# A Population-Based Study of Anterior Ischemic Optic Neuropathy Following Cataract Surgery



SASHA A. MANSUKHANI, JOHN J. CHEN, AARON M. FAIRBANKS, ROBERT C. FOSTER, JAY C. ERIE, KEITH H. BARATZ, DAVID O. HODGE, AND M. TARIQ BHATTI

- PURPOSE: To determine if there is an increased incidence rate of post-cataract surgery (pcs) anterior ischemic optic neuropathy (AION) compared to spontaneous AION (sAION).
- DESIGN: Retrospective, population-based cohort.
- METHODS: Patients diagnosed with AION from January 1, 1990, through December 31, 2016, while residing in Olmsted County, Minnesota. Patients with cataract surgery preceding AION were included in the pcsAION cohort defined in 2 ways: AION within 2 months and AION within 1 year of cataract surgery. The incidence rates of pcsAION and sAION were compared using Poisson regression models.
- RESULTS: During the study period, 102 residents developed AION. The median age was 65 years (range, 40-90 years), 44 (43.1%) were female. Twenty of 102 (19.6%) patients had previous cataract surgery, of which 2 and 9 developed AION within 2 months and 1 year of surgery, respectively. The annual incidence rate of pcsAION within 2 months of surgery (8.6 per 100,000) was not significantly greater than the annual incidence rate of sAION (6.9 per 100,000; P = .78). However, the annual incidence rate of pcsAION within 1 year of surgery (38.9 per 100,000) was significantly higher than the incidence rate of sAION (6.5 per 100,000; P < .001).
- CONCLUSION: The incidence of AION is increased in the first year after cataract surgery, but not in the early (i.e., 2 months) postoperative period. (Am J Ophthalmol 2021;222:157–165. © 2021 Elsevier Inc. All rights reserved.)

NTERIOR ISCHEMIC OPTIC NEUROPATHY (AION) has been reported to occur with increased frequency following cataract surgery. <sup>1–14</sup> In 2017, an institution-based study from the Wilmer Eye Institute

Accepted for publication Aug 8, 2020.

From the Departments of Ophthalmology (S.A.M., J.J.C., A.M.F., R.C.F., J.C.E., K.H.B., M.T.B.) and Neurology (J.J.C., M.T.B.), Mayo Clinic College of Medicine, Rochester, Minnesota and Department of Health Sciences Research (D.O.H.), Mayo Clinic College of Medicine, lacksonville, Florida, USA.

Inquiries to M. Tariq Bhatti, Mayo Clinic, Department of Ophthalmology, 200 1st Street SW, Rochester, MN 55905, USA; e-mail: bhatti.muhammad@mayo.edu

found no increased risk of AION within a year following cataract surgery. However in 2019, a large data study from South Korea reported contradictory findings, reporting an 80% increased risk of AION following cataract surgery. Although some studies have defined post–cataract surgery AION (pcsAION) as AION occurring within 1 year following the surgery, there is no consensus on the postoperative period of susceptibility. 5,12,15,16

We performed a population-based study in Olmsted County, Minnesota, to determine the incidence rate of pcsAION. The null hypothesis was that there is no difference in the incidence rates of spontaneous AION (sAION) compared with pcsAION, which was defined as AION occurring either within 2 months or within 1 year of surgery.

## **METHODS**

RETROSPECTIVE, POPULATION-BASED COHORT. INSTITUtional review board approval was obtained at the Mayo Clinic, Rochester, Minnesota, and the study adheres to the Declaration of Helsinki. The study was compliant with the Health Insurance Portability and Accountability Act and met all requirements for a waiver of informed consent.

- ROCHESTER EPIDEMIOLOGY PROJECT: The Rochester Epidemiology Project (REP) is a data linkage system, maintaining health information of the entire population of Olmsted County, Minnesota, including all encounters from several hospitals, clinics, and individual practitioners. This unique database enables epidemiologic research because of the relative isolation of the population from other urban centers. The usefulness and accuracy of the REP in providing a complete description of medical and surgical eye care used by the Olmsted County population and in describing trends and incidence is well established. <sup>18</sup>
- PATIENTS: The REP was used to identify patients with 57 broad optic neuropathy codes including Hospital International Classification of Disease Adaptation (HICDA) codes (January 1, 1990, to December 31, 2010) and International Classification of Diseases (ICD)-9 (January 1, 1995, to September 30, 2015) and ICD-10 codes (October

