

Ocular Adverse Events Following Coronavirus Disease 2019 Infection: A Self-controlled Case Series Study from the Entire Korean Population

Sungsoon Hwang, MD, PhD,¹ Se Woong Kang, MD, PhD,¹ Jaehwan Choi, MD,^{2,3} Kyung-Ah Park, MD, PhD,¹ Dong Hui Lim, MD, PhD,^{1,2} Ju-Young Shin, PhD,^{2,4} Danbee Kang, PhD,^{2,5} Juhee Cho, PhD,^{2,5} Sang Jin Kim, MD, PhD¹

Purpose: This study aimed to assess the risk of ocular adverse events, including retinal artery occlusion (RAO), retinal vein occlusion (RVO), noninfectious uveitis (NIU), noninfectious scleritis (NIS), optic neuritis (ON), ischemic optic neuropathy (ION), and ocular motor cranial nerve palsy (OMCNP), after coronavirus disease 2019 (COVID-19) infection.

Design: Population-based self-controlled case series (SCCS).

Participants: The study included patients from the entire Korean population of 52 million who experienced incident RAO, RVO, anterior NIU, nonanterior NIU, NIS, ON, ION, or OMCNP between January 1, 2021, and October 29, 2022.

Methods: This nationwide SCCS utilized data from the Korea National Health Insurance Service and the Korea Disease Control and Prevention Agency. The risk period after infection was defined as up to 24 weeks after COVID-19 infection. Conditional Poisson regression was used to calculate the relative incidence rate ratios (IRRs) for RAO, RVO, anterior NIU, nonanterior NIU, NIS, ON, ION, and OMCNP during the designated risk periods.

Main Outcome Measures: The IRRs for RAO, RVO, anterior NIU, nonanterior NIU, NIS, ON, ION, and OMCNP during the risk periods.

Results: The study included 9336, 103 362, 201 010, 25 428, 23 744, 3026, 69 933, and 16 335 cases of incident RAO, RVO, anterior NIU, nonanterior NIU, NIS, ON, ION, and OMCNP, respectively. The IRRs (95% confidence interval) during the early risk period (1–8 weeks) were 0.94 (0.83–1.07), 1.01 (0.97–1.04), 1.00 (0.98–1.03), 0.96 (0.90–1.03), 1.00 (0.94–1.07), 0.97 (0.81–1.17), 0.97 (0.93–1.01), and 1.02 (0.94–1.11), respectively. In the late risk period (9–24 weeks), the IRRs were 1.02 (0.92–1.12), 1.01 (0.98–1.04), 1.01 (0.99–1.03), 1.02 (0.97–1.08), 1.02 (0.97–1.08), 0.99 (0.85–1.15), 1.02 (0.99–1.06), and 0.97 (0.90–1.03), respectively. Stratified analyses showed that in patients with a history of cerebro-cardiovascular disease, the risk of RAO increased during the late risk period, with an IRR (95% confidence interval) of 1.19 (1.02–1.40).

Conclusions: The risk of incident RVO, anterior NIU, nonanterior NIU, NIS, ON, ION, or OMCNP did not increase after COVID-19 infection. The risk of incident RAO increased only in individuals with preexisting cardio-cerebrovascular disease.

Financial Disclosure(s): Proprietary or commercial disclosure may be found in the Footnotes and Disclosures at the end of this article. *Ophthalmology Science* 2025;5:100638 © 2024 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



Supplemental material available at www.ophtalmologyscience.org.

The coronavirus disease 2019 (COVID-19) pandemic has significantly impacted global health care.¹ Over 775 million people have been infected worldwide, resulting in approximately 7.0 million deaths. This crisis spurred the rapid development and deployment of COVID-19 vaccines, with 5.6 billion people receiving ≥ 1 dose.² This pandemic has sparked considerable interest in understanding the systemic effects of both COVID-19

infection and vaccination, leading to numerous epidemiological studies.

The COVID-19 vaccination is generally recognized for its favorable safety profile,³ with the potential for increased risk reported only for specific, rare conditions such as myocarditis, perimyocarditis, Guillain-Barré syndrome, and thrombosis with thrombocytopenia syndrome.^{4–8} In contrast, COVID-19 infection is

known to elevate the risk of major systemic diseases, including cardiovascular and cerebrovascular events, as well as autoimmune and inflammatory diseases.^{9–14} These differences in risk are thought to be due to the different immune responses elicited by vaccination and infection.¹⁵

In ophthalmology, large-scale population-based studies have examined the risk of ocular adverse events after COVID-19 vaccination.^{16–21} These studies, with adequate case numbers and statistical power, generally report an encouraging safety profile for COVID-19 vaccines. However, despite the widespread and prevalent nature of COVID-19 infection, there is relatively limited evidence on the risk of ocular adverse events after infection. Most existing studies are case series, with only a few cohort studies reported.^{22–24} These cohort studies face significant challenges: (1) a limited number of cases, resulting in low statistical power; and (2) potential bias due to difficulties in ensuring comparability between infected and noninfected groups, despite rigorous cohort design and statistical adjustments.

