (HR = 1.24 [95% CI, 1.11–1.40]; $P < 0.001$). Risk was significantly higher among patients with hypertension (HR = 1.17 [95% CI, 1.02–1.34]; $P = 0.024$), hypothyroidism (HR = 1.27 [95% CI, 1.06–1.51]; $P = 0.009$), and rheumatic diseases (HR = 1.25 [95% CI, 1.06–1.48]; $P = 0.009$) (Supplementary Table S4).

We further analyzed the association of MG with COVID-19 infection and vaccination, but found no significant increase when compared to the control group (Supplementary Fig. S5).

GBS/MFS incidence showed the greatest increase in the infection group relative to the control group. Multivariate analysis was used to identify the risk factors. Among the various factors, only hypothyroidism history (HR = 4.22 [95% CI, 1.12–15.90]; $P = 0.033$) was a statistically significant factor in the early phase, and only chronic kidney disease history was a statistically significant factor in the late phase (HR = 10.10 [95% CI, 1.24–81.70]; $P = 0.031$).

Discussion

Various studies have been published on neuro-ophthalmologic adverse events associated with COVID-19; however, several of these involved case reports, and analytical studies have been limited in confirming accurate associations by their small sample sizes. Our study was a nationwide, population-based study, which facilitated further confirmation of the associations observed in previous studies. For COVID-19 infection and vaccination, the incidence rate and risk of the majority of neuro-ophthalmic adverse events were low, showing minimal differences compared to the control group. For instance, no statistically significant difference was observed between COVID-19 infection, vaccination, and control groups for optic neuritis, in agreement with a recent paper that found no association between optic neuritis and vaccination.[30] However, some of the adverse events exhibited a higher incidence in the infection or vaccination groups than in the control group, with ptosis and GBS/MFS showing a statistically significant increase in incidence when considering the differences in incidence rates and the number of events.

Ptosis had a higher incidence rate in the vaccination, but not in the infection group, than in the control group. Particularly, its incidence rate was higher after 60 d than within 60 d (Fig. 2I and Supplementary Fig. S2I). Ptosis is commonly induced by third nerve palsy. However, this risk, as indicated by an HR <1 in the infection and vaccination groups, was not higher than that in the control group (Fig. 2D and Supplementary Fig. S2D).

We also assessed MG as another condition that can lead to ptosis. MG is an autoimmune disease where antibodies against the nicotinic acetylcholine receptors in the neuro-

Investigative Ophthalmology & Visual Science

muscular junction are produced, inducing fatigable muscle weakness, such as ptosis.[18,31,32] Occurrence of MG after COVID-19 infection or vaccination has been reported in several studies,[18,27–29,31] but the small sample size in these studies hampered conclusions of a direct correlation. We found no statistically significant association between COVID-19 infection and MG during the early phase, while during the late phase, COVID-19 infection was associated with a reduced MG risk (Supplementary Fig. S5). It is widely acknowledged that viral or bacterial infections can trigger myasthenic crises in individuals with pre-existing MG. However, no clear consensus exists on whether MG incidence is higher in COVID-19 patients.[18] Similar to previous studies on the relationship between general infections and MG, we found no association between COVID-19 infection and MG onset. Similar to the infection group, the MG incidence rate was not significantly increased in the vaccination group.

Given the above, the increased ptosis frequency in this study needs to be interpreted differently. The order of the cumulative incidence of ptosis in this study was vaccination group, infection group, and control group (Supplementary Fig. S1I), consistent with the order of mean age among these groups (Table). The prevalence of underlying diseases also showed significant increases, following the same order as age, across the three groups. Ptosis is generally more prevalent in older adults; therefore the difference in incidence is likely due to age rather than COVID-19, as with other comorbidities. Additionally, patients with pre-existing ptosis may have become aware of their condition after COVID-19 infection or vaccination. Therefore additional studies are necessary to clarify the association between ptosis and COVID-19 infection.