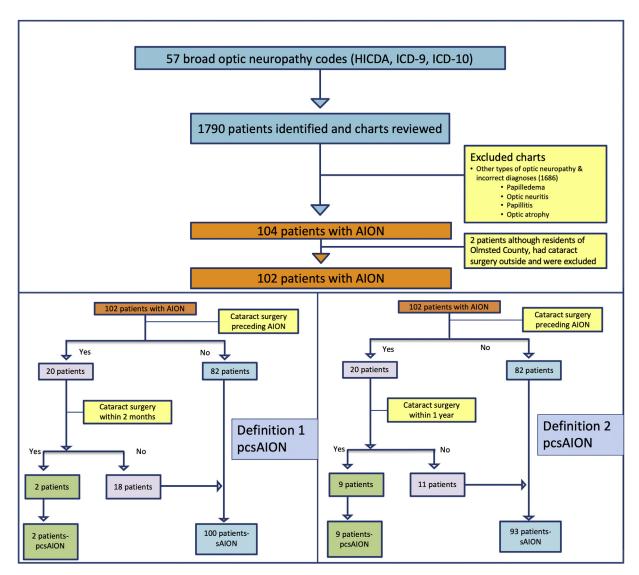


FIGURE 1. Flow chart depicting the method used to identify patients with anterior ischemic optic neuropathy (AION) and inclusion into post-cataract surgery (pcsAION) and spontaneous (sAION) cohorts based on the 2 definitions of pcsAION: AION within 2 months and within 1 year of cataract surgery. HICDA = Hospital International Classification of Disease Adaptation, ICD = International Classification of Diseases.

1, 2015, to December 31, 2016) for ischemic optic neuropathy, optic neuritis, papillitis, papilledema, and optic atrophy. The charts of 1,790 patients were reviewed to identify 104 patients with AION. Patients were excluded if they had other types of optic neuropathy, including those secondary to a systemic vasculitis such as giant cell arteritis, or were deemed not to have an optic neuropathy (1,686 patients). Of the 104 AION patients identified, 2 patients had AION 10 days and 12.7 years after cataract surgery, but the procedure was performed outside Olmsted County therefore were excluded from the final analysis. The remaining 102 patients were included in the final AION cohort (Figure 1). For the 20 (19.6%) patients with bilateral AION, one eye was chosen at

random to include in the study. The medical record charts were reviewed for demographics including gender, race, date of diagnosis, symptoms at onset, date of presentation, symptoms and signs at presentation, laboratory tests, and imaging. The ophthalmic data recorded included presenting visual acuity, presenting visual field defect, cup-to-disc ratio (CDR) prior to AION onset in the affected eye, CDR in the fellow eye, and history of fellow eye AION. Details about risk factors were abstracted including arterial hypertension, diabetes mellitus, hyperlipidemia, obstructive sleep apnea, coronary artery disease, transient ischemic attack or stroke, and history of phosphodiesterase 5-inhibitor use. These risk factors were assessed at the time of AION onset.

**TABLE 1.** Historical, Demographic, and Examination Characteristics of Post–Cataract Surgery Anterior Ischemic Optic Neuropathy (pcsAION) Within 1 Year of Surgery and Spontaneous Anterior Ischemic Optic Neuropathy (sAION) From 1990 Through 2016

| Characteristic                   | pcsAION (n = 9) | sAION (n = 93) | Total (N = 102) | P Value                    |
|----------------------------------|-----------------|----------------|-----------------|----------------------------|
| Sex, n (%)                       |                 |                |                 |                            |
| Female                           | 4 (44.4)        | 40 (43.0)      | 44 (43.1)       | >.99                       |
| Male                             | 5 (55.6)        | 53 (56.4)      | 58 (56.3)       |                            |
| Race, n (%)                      |                 |                |                 | .54 (white vs other races) |
| Native American                  | 0 (0.0)         | 1 (1.1)        | 1 (1.0)         |                            |
| Asian                            | 1 (11.1)        | 0 (0.0)        | 1 (1.0)         |                            |
| White                            | 8 (88.9)        | 85 (92.4)      | 93 (92.1)       |                            |
| Other                            | 0 (0.0)         | 1 (1.1)        | 1 (1.0)         |                            |
| Unknown                          | 0 (0.0)         | 5 (5.4)        | 5 (4.9)         |                            |
| Other eye AION, n (%)            |                 |                |                 |                            |
| Yes                              | 1 (11.1)        | 19 (20.4)      | 20 (19.6)       | .68                        |
| Age at onset, y                  |                 |                |                 |                            |
| Median                           | 79              | 64             | 65              | .04                        |
| Range                            | 59-84           | 40-90          | 40-90           |                            |
| Risk factors, n (%)              |                 |                |                 |                            |
| Hypertension                     | 9 (100.0)       | 66 (71.0)      | 75 (73.5)       | .11                        |
| Hyperlipidemia                   | 8 (88.9)        | 59 (63.4)      | 67 (65.7)       | .16                        |
| Diabetes mellitus                | 2 (22.2)        | 35 (37.6)      | 37 (36.3)       | .48                        |
| Coronary artery disease          | 4 (44.4)        | 28 (30.1)      | 32 (31.4)       | .46                        |
| Myocardial infarction            | 3 (33.3)        | 11 (11.8)      | 14 (13.7)       | .11                        |
| Obstructive sleep apnea          | 2 (22.2)        | 17 (18.3)      | 19 (18.6)       | .67                        |
| Stroke/TIA                       | 3 (33.3)        | 26 (28.0)      | 29 (28.4)       | .71                        |
| Smoker                           | 4 (44.4)        | 40 (43.0)      | 44 (43.1)       | >.99                       |
| PDE5 inhibitor                   | 0 (0.0)         | 2 (2.2)        | 2 (2.0)         | >.99                       |
| Cup-to-disc ratio                |                 |                |                 |                            |
| Median                           | 0.1             | 0.2            | 0.2             | .08                        |
| Range                            | 0.1-0.2         | 0.0-0.7        | 0.0-0.7         |                            |
| Presenting visual acuity, logMAR |                 |                |                 |                            |
| Median                           | 0.3             | 0.3            | 0.3             | .71                        |
| Range                            | 0.0-1.7         | 0.0-2.9        | 0.0-2.9         |                            |