Conducting cohort studies on COVID-19 infection using health care databases poses challenges in group comparability for several reasons. Firstly, individuals in the COVID-19 infected group may differ from the noninfected group in terms of their level of social activity, adherence to government quarantine and health policies, and health care utilization, which cannot be statistically adjusted. Secondly, due to quarantine protocols, many infected individuals, especially those who need to work, might not report their infection, leading to potential misclassification bias where many in the noninfected group might have actually been infected. Additionally, the noninfected group might include individuals who are actually residing abroad, thus having no exposure or diagnosis opportunity within the country. The self-controlled case series (SCCS) method effectively addresses these issues.^{25,26} Unlike traditional cohort designs that compare different groups, the SCCS approach treats individuals as their own controls, emphasizing "when" the event occurs rather than "who" is affected. This methodology inherently adjusts for all measured and unmeasured time-invariant confounders, making it especially suitable for studies on COVID-19 vaccination and infection where establishing adequate control groups is challenging.

To overcome the limitations of previous epidemiologic studies on ocular adverse events after COVID-19 infection, this study conducts a comprehensive evaluation of the association between COVID-19 infection and a range of adverse ophthalmic events by undertaking the largest SCCS analysis on the entire Korean population.

Methods

Setting

This nationwide, population-based SCCS utilized data from the Korean National Health Insurance Service (NHIS) and the Korea Disease Control and Prevention Agency (KDCA). The NHIS, a mandatory universal health care system in South Korea, provides

comprehensive data on demographics, health claims, and mortality for the entire Korean population. Demographic data included age, sex, and income, while claims data encompassed clinical visit dates, prescription codes, and diagnostic codes based on the Korean Classification of Diseases eighth revision, aligned with the International Classification of Diseases, 10th revision, with specific adaptations for Korea. The KDCA database provided information on COVID-19 infection, including diagnosis dates. These infection records were linked to NHIS claims data using anonymized identifiers. Detailed information about the databases is available in the literature.²⁷

Outcome Measures and Other Parameters

The outcomes of interest in determining the association with COVID-19 infection in this study were retinal artery occlusion (RAO), retinal vein occlusion (RVO), noninfectious uveitis (NIU), noninfectious scleritis (NIS), optic neuritis (ON), ischemic optic neuropathy (ION), and ocular motor cranial nerve palsy (OMCNP). Outcome measures were defined based on the presence of diagnostic and medication prescription codes. The precise definitions are provided in Table S1 (available at www.ophtalmologyscience.org), which have also been applied in previous epidemiological studies.^{28–30}

Additional parameters, including age, sex, income level, and residential area, were extracted from the NHIS database. Income was categorized into low or moderate-to-high, with low income encompassing the lower 25th percentile based on household income. Residential areas were classified as urban or rural, with urban areas defined by the Korean government as those residing in 7 designated metropolitan/special cities. Data on past cardio-cerebrovascular and rheumatic autoimmune diseases over the last 5 years were also collected, with definitions provided in Table S1 (available at www.ophtalmologyscience.org).

Study Population and Observation Period

The SCCS is a case-only design with a predetermined observation period. The observation period of the present study was defined from January 1, 2021, to October 29, 2022. Due to the small number of COVID-19 infection cases before 2021, which raised concerns about the identifiability of individual characteristics, the government did not permit the linkage of these COVID-19 cases with claim data. Consequently, the observation period did not include dates prior to 2021, and individuals diagnosed with COVID-19 before 2021 were excluded from the study population. Individuals diagnosed with the specified ocular diseases (RAO, RVO, NIU, NIS, ON, ION, or OMCNP) during this observation period were identified. Exclusions were made for those with a prior history of these ocular diseases within the 6 years before the observation period, those who died during the study period, and those with missing infection or demographic data. The final dataset for the SCCS analyses comprised incident cases of outcome measures without censoring or missing data (Fig 1).

Statistical Analysis

For SCCS analysis, we divided the observation period of the study subjects into distinct risk and control periods. The risk period extended up to 24 weeks (168 days) postinfection, divided into an early risk period (8 weeks or 56 days) and a late risk period (up to 24 weeks). In cases of reinfection within 24 weeks, the risk period restarted from the new infection date, with observation censored if it concluded before the full 24 weeks. All other times during the study were considered control periods. A detailed scheme of risk and control periods for a typical clinical scenario is illustrated in Figure 2.