GBS/MFS also showed a higher incidence rate in COVID-19 patients. Several case reports and studies on GBS after COVID-19 infection and vaccination have been published.[33–36] MFS is a GBS subtype. GBS is an immune-mediated postinfectious syndrome that affects peripheral nerves and their roots. This is a consequence of molecular mimicry caused by viral or bacterial infection, leading to the production of anti-ganglioside antibodies that attack proteins expressed on the axon membrane. A significant association is suggested to exist between COVID-19 and GBS, including MFS, given the disease epidemiology and symptom pathogenesis.[35] Similarly, we found a significantly higher HR and incidence rate in the infection than in the control group, with incidence rates of 13.1 per 100,000 person-years within 60 days. These results were higher than the previously reported incidence rates of GBS (1.1–1.8 per 100,000 person-years).[37] Considering that MFS is a GBS subtype, this incidence is extremely high. This suggests that the COVID-19 infection influences MFS development, as suggested by several previous studies, and is predictable considering MFS pathogenesis. Furthermore, in this study, significant results were observed only in the early phase, with no significant differences in the late phase. This aligns with the typical onset of GBS/MFS, which usually occurs within four weeks after the predisposing infection. This was also evident in the cumulative incidence rate, which exhibited a significant increase until approximately 4 weeks, after which it remained relatively stable (Supplementary Fig. S1L). Therefore the risk factors for GBS/MFS in patients with COVID-19 (age [HR =1.04 {95% CI, 1.00–1.08}; $P = 0.043$] and hypothyroidism history [HR = 4.22 {95% CI, 1.12–15.90} $P = 0.033$]) identified in the early phase of follow-up are likely to be valid.

Throughout the entire follow-up period, the vaccination and control groups showed no significant differences in GBS/MFS (Fig. 2L and Supplementary Fig. S2L). In the subanalyses based on vaccine types, during the early phase, no vaccines showed a significant difference compared to the control group. In the late phase, only ChAdOx1 exhibited a significant difference compared to the control group, whereas the other vaccines showed no significant differences. Although ChAdOx1 showed significant results in the late phase, considering GBS/MFS onset, the association with vaccination is unlikely to be significant. A recent report on the association between COVID-19 vaccines and GBS using the US vaccine Adverse Event Reporting System[38] confirmed findings similar to that of our study. In that report, the portion of Ad26.COV2.S among the administered vaccines was only 3.7%; however, the GBS incidence was 27.8% in all cases, compared to 35.3% and 36.3% for BNT162b2 and mRNA-1273, respectively. This represents a nine- to 12-fold increase in reported GBS after Ad26.COV2.S as compared to BNT162b2 or mRNA-1273. Compared to the expected incidence, the difference between the BNT162b2 and mRNA-1273 vaccines was insignificant, whereas a two- to three-fold higher incidence was found in patients administered the Ad26.COV2.S than in those administered other vaccines.[38] The aforementioned study showed a significant association of GBS with Ad26.COV2.S. This was in contrast to our findings, which is likely because of the significantly lower number of patients who received mRNA-1273 and Ad26.COV2.S in our study than those who received other vaccines. As MFS is a GBS subtype and has similar pathogenesis, it would show similar results to those of GBS.

The strengths of this study are its large sample size and nationwide estimates representing the entire Korean population. This enabled us to focus on identifying the incidence of individual diseases, rather than relying on previously published case reports and studies involving clinical patterns. However, this study has several limitations. First, there are some limitations inherent to the data per se. Analyzing information not registered in the database was impossible. For example, the clinical characteristics of neuro-ophthalmologic adverse events in patients with COVID-19 cannot be determined because the clinical presentation of each patient is not registered in the database. Additionally, the ICD-10 codes for identifying diagnoses in this study were not fully representative of the adverse events. We attempted using the ICD-10 codes comprising a single disease as much as possible; however, in some cases, such as in GBS/MFS, individual GBS subtypes are grouped under a single ICD-10 code and were unavoidably included. Furthermore, the baseline characteristics of each group were heterogeneous, largely due to the way we defined the control group and the vaccine supply of South Korea. In principle, the control group should consist of individuals who are uninfected and simultaneously unvaccinated. However, because >98% of adults in South Korea have been vaccinated, a potential for bias existed during the analysis because of the limited sample size of the control group. Therefore, in our study, the control group comprised individuals who were not infected at the outset but who subsequently received the vaccine, which led to a relatively higher proportion of younger than older patients, leading to a substantial difference in age among groups. Additionally, the shortage in the global vaccine supply in the early

Investigative Ophthalmology & Visual Science

stages of vaccine distribution led to more relatively older patients receiving vaccinations early during the pandemic course, leading to a higher proportion of older patients than younger patients in the vaccination group. Multivariate Cox analysis, using all the demographic variables included in this study, was conducted to address these biases, and the results obtained remained consistent with those obtained from the pre-adjusted analysis. However, it is possible that the Cox analysis may not have been adequately adjusted. Therefore conducting additional research using cohort matching could provide a more definitive confirmation of the results. Moreover, ChAdOx1 was distributed relatively earlier than the other vaccines at the beginning of the pandemic and was mainly distributed to military personnel in South Korea. Therefore groups administered the ChAdOx1 vaccine were younger and more male dominated than those administered other vaccines. Finally, this study was conducted exclusively in South Korea with a relatively homogenous population; therefore our findings may not be generalizable to other populations worldwide.