pcsAION = post-cataract surgery anterior ischemic optic neuropathy, PDE = phosphodiesterase, sAION = spontaneous anterior ischemic optic neuropathy, TIA = transient ischemic attack.

Bold values denote statistical significance at the P < .05 level.

• DIAGNOSIS OF SAION AND PCSAION: AION was diagnosed when acute unilateral vision loss occurred with a visual field defect, relative afferent pupillary defect, documented optic disc edema by an ophthalmologist, and other potential causes such as giant cell arteritis or compressive lesions were excluded. Old or prior AION and patients presenting with optic disc pallor and presumed AION were not included. The charts of the identified 102 patients with AION were reviewed by a neuro-ophthalmologist to confirm the diagnosis. Post-cataract surgery AION was defined in 2 ways: AION occurring within 2 months of surgery and AION occurring within 1 year of cataract surgery, in the same eye as that of the cataract surgery. The first definition was thought to be a more biologically plausible time period during which perioperative events could affect optic disc perfusion. The second definition was based on criteria adopted from previous studies.<sup>5,15</sup> The remaining AION cases were defined as spontaneous. The date of diagnosis recorded by the ophthalmologist was taken as the date of onset, because the patients were not always able to determine the exact time of vision loss.

- CAPTURING ALL AION CASES: We used 52 broad codes optic nerve disease codes to identify our AION cohort. This was important because less than half of the included cohort (45 of 102) had billing codes for ischemic optic neuropathy on the event date. Patients were incorrectly coded as unspecified papilledema (n = 26), unspecified optic neuritis (n = 18), papillitis (n = 6), optic atrophy (n = 5), and other unspecified disorders of optic nerve (n = 2). Using broad codes ensured that all new AION cases in the 27-year period were included in our study cohort.
- TOTAL NUMBER OF CATARACT SURGERIES: To calculate the incidence rate of pcsAION, we used previously collected REP population-based cataract surgery data that

included all primary cataract surgeries performed from 1990 through 2018. <sup>19–21</sup> Incident primary cataract surgeries were retrospectively identified using the ICD-9 procedure codes and Current Procedural Terminology (CPT) procedure codes, as described previously. <sup>21</sup> We identified cataract surgery in 23,169 eyes over the 27-year study period from 1990 to 2016.

- ANALYSIS: The baseline patient characteristics were compared for the pcsAION and sAION cohorts using the Fisher exact test for categorical data and Wilcoxon ranksum test for numerical data. We estimated the incidence rate of pcsAION using the total number of cataract surgeries as the denominator. Because there were no bilateral cases of pcsAION, bilateral cataract surgeries performed on the same patient were included in the final analysis to prevent overestimation of the pcsAION rate. The incidence rate of sAION was determined using the population of Olmsted County above the age of 40 years who had not undergone cataract surgery, which was 1,457,651. The incidence rates were also age- and/or gender-adjusted to the 2010 US census figures for the white population to enable comparison with national estimates. Population figures for 1990, 2000, and 2010 were based on the US census data, and population figures for the inter-census years were estimated by linear interpolation. The yearwise population figures are provided in Supplemental Table S1. We then calculated the 95% confidence interval (CI) for the overall incidence to provide a range of the true incidence. The sAION and pcsAION incidence rates were compared using Poisson regression models. Essentially this was just a simple Poisson regression model comparing the number of cases using the offset of the log of the population over that time period.<sup>22</sup> We also calculated the difference between the incidence rates by subtracting the incidence rate of sAION from pcsAION and the 95% CI around those differences. Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Inc, Cary, North Carolina, USA).
- SECONDARY ANALYSIS: A secondary analysis was performed comparing the incidence rates between patients developing AION any time after cataract surgery and sAION (no cataract surgery preceding development of AION). This was done to make our data comparable to Yang et al<sup>12</sup> who considered AION occurring any time after cataract surgery as pcsAION. Recognizing that definitions of pcsAION adopted by prior studies have been somewhat arbitrary and that there is no consensus on the postoperative period of susceptibility, we calculated the incidence of pcsAION and sAION using monthly time points until the last case of AION occurring after cataract surgery. Specifically, we defined pcsAION as cases occurring within 1 month, and then compared this to sAION, which was defined as cases occurring with no preceding cataract surgery or having had cataract surgery 1 month or longer prior to AION. This analysis was done at

2 months, 3 months, et cetera extending to 149 months after cataract surgery.