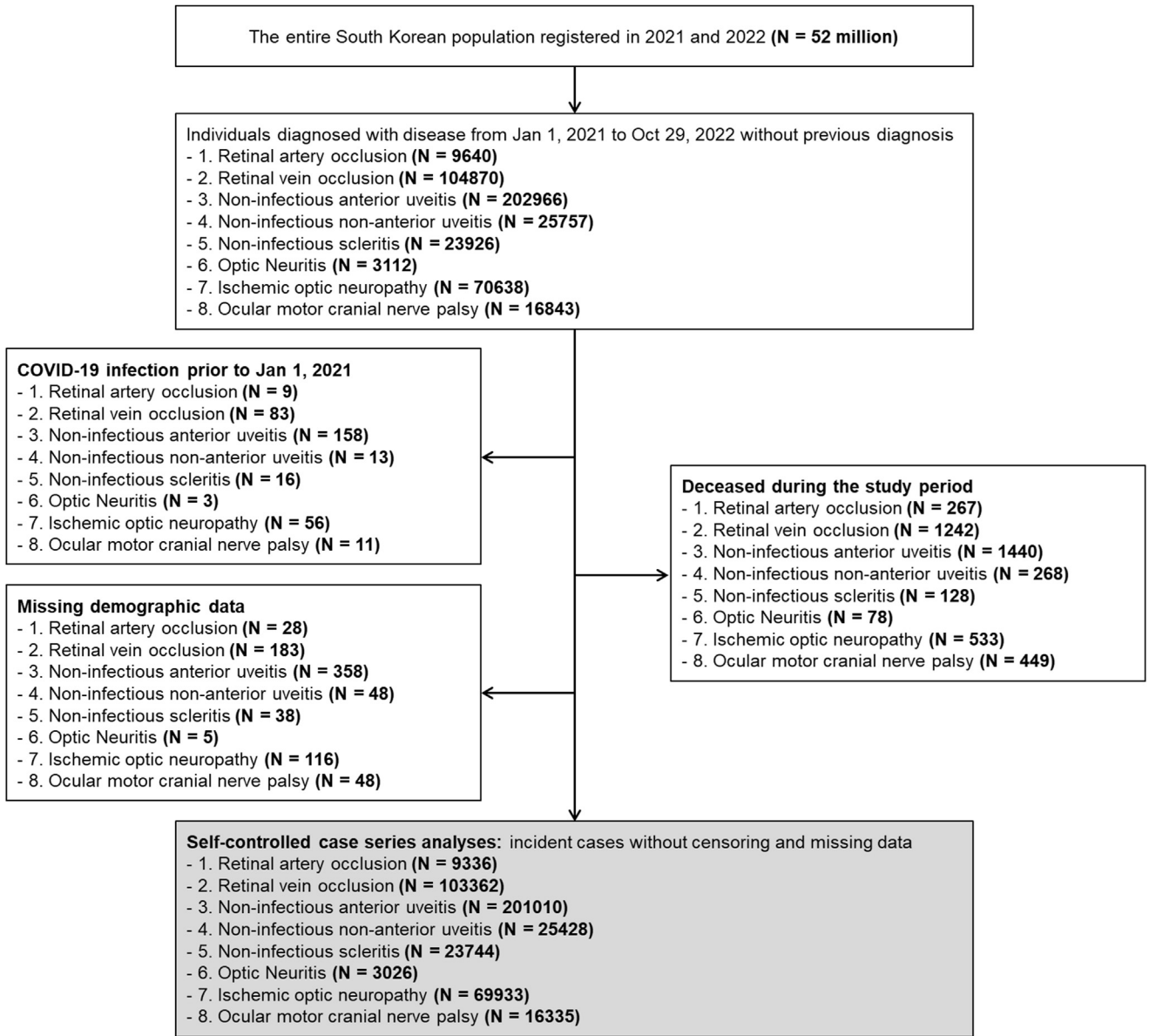


Figure 1. Flow chart of subject selection for the self-controlled case series. COVID-19 = coronavirus disease 2019.

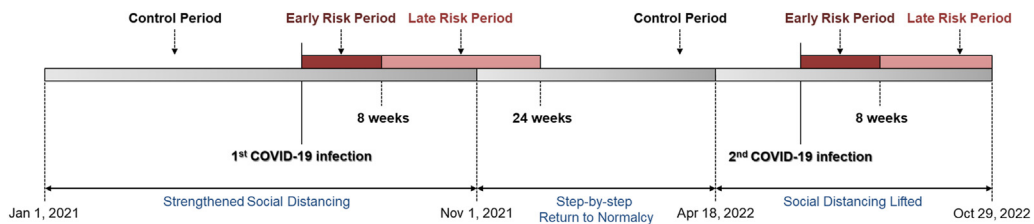


Figure 2. Illustration of self-controlled case series design in a common clinical scenario. The risk period was up to 24 weeks (168 days) after infection and was divided into an early risk phase (8 weeks or 56 days) and a late risk phase (9 to 24 weeks). All other times during the study were deemed control periods. The observation period was divided into 3 segments: before November 1, 2021; between November 1, 2021, and April 18, 2022; and after April 18, 2022. November 1, 2021, marked the start of the nationwide shift from social distancing to a gradual normalization, while April 18, 2022, marked the official end of social distancing measures in Korea. COVID-19 = coronavirus disease 2019.

To estimate the incidence rate ratios (IRRs) and 95% confidence intervals for ocular adverse events during risk periods compared with control periods, we used conditional Poisson regression, accounting for within-individual correlation structure. Given that the degree of social distancing could influence health care utilization and act as a time-varying confounder, we adjusted for this by dividing the observation period into 3 phases: before November 1, 2021; between November 1, 2021, and April 18, 2022; and after April 18, 2022. November 1, 2021, marked the commencement of a nationwide transition from social distancing to a gradual return to normalcy, and April 18, 2022, marked the official lifting of social distancing in Korea. Sensitivity analyses were conducted by excluding patients who were not infected with COVID-19 during the observation period to minimize potential misclassification bias related to incorrect classification of COVID-19 exposure (Sensitivity Analysis 1) and extending the control period only up to 1 week prior to the positive test result to allow for asymptomatic or paucisymptomatic infection resulting in ocular sequelae (Sensitivity Analysis 2). Additionally, stratified analyses were performed based on age, sex, income, residential area, and history of cardio-cerebrovascular and rheumatic autoimmune diseases.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc) and R version 4.0.4 (The R Foundation for Statistical Computing; <http://www.r-project.org>).