In conclusion, we found no association between neuro-ophthalmic adverse events other than ptosis and GBS/MFS with COVID-19 infection or COVID-19 vaccination. However, we found a higher incidence rate of ptosis in patients who were vaccinated against COVID-19 than in those without vaccination. Additionally, patients diagnosed with COVID-19 had significantly higher incidence rates of GBS/MFS. Although the COVID-19 pandemic is being brought under control, several patients still suffer from infection and vaccine sequelae. Our findings may help clinicians to diagnose and treat the adverse events related to COVID-19 infection and vaccination.

Acknowledgments

This study used the database of the Korea Disease Control and Prevention Agency (KDCA) and the National Health Insurance Service (NHIS, for policy and academic research). The research number of this study is KDCA-NHIS-2022-1-624.

Supported by the Basic Science Research Program through the National Research Foundation (NRF) of Korea and funded by the Ministry of Education (2022R1I1A1A01059209). Also supported by a faculty research grant from Yonsei University College of Medicine (6-2022-0067). The funding organization had no role in the design or conduct of this research.

Disclosure: **J.Y. Han**, None; **S. Kim**, None; **J. Han**, None; **S.S. Kim**, None; **S.-H. Han**, None; **S.W. Lee**, None; **Y.J. Kim**, None

References

1. Guan W-J. Clinical characteristics of coronavirus disease in China. *N Eng J Med.* 2019;2020(382):1708.
2. Peeri NC, Shrestha N, Rahman MS, et al. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? *Int J Epidemiol.* 2020;49(3):717–726.
3. Organization WH. *World Health Organization (WHO) Coronavirus (COVID-19) Dashboard (2022)*. World Health Organization, URL: https://covid19.who.int/. (Accessed: February 28, 2022). 2022.
4. Dockery DM, Rowe SG, Murphy MA, Krzystolik MG. The ocular manifestations and transmission of COVID-19: recommendations for prevention. *J Emerg Med.* 2020;59(1):137–140.
5. Douglas KA, Douglas VP, Moschos MM. Ocular manifestations of COVID-19 (SARS-CoV-2): a critical review of current literature. *In Vivo.* 2020;34(3 suppl):1619–1628.
6. Eleiwa T, Abdelrahman SN, ElSheikh RH, Elhusseiny AM. Orbital inflammatory disease associated with COVID-19 infection. *J AAPOS.* 2021;25(4):232–234.
7. Ho D, Low R, Tong L, Gupta V, Veeraraghavan A, Agrawal R. COVID-19 and the ocular surface: a review of transmission and manifestations. *Ocul Immunol Inflamm.* 2020;28(5):726–734.
8. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA.* 2020;323(11):1061–1069.
9. Benito-Pascual B, Gegúndez JA, Díaz-Valle D, et al. Panuveitis and optic neuritis as a possible initial presentation of the novel coronavirus disease 2019 (COVID-19). *Ocul Immunol Inflamm.* 2020;28(6):922–925.
10. Parvez Y, AlZarooni F, Khan F. Optic neuritis in a child with COVID-19: a rare association. *Cureus.* 2021;13(3).
11. Sawalha K, Adeodokun S, Kamoga G-R. COVID-19-induced acute bilateral optic neuritis. *High Impact case Rep.* 2020;8:2324709620976018.
12. de Oliveira MR, Lucena ARV, Higino TM, Ventura CV. Oculomotor nerve palsy in an asymptomatic child with COVID-19. *J AAPOS* 2021;25(3):169–170.
13. Dinkin M, Gao V, Kahan J, et al. COVID-19 presenting with ophthalmoparesis from cranial nerve palsy. *Neurology.* 2020.
14. Falcone MM, Rong AJ, Salazar H, Redick DW, Falcone S, Cavuoto KM. Acute abducens nerve palsy in a patient with the novel coronavirus disease (COVID-19). *J AAPOS.* 2020;24(4):216–217.
15. Francis JE. Abducens palsy and anosmia associated with COVID-19: a case report. *The BIOJ.* 2021;17(1):8.
16. Gold DM, Galetta SL. Neuro-ophthalmologic complications of coronavirus disease 2019 (COVID-19). *Neurosci Lett.* 2021;742:135531.
17. Lonardi V, Meneghesso D, Debertolis G, Pin JN, Nosadini M, Sartori S. Isolated third cranial nerve palsy and COVID-19 infection in a child. *Pediatr Neurol.* 2021;120:11.
18. Sriwastava S, Tandon M, Kataria S, Daimee M, Sultan S. New onset of ocular myasthenia gravis in a patient with COVID-19: a novel case report and literature review. *J Neurol.* 2021;268:2690–2696.
19. Eleiwa TK, Gaier ED, Haseeb A, ElSheikh RH, Sallam AB, Elhusseiny AM. Adverse ocular events following COVID-19 vaccination. *J Inflamm.* 2021;70:1005–1009.
20. Kang K, Lee SY, Lee DC. Neuro-ophthalmologic symptoms after coronavirus disease 2019 vaccination: a retrospective study. *BMC ophthalmol.* 2023;23(1):1–12.
21. Manea MM, Dragoş D, Enache I, Sirbu AG, Tuta S. Multiple cranial nerve palsies following COVID-19 vaccination—Case report. *Acta Neurol Scand.* 2022;145(2):257–259.
22. Pappaterra MC, Rivera EJ, Oliver AL. Transient oculomotor palsy following the administration of the messenger RNA-1273 vaccine for SARS-CoV-2 diplopia following the COVID-19 vaccine. *J Neuroophthalmol.* 2022.
23. Reyes-Capo DP, Stevens SM, Cavuoto KM. Acute abducens nerve palsy following COVID-19 vaccination. *J AAPOS.* 2021;25(5):302–303.
24. Seong SC, Kim Y-Y, Park SK, et al. Cohort profile: the national health insurance service-national health screening cohort (NHIS-HEALS) in Korea. *BMJ open.* 2017;7(9):e016640.
25. Cheol Seong S, Kim Y-Y, Khang Y-H, et al. Data resource profile: the national health information database of the