#### **RESULTS**

OF THE 102 PATIENTS WITH AION, 44 (43.1%) WERE FEMALE and 93 (91.1%) were white. The median age at the time of diagnosis was 65 years (range, 40-90 years). Twenty (19.6%) patients had cataract surgery preceding the development of AION.

- BASELINE CHARACTERISTICS AND RISK FACTORS: Table 1 summarizes the baseline patient characteristics of the pcsAION and sAION cohorts. The pcsAION cohort was significantly older than the sAION (median age, 79 years vs 64 years; P = .04), but were similar in other features such as race, CDR, diabetes mellitus, hyperlipidemia, obstructive sleep apnea, coronary artery disease, myocardial infarction, transient ischemic attack or stroke, and history of phosphodiesterase 5-inhibitor use. None of the patients had intraoperative complications. One patient had an intraocular pressure of 24 mm Hg on postoperative day 1, and 1 patient had persistent anterior chamber inflammation on postoperative day 7 requiring increased steroid eye drops (Table 2). The fellow eye had a history of AION in 1 of 9 (11.1%) in the pcsAION cohort vs 19 of 93 (20.4%) in the sAION cohort (P = .68).
- TEMPORAL DISTRIBUTION OF PCSAION: The median time to the development of AION following cataract surgery was 25.5 months (range, 38 days to 12.7 years). Two (1.9%) and 9 (8.7%) of the 102 patients developed AION within 2 months and 1 year of cataract surgery, respectively.

Among the 9 pcsAION patients, 2 patients developed AION within 2 months, 4 patients between 2 and 6 months, and 3 patients between 6 and 12 months following surgery (Figure 2, A). The remaining 11 patients developed AION greater than 12 months after surgery. Figure 2, B, shows the temporal distribution of all 20 patients developing AION following cataract surgery.

• INCIDENCE RATE OF PCSAION AND SAION: The incidence rate of pcsAION within 2 months and sAION was 8.6 (95% CI 2.2-34.5) and 6.9 (95% CI 5.7-8.4) per 100,000 per year, respectively (P=.78), with a difference of 1.7 (95% CI -10.3 to 13.7) per 100,000 per year. The incidence rate of pcsAION within 1 year and sAION was 38.9 (95% CI 20.2-74.7) per 100,000 and 6.5 (95% CI 5.3-7.9) per 100,000 per year, respectively (P < .001), with a difference of 32.4 (95% CI 7.0-57.8) per 100,000 per year (Figure 2, C).

**TABLE 2.** Surgical Details of 20 Patients Developing Anterior Ischemic Optic Neuropathy at Any Time After Cataract Surgery From 1990 Through 2016

| Patient | Time Interval to AION | Surgery | Year of Surgery | Anesthesia | Complications                | Intraocular Lens | Fellow Eye NAION                   |
|---------|-----------------------|---------|-----------------|------------|------------------------------|------------------|------------------------------------|
| 1       | 1 mo 7 d              | Phaco   | 2009            | RB         | None                         | PCIOL            | No                                 |
| 2       | 1 mo 12 d             | Phaco   | 1997            | RB         | None                         | PCIOL            | No                                 |
| 3       | 3 mo 14 d             | Phaco   | 2011            | RB         | Persistent inflammation POD7 | PCIOL            | No                                 |
| 4       | 4 mo 9 d              | Phaco   | 2013            | PB         | None                         | PCIOL            | No                                 |
| 5       | 4 mo 22 d             | Phaco   | 2008            | RB         | None                         | PCIOL            | No                                 |
| 6       | 5 mo 10 d             | Phaco   | 2000            | RB         | None                         | PCIOL            | No                                 |
| 7       | 6 mo 2 d              | Phaco   | 2012            | RB         | None                         | PCIOL            | No                                 |
| 8       | 6 mo 22 d             | Phaco   | 1995            | PB         | IOP of 24 on POD1            | PCIOL            | Yes, sAION 15 y prior <sup>a</sup> |
| 9       | 11 mo 22 d            | Phaco   | 2001            | PB         | None                         | PCIOL            | No                                 |
| 10      | 1 y 1 mo 21 d         | Phaco   | 1998            | RB + VL    | None                         | PCIOL            | No                                 |
| 11      | 2 y 1 mo 14 d         | Phaco   | 1999            | ?          | None                         | PCIOL            | No                                 |
| 12      | 2 y 6 mo 4 d          | Phaco   | 2012            | RB         | None                         | PCIOL            | No                                 |
| 13      | 3 y 6 mo 27 d         | Phaco   | 2010            | ?          | None                         | PCIOL            | No                                 |
| 14      | 4 y 0 mo 20 d         | Phaco   | 1998            | RB + VL    | None                         | PCIOL            | No                                 |
| 15      | 7 y 7 mo 12 d         | Phaco   | 2008            | RB or PB   | None                         | PCIOL            | No                                 |
| 16      | 8 y 2 mo 21 d         | ECCE    | 1982            | RB         | None                         | PCIOL            | No                                 |
| 17      | 8 y 3 mo 9 d          | Phaco   | 2001            | RB         | None                         | PCIOL            | No                                 |
| 18      | 9 y 1 mo 11 d         | Phaco   | 1997            | RB         | None                         | PCIOL            | No                                 |
| 19      | 10 y 4 mo 30 d        | Phaco   | 2005            | PB         | None                         | PCIOL            | No                                 |
| 20      | 12 y 4 mo 28 d        | ECCE    | 1982            | ?          | ?                            | PCIOL            | No                                 |