Ethics Statement

The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Samsung Medical Center (IRB File Number SMC 2023-05-132). The requirement for informed consent was waived due to the use of deidentified public data and the retrospective nature of the study. Approval for the use of NHIS and KDCA databases was obtained (Research Number KDCA-NHIS-2024-1-190).

Results

Demographics

A total of 9336 RAO, 103 362 RVO, 212 953 anterior NIU, 25 428 nonanterior NIU, 23 744 NIS, 3026 ON, 69 933 ION, and 16 335 OMCNP cases were included in the study. The average age varied across the diseases, ranging from 51 years (ON) to 68 years (RAO). In the RAO and OMCNP groups, the proportion of males was >1.5 times higher than females. There were no noticeable differences in income level or residential area among the disease groups. In the RAO group, >30% of individuals had a history of cerebro-cardiovascular disease. Detailed demographic information is provided in Table 2. Among these patients, the number of individuals infected with COVID-19 was 3356, 40 039, 90 320, 10 715, 10 836, 1308, 32 104, and 6855, respectively, representing approximately 40% of the study population. The COVID-19 infection characteristics of the study population are detailed in Table 3. Baseline characteristics of patients infected with COVID-19 (subjects of the sensitivity analysis) are shown in Table S4 (available at www.ophtalmologyscience.org), with no notable differences in overall clinical characteristics trends.

Risk of Ocular Adverse Events

The IRRs for ocular adverse events during the postinfection period compared with those during the control period for all disease groups are detailed in Figure 3. None of the diseases showed an increased incidence rate during the postinfection period. These results were consistent even in sensitivity analyses excluding patients without a history of COVID-19 infection (Sensitivity Analysis 1, detailed in Table S5, available at www.ophtalmologyscience.org) and excluding the 1-week period prior to infection from the control period (Sensitivity Analysis 2, detailed in Table S6, available at www.ophtalmologyscience.org).

Stratified Analyses

Stratified analyses were conducted for each disease, with detailed results presented in Figures S4 to S11 (available at www.ophtalmologyscience.org; RAO, RVO, anterior NIU, nonanterior NIU, NIS, ON, ION, and OMCNP, respectively). Overall, most stratified groups did not show an increased incidence rate during the postinfection period. However, in patients with a history of cerebro-cardiovascular disease, the risk of RAO increased, with an IRR (95% confidence interval) of 1.19 (1.02–1.40) during the late-risk period (Fig S4, available at www.ophtalmologyscience.org).

Discussion

In this nationwide SCCS study involving the entire Korean population, we found no general increase in the risk of ocular adverse events after COVID-19 infection. However, further stratified analyses revealed that individuals with a history of cardio-cerebrovascular disease exhibited an increased incidence rate of RAO during the late risk period.

The postulated mechanism for the increased risk of cardiovascular and systemic autoimmune diseases after COVID-19 infection is the inflammatory response driven by the infection.^{9,31–35} The release of pro-inflammatory cytokines such as interleukin-6, tumor necrosis factor- α , and interleukin-1 β results in a heightened inflammatory state that can induce vascular endothelial injury and promote hypercoagulability.³³ This inflammatory environment can also contribute to the development of autoimmune conditions.¹⁰ Additionally, the formation of antibodies against severe acute respiratory syndrome coronavirus 2 could directly influence target organs through molecular mimicry.³⁴ The host immune response to COVID-19 infection begins with the innate immune response at 0 to 3 days postinfection, followed by the adaptive immune response starting 4 to 10 days postinfection.³⁵ Immunoglobulins specific to the severe acute respiratory syndrome coronavirus 2 spike protein increase 10 to 14 days postinfection to neutralize the virus and start to decrease around 8 weeks postinfection, indicating a subsidence of the overall immune response to COVID-19 infection.^{35,36} Therefore, we designated an 8-week early

Table 2. Baseline Characteristics of the Study Population in the Self-Controlled Case Series Study

Characteristics	RAO	RVO	Anterior NIU	Nonanterior NIU
Number of patients, No.	9336	103 362	201 010	25 428
Age, yrs				
Mean \pm SD	67.46 \pm 13.29	63.49 \pm 13.80	55.12 \pm 18.99	57.61 \pm 16.60
Median (interquartile range)	70 (61–76)	64 (55–73)	59 (43–69)	60 (49–69)
Sex, No. (%)				
Male	5772 (61.83)	47 498 (45.95)	96 754 (48.13)	10 984 (43.20)
Female	3564 (38.17)	55 864 (54.05)	104 256 (51.87)	14 444 (56.80)
Income level, No. (%)				
Low	2436 (26.09)	28 300 (27.38)	48 984 (24.37)	6661 (26.20)
Moderate to high	6900 (73.91)	75 062 (72.62)	152 026 (75.63)	18 767 (73.80)
Residential area, No. (%)				
Urban	3929 (42.08)	41 317 (39.97)	72 097 (35.87)	11 377 (44.74)
Rural	5407 (57.92)	62 045 (60.03)	128 913 (64.13)	14 051 (55.26)
Previous disease history, No. (%)				
Cerebro-cardiovascular	3130 (33.53)	23 338 (22.58)	29 956 (14.9)	4217 (16.58)
Rheumatic autoimmune	1452 (15.55)	14 223 (13.76)	23 731 (11.81)	3561 (14.00)