National Health Insurance Service in South Korea. *Int J Epidemiol.* 2017;46(3):799–800.

26. Kim HR, Lee NK, Lee CS, et al. Retinal vascular occlusion risks in high blood pressure and the benefits of blood pressure control. *Am J Ophthalmol.* 2023;250:111–119.
27. Chavez A, Pougnier C. A case of COVID-19 vaccine associated new diagnosis myasthenia gravis. *J Prim Care Community Health.* 2021;12:21501327211051933.
28. Lee MA, Lee C, Park JH, Lee JH. Early-onset myasthenia gravis following COVID-19 vaccination. *J Korean Med Sci.* 2022;37(10).
29. Maher DI, Hogarty D, Ben Artsi E. Acute onset ocular myasthenia gravis after vaccination with the Oxford-AstraZeneca COVID-19 vaccine. *Orbit.* 2022:1–5.
30. Hashimoto Y, Yamana H, Iwagami M, et al. Ocular adverse events after coronavirus disease 2019 mRNA vaccination: matched cohort and self-controlled case series studies using a large database. *Ophthalmology.* 2023;130(3):256–264.
31. Abbas AS, Hardy N, Ghozy S, et al. Characteristics, treatment, and outcomes of Myasthenia Gravis in COVID-19 patients: a systematic review. *Clin Neurol Neurosurg.* 2022;213:107140.
32. Koneczny I, Herbst R. Myasthenia gravis: pathogenic effects of autoantibodies on neuromuscular architecture. *Cells.* 2019;8(7):671.
33. Abičić A, Adamec I, Habek M. Miller Fisher syndrome following Pfizer COVID-19 vaccine. *Neurological Sciences.* 2022;1–3.
34. Gutiérrez-Ortiz C, Méndez-Guerrero A, Rodrigo-Rey S, et al. Miller Fisher syndrome and polyneuritis cranialis in COVID-19. *Neurology.* 2020;95(5):e601–e605.
35. Pimentel V, Luchsinger VW, Carvalho GL, et al. Guillain–Barré syndrome associated with COVID-19: a systematic review. *Brain Behav Immun.* 2023;100578.
36. Siddiqi AR, Khan T, Tahir MJ, Asghar MS, Islam MS, Yousaf Z. Miller Fisher syndrome after COVID-19 vaccination: case report and review of literature. *Medicine.* 2022;101(20):e29333.
37. McGrogan A, Madle GC, Seaman HE, De Vries CS. The epidemiology of Guillain-Barré syndrome worldwide. *Neuroepidemiology.* 2009;32(2):150–163.
38. Abara WE, Gee J, Marquez P, et al. Reports of guillain-barré syndrome after COVID-19 vaccination in the United States. *JAMA Netw Open.* 2023;6(2):e2253845–e2253845.