AION = anterior ischemic optic neuropathy, ECCE = extracapsular cataract extraction, GA = general anesthesia, NAION = nonarteritic anterior ischemic optic neuropathy, PB = peribulbar, PCIOL = posterior chamber intraocular lens, pcsAION = post-cataract surgery anterior ischemic optic neuropathy, Phaco = phacoemulsification, POD = postoperative day, q1hr = every one hour, RB = retrobulbar, VL = van Lindt facial nerve block.

Shaded area represents the pcsAION cohort used in incidence calculation

• INCIDENCE OF AION AT VARIOUS TIME POINTS: We performed a secondary analysis in which we included the patients developing AION any time after cataract surgery in the study cohort (20 patients). The incidence rate of pcsAION occurring any time after cataract surgery was 86.3 per 100,000 per year (Figure 2, C). This was significantly higher than the incidence of sAION (5.6 per 100,000; P < .001). The baseline characteristics are presented in Supplemental Table 2. The pcsAION (any time after cataract surgery) cohort was older with significantly more prevalent comorbidities (coronary artery disease, history of myocardial infarction, and obstructive sleep apnea). We also compared the incidence rates of pcsAION and sAION at monthly time points over 149 months (Supplemental Table 3 and Supplemental Figure).

#### **DISCUSSION**

OUR POPULATION-BASED STUDY FOUND NO INCREASED risk of AION within the first 2 months following cataract surgery; however, we did find an increased risk of AION

within 1 year of surgery. There were no acute (days to weeks after cataract surgery) cases of pcsAION, and most of our cases occurred 2-6 months after surgery.

There have been several studies that have reported the incidence rate or risk factors of pcsAION with varying results and conclusions (Table 3). <sup>2,5,6,9,12,13,15,16,23</sup> Hayreh in 1980 described 13 eyes in 11 patients who developed AION within days to weeks of undergoing intracapsular cataract extraction. <sup>2</sup> Of the 13 eyes, only 4 were documented to have optic disc edema at the time of vision loss, whereas the rest were presumed AION based on the presence of optic disc atrophy at a later time. Hayreh stressed that pcsAION in the early postoperative period was related to high intraocular pressure and should be differentiated from "ordinary AION" occurring months later. Following this initial report, investigators have studied both the immediate and delayed type of pcsAION.

McCulley and associates in 2001 performed a retrospective cohort study of 5,787 cataract surgery patients to determine the occurrence of AION within 1 year after cataract surgery and found 3 patients with AION within the first 6 months of surgery. The authors calculated an incidence rate of 51.8 and 34.6 per 100,000 within 6 months and

<sup>&</sup>lt;sup>a</sup>In relation to study eye AION event.

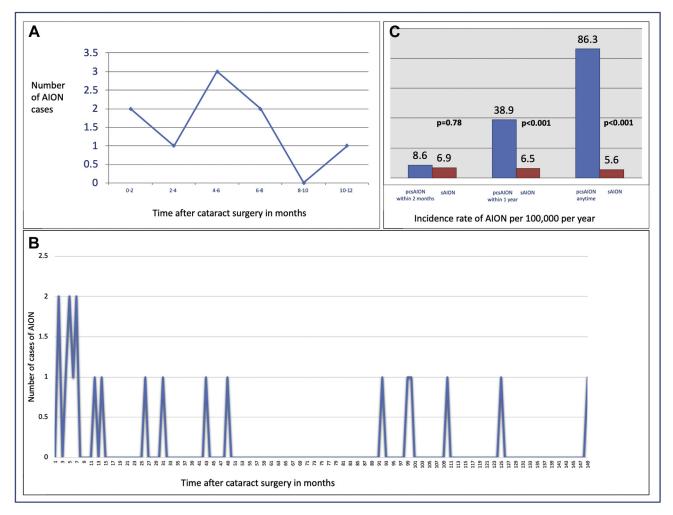


FIGURE 2. Temporal distribution of post–cataract surgery anterior ischemic optic neuropathy (pcsAION). (A) Temporal distribution of cases of pcsAION in the year following cataract surgery. (B) Temporal distribution of cases of pcsAION occurring any time following cataract surgery depicting clustering of cases in the first 9 months following cataract surgery. (C) Incidence rate of pcsAION and spontaneous anterior ischemic optic neuropathy (sAION). The incidence rate of pcsAION within 2 months was 8.6 per 100,000 per year (95% CI 2.2-34.5 per 100,000 per year), compared to the incidence rate of sAION, which was 6.9 per 100,000 per year (95% CI 5.7-8.4 per 100,000 per year), that did not reach statistical significance, with a difference of 1.7 (95% CI –10.3 to 13.7). The incidence rate of pcsAION within 1 year was 38.9 per 100,000 per year (95% CI 20.2-74.7 per 100,000 per year), compared with the incidence rate of sAION, which was 6.5 per 100,000 per year (95% CI 5.3-7.9 per 100,000 per year), that was statistically significant, with a difference of 32.4 (95% CI 7.0-57.8). The incidence rate of pcsAION occurring anytime following cataract surgery was high (86.3 per 100,000 per year), compared with the incidence rate of sAION, which was 5.6 per 100,000 per year, which was statistically significant (P < .001).