Characteristics	NIS	ON	ION	OMCNP
Number of patients, No.	23 744	3026	69 933	16 335
Age, yrs				
Mean \pm SD	51.29 \pm 18.78	51.13 \pm 19.05	52.34 \pm 21.32	56.24 \pm 21.61
Median (interquartile range)	53 (38–65)	54 (37–66)	57 (40–68)	62 (48–71)
Sex, No. (%)				
Male	11 359 (47.84)	1367 (45.18)	31 628 (45.23)	9878 (60.47)
Female	12 385 (52.16)	1659 (54.82)	38 305 (54.77)	6457 (39.53)
Income level, No. (%)				
Low	5328 (22.44)	769 (25.41)	16 611 (23.75)	3986 (24.40)
Moderate to high	18 416 (77.56)	2257 (74.59)	53 322 (76.25)	12 349 (75.60)
Residential area, No. (%)				
Urban	11 113 (46.80)	1370 (45.27)	26 758 (38.26)	7230 (44.26)
Rural	12 631 (53.20)	1656 (54.73)	43 175 (61.74)	9105 (55.74)
Previous disease history, No. (%)				
Cerebro-cardiovascular	3068 (12.92)	405 (13.38)	10 964 (15.68)	3366 (20.61)
Rheumatic autoimmune	2722 (11.46)	375 (12.39)	7617 (10.89)	1645 (10.07)

ION = ischemic optic neuropathy; NIS = noninfectious scleritis; NIU = noninfectious uveitis; OMCNP = ocular motor cranial nerve palsy; ON = optic neuritis; RAO = retinal artery occlusion; RVO = retinal vein occlusion; SD = standard deviation.

Table 3. Characteristics of Coronavirus Disease 2019 Infection of the Study Population for Self-Controlled Case Series Studies

Characteristics	RAO	RVO	Anterior NIU	Nonanterior NIU
Number of patients, No.	9336	103 362	201 010	25 428
Infected patients, No. (%)	3356 (35.95)	40 039 (38.74)	85 216 (42.39)	10 715 (42.14)
Number of infection, No. (%)				
Never been infected	5980 (64.05)	63 323 (61.26)	115 794 (57.61)	14 713 (57.86)
Once	3312 (35.48)	39 425 (38.14)	83 554 (41.57)	10 522 (41.38)
≥ 2 times	44 (0.47)	614 (0.59)	1662 (0.83)	193 (0.76)

Characteristics	NIS	ON	ION	OMCNP
Number of patients, No.	23 744	3026	69 933	16 335
Infected patients, No. (%)	10 836 (45.64)	1308 (43.23)	32 104 (45.91)	6855 (41.97)
Number of infection, No. (%)				
Never been infected	12 908 (54.36)	1718 (56.77)	37 829 (54.09)	9480 (58.03)
Once	10 638 (44.80)	1277 (42.20)	31 320 (44.79)	6696 (40.99)
≥ 2 times	198 (0.83)	31 (1.02)	784 (1.12)	159 (0.97)

ION = ischemic optic neuropathy; NIS = noninfectious scleritis; NIU = noninfectious uveitis; OMCNP = ocular motor cranial nerve palsy; ON = optic neuritis; RAO = retinal artery occlusion; RVO = retinal vein occlusion.

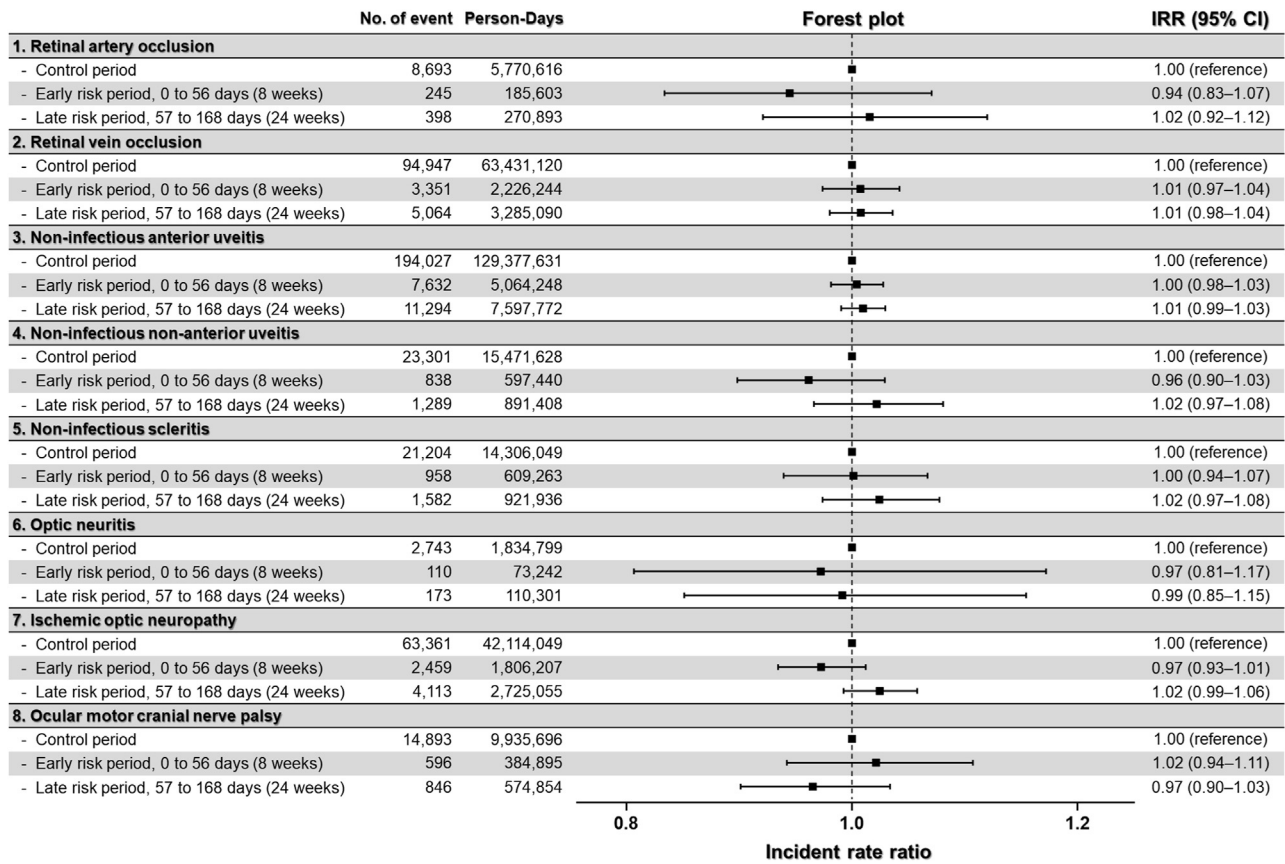


Figure 3. Incidence rate ratios of ocular adverse events during the risk periods in the self-controlled case series study. There was no increase in the incidence rate among any disease group during the postinfection period. CI = confidence interval; IRR = incidence rate ratio.

risk period, acknowledging these temporal dynamics. Given that COVID-19 can induce long-term immune status alterations, direct endothelial damage, and a prothrombotic state, we extended the observation to a late-risk period of up to 6 months (24 weeks) postinfection to explore these potential risks further.

Various ocular diseases have been documented in case series following the COVID-19 infection.³⁷ However, limited population-based studies have been conducted on ophthalmic diseases after COVID-19 infection. Most of the studies focused on retinal vascular occlusion and have presented conflicting conclusions.^{22,24,38} Park et al conducted a cohort study in Korea, utilizing randomly sampled data to compare the incidence rates of RAO and RVO between COVID-19 infection and control groups.²² Their study found no significant differences in the incidence rates of RAO and RVO between the 2 groups. In contrast, Modjtahedi et al conducted a cohort study using the data of patients diagnosed with COVID-19 in an integrated health care organization in the United States.²⁴ While they did not observe a significant increase in the risk of RAO, they reported a significant increase in the risk of RVO after COVID-19 infection, with an adjusted IRR of 1.54 (95% confidence interval: 1.05–2.26). Furthermore, Li et al performed a cohort study using the TriNetX network in the United States.³⁸ They compared

patients with COVID-19 infection to those without a history of the infection and found a significant increase in the risk of RVO within 12 weeks postinfection in the COVID-19 group.

The challenges in the aforementioned studies lie in ensuring comparability between cohort groups. Individuals with COVID-19 may engage in different social activities, adhere differently to health care policies, and utilize health care services to a different degree compared with those without COVID-19. These unmeasured confounders can introduce significant bias into the assessment of ocular adverse event incidence. Additionally, many infected individuals do not get tested or disclose their infection, particularly self-employed individuals concerned about quarantine issues. This may lead to misclassification bias, where infected individuals of specific subsets of population are incorrectly included in the control group. Moreover, in Park et al's study, only 4 cases of RAO and 66 cases of RVO were reported within the COVID-19 infection cohort during the study period. Similarly, in Modjtahedi et al's study, the post-COVID infection period included only 16 cases of RAO and 65 cases of RVO. These small case numbers are insufficient to achieve robust statistical power. The limited number of cases in these studies is likely due to their focus on the early COVID-19 pandemic period before 2022. As a result, they are less representative of later

variants, such as the Omicron variant, which has much higher transmissibility and has resulted in a significantly larger number of infections worldwide. The present study addresses these limitations of previous research by using a large SCCS and offers evidence on the risk of ocular adverse events after COVID-19 infection.

Overall, our study found that COVID-19 infection does not significantly impact ocular diseases. However, for patients with preexisting cardio-cerebrovascular disease, COVID-19 infection appears to increase the risk of RAO. This finding aligns with existing research indicating that COVID-19 infection can cause vascular endothelial damage and a hyperthrombotic state, thereby increasing the risk of myocardial infarction and stroke.^{9,11,12} Conversely, the frequency of ocular inflammatory events such as uveitis, scleritis, and ON was not particularly elevated in the postinfection period. This may possibly be attributed to the specificity of privileged ocular immunity, which differs from the systemic immune system, potentially leading to a less pronounced immune response in the eyes despite systemic inflammation caused by COVID-19 infection.