6 weeks following cataract surgery, respectively. There were several limitations to the study. It was conducted at a tertiary care center in Miami, Florida, and therefore was subject to a referral bias. Their comparison cohort was not from the same population as the study cohort but rather the incidence rate of nonarteritic AION (NAION) in Olmsted County, Minnesota.<sup>24</sup> There were only 3 pcsAION cases and a narrow search code (ischemic optic neuropathy) was used to identify the study cohort. In contrast, our study was population-based, thus minimizing referral bias, and our comparison cohorts were from the

same population pool. In addition, we performed the initial search using 57 broad codes for various types of optic neuropathies and less than half of the included patients in our cohort had billing codes for ischemic optic neuropathy. Thus, several patients would have been missed had we used a narrower code search.

Moradi and associates performed a retrospective cohort study and reported an incidence of pcsAION of 10.9 per 100,000 within 1 year and 5.5 per 100,000 within 2 months. <sup>15</sup> The authors concluded that this was not significantly different when compared with the population risk

TABLE 3. Prior Studies: Incidence and Risk Factors for Post-Cataract Surgery Anterior Ischemic Optic Neuropathy

| Year | Author                        | Study Design   | Salient Points   |
|------|-------------------------------|--|--|
| 1980 | Hayreh <sup>2</sup>           | Case series  | 13 eyes underwent intracapsular cataract extractions; all high IOP   |
| 2001 | McCulley et al <sup>5</sup>   | Retrospective cohort, incidence                                  | postoperative; occurring within days to weeks after surgery 3 patients with pcsAlON; 6-mo incidence of 51.8 in 100,000 and a 6-wk incidence of 34.6 in 100,000   |
| 2003 | McCulley et al <sup>6</sup>   | Retrospective cohort, temporal distribution of cases             | 18 eyes within 6 mo of cataract surgery, significantly different from a uniform distribution ( $P < .001$ ).   |
| 2005 | McCulley et al <sup>22</sup>  | Retrospective cohort, risk factors                               | 12 eyes with pcsAlON; prevalence of hypertension and low cup-to-disc ratio significantly lower   |
| 2006 | Nguyen et al <sup>16</sup>    | Retrospective case series, delayed pcsAION                       | 6 eyes with pcsAlON between 2 and 6 mo; not enough evidence for causal relationship  |
| 2007 | Lam et al <sup>9</sup>        | Retrospective cohort, incidence in patients with unilateral AION | 9 eyes with pcsAlON; fellow eye AlON risk higher if undergoing cataract surgery (53% vs 19%)   |
| 2017 | Al-Madani et al <sup>13</sup> | Prospective cohort   | 13 eyes with pcsAlON; followed 540 patients for 6 months from time of presentation or surgery; 56% of them had cataract surgery; AlON risk was higher for cataract surgery patients (4.2%-4.3%) compared with nonsurgical patients (0-0.2%)                            |
| 2017 | Moradi et al <sup>15</sup>    | Retrospective cohort, incidence                                  | 18 patients with pcsAION; incidence 10.9 cases per 100,000   |
| 2019 | Yang et al <sup>12</sup>      | Retrospective, big data, population based                        | 139 patients with pcsAlON; 10-y incidence probability of NAION after cataract surgery was 0.70% (95% CI 0.55-0.86), with increased risk compared with the non-cataract surgery group (HR=1.80, 95% CI 1.46-2.21); 78% of patients had AlON >1 y after cataract surgery |

AION = anterior ischemic optic neuropathy, IOP = intraocular pressure, NAION = non-arteritic anterior ischemic optic neuropathy, pcsAION = post-cataract surgery AION.

of NAION in Olmsted County, Minnesota.<sup>24</sup> The authors concluded that modern cataract surgery is not associated with an increased risk of AION. The study was conducted at the Wilmer Eye Network system and had similar limitations of an institution-based study as with the study by McCulley and associates.<sup>5</sup> Furthermore, they could have underestimated the incidence risk because they used only ischemic optic neuropathy billing codes to identify cases and assumed that patients having cataract surgery would return to their institute for postoperative care over the entire year following surgery.