The strengths of this study include the large sample size and the use of the SCCS design, which inherently corrects for time-invariant confounding factors. Moreover, this study investigated the risk of various ocular conditions associated with COVID-19 infection, filling gaps left by previous population-based studies. However, there are some limitations to consider. First, the diagnoses of ophthalmic diseases were based on diagnostic codes entered by physicians into

claims data, preventing us from performing imaging or survey-based verification of these conditions or capturing all relevant clinical details. Additionally, this study was conducted within a specific timeframe and population, so the findings should be generalized with caution. Moreover, differences in ophthalmic complications may exist based on the severity of COVID-19, but analyzing this with the current dataset is not feasible, highlighting the need for further research. Lastly, this study could only effectively evaluate the risk within a 6-month period, limiting the assessment of long-term risks. The exponential increase in COVID-19 cases in Korea occurred from February 2022 to April 2022, with infections before this period accounting for <10% of the total cases. Considering the observation period ended in October 2022, there were a small proportion of individuals with follow-up periods exceeding 6 months. Although we attempted to analyze the risk beyond 6 months, the relatively small number of individuals observed for longer periods precluded the derivation of meaningful results. Further studies are needed to evaluate the long-term risks.

In conclusion, this comprehensive SCCS study of the entire Korean population found that the incidence of ocular adverse events did not increase after COVID-19 infection, except for individuals with preexisting cardio-cerebrovascular disease, who exhibited an increased risk of RAO after COVID-19 infection. This study may contribute valuable evidence to the expanding body of research on the ophthalmic complications of COVID-19.

Footnotes and Disclosures

Originally received: June 18, 2024.

Final revision: August 26, 2024.

Accepted: October 21, 2024.

Available online: October 26, 2024. Manuscript no. XOPS-D-24-00193.

¹ Department of Ophthalmology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea.

² Department of Clinical Research Design and Evaluation, Samsung Advanced Institute for Health Sciences and Technology (SAIHST), Sungkyunkwan University, Seoul, Republic of Korea.

³ Department of Ophthalmology, Kyung Hee University Medical Center, Kyung Hee University, Seoul, Republic of Korea.

⁴ School of Pharmacy, Sungkyunkwan University, Suwon, Gyeonggi-do, Republic of Korea.

⁵ Center for Clinical Epidemiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea.

Disclosures:

All authors have completed and submitted the ICMJE disclosures form.

The authors made the following disclosures:

S.W.K.: Grants — Novartis, Bayer, Samsung Bioepis, Alexion Pharmaceuticals Inc., Roche, Altos Biologics, Opthea, Hanlim Pharm. Co. Ltd.; Consulting fees — Bayer, Novartis, Roche, SamChunDang Pharm. Co. Ltd.

HUMAN SUBJECTS: Human subjects were included in this study. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Samsung Medical Center (IRB File Number SMC 2023-05-132). The requirement for informed consent was

waived due to the use of deidentified public data and the retrospective nature of the study.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Hwang, Kang, Choi, Shin, Kang, Cho, Kim

Data collection: Hwang, Kang, Choi, Kim

Analysis and interpretation: Hwang, Kang, Choi, Park, Lim, Shin, Kang, Cho, Kim

Obtained funding: N/A

Overall responsibility: Hwang, Kang, Park, Lim

Abbreviations and Acronyms:

COVID-19 = coronavirus disease 2019; **ION** = ischemic optic neuropathy; **IRR** = incidence rate ratio; **KDCA** = Korea Disease Control and Prevention Agency; **NHIS** = National Health Insurance Service; **NIS** = noninfectious scleritis; **NIU** = noninfectious uveitis; **OMCNP** = ocular motor cranial nerve palsy; **ON** = optic neuritis; **RAO** = retinal artery occlusion; **RVO** = retinal vein occlusion; **SCCS** = self-controlled case series.

Keywords:

Coronavirus disease 2019, COVID-19, Ocular adverse events, Self-controlled case series.

Correspondence:

Se Woong Kang, MD, PhD, Department of Ophthalmology, Samsung Medical Center, Sungkyunkwan University School of Medicine, #81 Irwon-ro, Gangnam-gu, Seoul 06351, Republic of Korea. E-mail: kangsewoong@gmail.com.