Most recently, Yang and associates performed a large data study in South Korea using an insurance claims database and categorized pcsAION in any patient who developed AION no matter how many years after cataract surgery. 12 They found that the cumulative probability of AION in the cataract surgery group was nearly 3 times higher compared to the non-cataract surgery group (10year probability was 0.70% vs 0.27%; P < .001). Seventyeight percent of their cohort developed AION 1 year after cataract surgery. Interestingly, the survival analysis curves for the incidence probability of AION ran together for the first year, after which time the curve of the cataract surgery cohort became steeper than the non-cataract surgery cohort. The study relied on diagnosis codes without the ability to confirm the diagnosis with evaluation of the patient charts. We similarly found high incidence rates of pcsAION in patients with cataract surgery any time preceding the AION. Our cohort however was older with higher prevalence of vasculopathic risk factors and comorbidities, which are major confounding factors. As shown in the monthly incidence rate calculation, once one got past 5 months, the cumulative incidence of the pcsAION cohort was significantly higher. As shown in Figure 2, B, the post–cataract surgery cases seemed clustered in the first 9 months.

There are various risk factors that have been reported to be associated with pcsAION. 2,9,12,13,16,23 Hayreh<sup>2</sup> found that postoperative raised intraocular pressure was a major risk factor, although Yang and associates did not reach that same conclusion. In comparison, only 1 patient in our pcsAION cohort had a high postoperative intraocular pressure, which was only mildly elevated at 24 mm Hg. Lam and associates reported that cataract surgery in the fellow eye of patients with a history of NAION in the other eye increased the risk of NAION by 3.6-fold (53% vs 19%). In comparison, we did not find that a history of fellow eye AION was a significant risk factor for the development of pcsAION (fellow eye AION 11.1% in the pcsAION cohort vs 21.3% in the sAION cohort; P =.5). McCulley and associates reported a significantly lower prevalence of hypertension and lower prevalence of CDR less than 0.2 in patients with pcsAION.<sup>23</sup> We found a higher prevalence of hypertension in our pcsAION cohort; however, this did not reach statistical significance, and the median CDR was similar between our 2 cohorts.

The acute (hours to days) type of pcsAION has been hypothesized to occur because of intraoperative raised intrapressure and intraorbital pressure, intraoperative hypotension.<sup>2,16</sup> The delayed type of pcsAION is not as easily explained based on our current understanding of the pathogenesis of AION. 16 McCulley et al theorized that cataract surgery resulted in microvascular compression of the optic disc vessels due to interstitial edema resulting in a compartment syndrome weeks to months after surgery.<sup>23</sup> Yang and associates suggested that subclinical prolonged inflammation as detected by laser photometry could explain the development of AION months after cataract surgery. 12 It is well established that there is an upregulation of inflammatory mediators in the aqueous and vitreous humors after intraocular surgical manipulation that could possibly lead to increased vascular permeability of the optic disc, resulting in the "optic nerve version" of the Irvine Gass syndrome. 25 However, these theories do not explain the higher risk of AION several months and years after cataract surgery. Other explanations that need further investigation include a possible protective effect of the natural crystalline lens on the optic disc or some other unidentified process related to the cataract surgery.

Our study was limited by its retrospective design. To minimize any inaccuracies, we applied uniform criteria and did not rely on the diagnosis recorded in the medical record chart. Our pcsAION cohort was older than the sAION cohort, and because age is a risk factor for NAION,

it is possible that these patients may have developed sAION even if they had not undergone cataract surgery. Because of the small number of patients in the pcsAION within the 1-year cohort, we were unable to perform a subanalysis to adjust for age. The date of diagnosis of AION was taken as the date of onset, which may have been 1 or more days before the onset of vision loss. However, because we only included incident cases with disc edema at the time of diagnosis, we do not think these dates were far apart. Cataract surgeons, aware of the previously reported link between AION and cataract surgery, may have been reluctant to operate on the fellow eye of a unilateral AION patient, thus skewing the results. Our study was conducted over 27 years, and during that time there has been significant advancements in the surgical instruments and refinement of cataract surgical techniques. However, we do not believe this had a major influence on the findings because the pcsAION cases were equally distributed on either side of the midpoint of the study period (ie, 4 cases occurred prior to 2003 and 5 after 2003). Lastly, Olmsted County has a predominantly white population that could translate to poor generalizability of our findings to other parts of the country; however, sAION is predominately a disease of whites, and therefore this bias may not be applicable to our study.

In conclusion, we found a greater incidence of pcsAION in the first 1 year following cataract surgery, but not in the early (2 month) postoperative period. The reason for this discrepancy is unclear.

FUNDING/SUPPORT: THIS STUDY WAS SUPPORTED BY THE MAYO FOUNDATION. FINANCIAL DISCLOSURES: THE AUTHORS INDIcate no financial support or conflicts of interest. All authors attest that they meet the current ICMJE criteria for authorship.

## REFERENCES

- 1. Michaels DD, Zugsmith GS. Optic neuropathy following cataract extraction. *Ann Ophthalmol* 1973;5(3):303–306.
- Hayreh SS. Anterior ischemic optic neuropathy. IV. Occurrence after cataract extraction. Arch Ophthalmol 1980;98(8): 1410–1416.
- Garvin JC, Weber PA. Intermediate post cataract extraction ischemic optic neuropathy associated with an intraocular lens implant. J Am Intraocul Implant Soc 1982;8(2):144–147.
- Serrano LA, Behrens MM, Carroll FD. Postcataract extraction ischemic optic neuropathy. Arch Ophthalmol 1982; 100(7):1177–1178.
- McCulley TJ, Lam BL, Feuer WJ. Incidence of nonarteritic anterior ischemic optic neuropathy associated with cataract extraction. Ophthalmology 2001;108(7):1275–1278.
- McCulley TJ, Lam BL, Feuer WJ. Nonarteritic anterior ischemic optic neuropathy and surgery of the anterior segment: temporal relationship analysis. Am J Ophthalmol 2003;136(6):1171–1172.
- 7. Elston J. Non-arteritic anterior ischaemic optic neuropathy and cataract surgery. Br J Ophthalmol 2007;91(5):563.

- 8. Fontes BM, Jung LS, Soriano ES, Chicani CF. Nonarteritic anterior ischemic optic neuropathy after uneventful phacoemulsification: case report. *Arq Bras Oftalmol* 2007;70(3): 544–546.
- 9. Lam BL, Jabaly-Habib H, Al-Sheikh N, et al. Risk of non-arteritic anterior ischaemic optic neuropathy (NAION) after cataract extraction in the fellow eye of patients with prior unilateral NAION [published correction appears in Br J Ophthalmol. 2010 Dec;94(12):1695]. Br J Ophthalmol 2007; 91(5):585–587.
- Lee H, Kim CY, Seong GJ, Ma KT. A case of decreased visual field after uneventful cataract surgery: nonarteritic anterior ischemic optic neuropathy. Korean J Ophthalmol 2010;24(1): 57–61.
- McCulley TJ, Lam BL, Feuer WJ. Nonarteritic anterior ischemic optic neuropathy and intraocular surgery. Am J Ophthalmol 2017;175:xiv—xvi.
- Yang HK, Park SJ, Byun SJ, Park KH, Hwang JM. Risk of nonarteritic anterior ischemic optic neuropathy after cataract surgery. Am J Ophthalmol 2019;207:343–350.
- Al-Madani MV, Al-Raqqad NK, Al-Fgarra NA, Al-Thawaby AM, Jaafar AA. The risk of ischemic optic

- neuropathy post phacoemulsification cataract surgery. *Pan Afr Med J* 2017;28:53.
- Luscavage LE, Volpe NJ, Liss R. Posterior ischemic optic neuropathy after uncomplicated cataract extraction. Am J Ophthalmol 2001;132(3):408–409.
- 15. Moradi A, Kanagalingam S, Diener-West M, Miller NR. Post-cataract surgery optic neuropathy: prevalence, incidence, temporal relationship, and fellow eye involvement. *Am J Ophthalmol* 2017;175:183–193.
- 16. Nguyen LT, Taravella MJ, Pelak VS. Determining whether delayed nonarteritic ischemic optic neuropathy associated with cataract extraction is a true entity. *J Cataract Refract Surg* 2006;32(12):2105–2109.
- 17. Rocca WA, Yawn BP, St Sauver JL, Grossardt BR, Melton LJ 3rd. History of the Rochester Epidemiology Project: half a century of medical records linkage in a US population. *Mayo Clin Proc* 2012;87(12):1202–1213.
- 18. St Sauver JL, Grossardt BR, Leibson CL, Yawn BP, Melton LJ 3rd, Rocca WA. Generalizability of epidemiological findings and public health decisions: an illustration from the Rochester Epidemiology Project. *Mayo Clin Proc* 2012;87(2):151–160.
- Baratz KH, Gray DT, Hodge DO, Butterfield LC, Ilstrup DM. Cataract extraction rates in Olmsted County, Minnesota,

- 1980 through 1994. Arch Ophthalmol 1997;115(11): 1441–1446.
- Erie JC, Baratz KH, Hodge DO, Schleck CD, Burke JP. Incidence of cataract surgery from 1980 through 2004: 25-year population-based study. J Cataract Refract Surg 2007;33(7): 1273–1277.
- Erie JC, Hodge DO, Mahr MA. Long-term trends and stabilization of cataract surgery rates: a population-based study. J Cataract Refract Surg 2020;46(7):1056–1057.
- Bergstralh EJ, Offord KP, Chu CP, Beard CM, O'Fallon WM, Melton LJ. Calculating incidence, prevalence and mortality rates for Olmsted county, Minnesota: an update. Technical report no. 49. Available at https://www.mayo.edu/research/ documents/biostat-49pdf/doc-10027851. Accessed July 26, 2020.
- McCulley TJ, Lam BL, Feuer WJ. A comparison of risk factors for postoperative and spontaneous nonarteritic anterior ischemic optic neuropathy. J Neuroophthalmol 2005;25(1): 22–24.
- 24. Hattenhauer MG, Leavitt JA, Hodge DO, Grill R, Gray DT. Incidence of nonarteritic anterior ischemic optic neuropathy. *Am J Ophthalmol* 1997;123(1):103–107.
- 25. Benitah NR, Arroyo JG. Pseudophakic cystoid macular edema. *Int Ophthalmol Clin* 2010;50(1):139–153.