References

1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet*. 2020;395:470–473.
2. World Health Organization Data. WHO COVID-19 dashboard. <https://data.who.int/dashboards/covid19/>. Accessed June 12, 2024.
3. Beatty AL, Peyser ND, Butcher XE, et al. Analysis of COVID-19 vaccine type and adverse effects following vaccination. *JAMA Netw Open*. 2021;4:e2140364.
4. Diaz GA, Parsons GT, Gering SK, et al. Myocarditis and pericarditis after vaccination for COVID-19. *JAMA*. 2021;326:1210–1212.
5. Long B, Bridwell R, Gottlieb M. Thrombosis with thrombocytopenia syndrome associated with COVID-19 vaccines. *Am J Emerg Med*. 2021;49:58–61.
6. Abara WE, Gee J, Marquez P, et al. Reports of guillain-barre syndrome after COVID-19 vaccination in the United States. *JAMA Netw Open*. 2023;6:e2253845.
7. Patone M, Mei XW, Handunnetthi L, et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. *Nat Med*. 2022;28:410–422.
8. CDC: Centers for Disease Control and Prevention. Selected adverse events reported after COVID-19 vaccination. <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html>. Accessed June 12, 2024.
9. Nishiga M, Wang DW, Han Y, et al. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. *Nat Rev Cardiol*. 2020;17:543–558.
10. Liu Y, Sawalha AH, Lu Q. COVID-19 and autoimmune diseases. *Curr Opin Rheumatol*. 2021;33:155–162.
11. Katsoularis I, Fonseca-Rodríguez O, Farrington P, et al. Risk of acute myocardial infarction and ischaemic stroke following COVID-19 in Sweden: a self-controlled case series and matched cohort study. *Lancet*. 2021;398:599–607.
12. Merkler AE, Parikh NS, Mir S, et al. Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) vs patients with influenza. *JAMA Neurol*. 2020;77:1–7.
13. Tang KT, Hsu BC, Chen DY. Autoimmune and rheumatic manifestations associated with COVID-19 in adults: an updated systematic Review. *Front Immunol*. 2021;12:645013.
14. Lim SH, Ju HJ, Han JH, et al. Autoimmune and auto-inflammatory connective tissue disorders following COVID-19. *JAMA Netw Open*. 2023;6:e2336120.
15. Jaycox JR, Lucas C, Yildirim I, et al. SARS-CoV-2 mRNA vaccines decouple anti-viral immunity from humoral autoimmunity. *Nat Commun*. 2023;14:1299.
16. Tomkins-Netzer O, Sar S, Barnett-Griness O, et al. Association between vaccination with the BNT162b2 mRNA coronavirus disease 2019 vaccine and noninfectious uveitis: a population-based study. *Ophthalmology*. 2022;129:1087–1095.
17. Kumar A, Miller DC, Sun Y, et al. Risk of noninfectious uveitis after coronavirus disease 2019 vaccination in a United States claims database. *Ophthalmology*. 2023;130:1269–1278.
18. Chang MS, Kim HR, Kim S, et al. Noninfectious uveitis risk after COVID-19 vaccination: a nationwide retrospective cohort study. *Am J Ophthalmol*. 2024;258:22–31.
19. 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;130:256–264.
20. Dorney I, Shaia J, Kaelber DC, et al. Risk of new retinal vascular occlusion after mRNA COVID-19 vaccination within aggregated electronic health record data. *JAMA Ophthalmol*. 2023;141:441–447.
21. Shukla P, Sharma N, Shaia JK, et al. The risk of optic neuritis following mRNA coronavirus disease 2019 vaccination compared to coronavirus disease 2019 infection and other vaccinations. *Ophthalmology*. 2024;131:1076–1082.
22. Park HS, Lee NK, Lee CS, et al. Retinal artery and vein occlusion risks after coronavirus disease 2019 or coronavirus disease 2019 vaccination. *Ophthalmology*. 2024;131:322–332.
23. 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;64:37.
24. Modjtahedi BS, Do D, Luong TQ, Shaw J. Changes in the incidence of retinal vascular occlusions after COVID-19 diagnosis. *JAMA Ophthalmol*. 2022;140:523–527.
25. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. *BMJ*. 2016;354:i4515.
26. Baker MA, Lieu TA, Li L, et al. A vaccine study design selection framework for the postlicensure rapid immunization safety monitoring program. *Am J Epidemiol*. 2015;181:608–618.
27. Cheol SS, Kim YY, Khang YH, et al. Data resource profile: the national health information database of the national health insurance service in South Korea. *Int J Epidemiol*. 2017;46:799–800.
28. Choi DD, Park MS, Park KA. Incidence of optic neuritis in Korean children and adolescents: a Nationwide survey and National Registry Analysis. *J Neurol Sci*. 2020;408:116554.
29. Lee C, Han KD, Yoo J, et al. Hormone replacement therapy and the incidence of nonarteritic anterior ischemic optic neuropathy: a nationwide population-based study (2009-2018). *Graefes Arch Clin Exp Ophthalmol*. 2023;261:2019–2029.
30. Kim J, Han K, Jung JH, et al. Early-onset ocular motor cranial neuropathy is a strong predictor of dementia: a nationwide, population-based cohort study. *Ophthalmology*. 2024;131:288–301.
31. Bonaventura A, Vecchie A, Dagna L, et al. Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID-19. *Nat Rev Immunol*. 2021;21:319–329.
32. Jin Y, Ji W, Yang H, et al. Endothelial activation and dysfunction in COVID-19: from basic mechanisms to potential

- therapeutic approaches. *Signal Transduct Target Ther.* 2020;5:293.
33. Magadum A, Kishore R. Cardiovascular manifestations of COVID-19 infection. *Cells.* 2020;9:2508.
34. Vojdani A, Kharrazian D. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. *Clin Immunol.* 2020;217:108480.
35. Vabret N, Britton GJ, Gruber C, et al. Immunology of COVID-19: current state of the science. *Immunity.* 2020;52:910–941.
36. Adams E, Ainsworth M, Anand R, et al. Antibody testing for COVID-19: A report from the National COVID Scientific Advisory Panel. *Wellcome Open Res.* 2020;5:139.
37. Sen M, Honavar SG, Sharma N, Sachdev MS. COVID-19 and eye: a Review of ophthalmic manifestations of COVID-19. *Indian J Ophthalmol.* 2021;69:488–509.
38. Li JX, Wei JC, Wang YH, et al. Retinal vascular occlusion and COVID-19 diagnosis: a multicenter population-based study. *Retina.* 2024;44:345–352.