

Endophthalmitis Rate in Immediately Sequential versus Delayed Sequential Bilateral Cataract Surgery within the Intelligent Research in Sight (IRIS®) Registry Data

Megan Lacy, MS,¹ Timothy-Paul H. Kung, MBA,^{1,2} Julia P. Owen, PhD,¹ Ryan T. Yanagihara, MD,¹ Marian Blazes, MD,¹ Suzann Pershing, MD,^{3,4} Leslie G. Hyman, PhD,⁵ Russell N. Van Gelder, MD, PhD,^{1,6} Aaron Y. Lee, MD, MSCI,^{1,6,*} Cecilia S. Lee, MD, MS,^{1,6,*} on behalf of the IRIS® Registry Analytic Center Consortium

Purpose: To compare the rate of postoperative endophthalmitis after immediately sequential bilateral cataract surgery (ISBCS) versus delayed sequential bilateral cataract surgery (DSBCS) using the American Academy of Ophthalmology Intelligent Research in Sight (IRIS®) Registry database.

Design: Retrospective cohort study.

Participants: Patients in the IRIS Registry who underwent cataract surgery from 2013 through 2018.

Methods: Patients who underwent cataract surgery were divided into 2 groups: (1) ISBCS and (2) DSBCS (second-eye surgery ≥ 1 day after the first-eye surgery) or unilateral surgery. Postoperative endophthalmitis was defined as endophthalmitis occurring within 4 weeks of surgery by International Classification of Diseases (ICD) code and ICD code with additional clinical criteria.

Main Outcome Measures: Rate of postoperative endophthalmitis.

Results: Of 5 573 639 IRIS Registry patients who underwent cataract extraction, 165 609 underwent ISBCS, and 5 408 030 underwent DSBCS or unilateral surgery (3 695 440 DSBCS, 1 712 590 unilateral surgery only). A total of 3102 participants (0.056%) met study criteria of postoperative endophthalmitis with supporting clinical findings. The rates of endophthalmitis in either surgery eye between the 2 surgery groups were similar (0.059% in the ISBCS group vs. 0.056% in the DSBCS or unilateral group; $P = 0.53$). Although the incidence of endophthalmitis was slightly higher in the ISBCS group compared with the DSBCS or unilateral group, the odds ratio did not reach statistical significance (1.08; 95% confidence interval, 0.87–1.31; $P = 0.47$) after adjusting for age, sex, race, insurance status, and comorbid eye disease. Seven cases of bilateral endophthalmitis with supporting clinical data in the DSBCS group and no cases in the ISBCS group were identified.

Conclusions: Risk of postoperative endophthalmitis was not statistically significantly different between patients who underwent ISBCS and DSBCS or unilateral cataract surgery. *Ophthalmology* 2022;129:129–138 © 2021 by the American Academy of Ophthalmology



Supplemental material available at www.aaojournal.org.

Cataract surgery is the most commonly performed intraocular ophthalmic surgery in the United States, with more than 2 million surgeries annually.¹ Most cataract surgeries are considered elective, with both ophthalmologists and patients usually deciding the optimal timing of cataract surgeries. In the United States, most cataract surgeries are performed on separate days (delayed sequential bilateral cataract surgery [DSBCS]), but same-day surgery, or immediately sequential bilateral cataract surgery (ISBCS), is the preferred approach in many other countries, where it has been performed for many years without apparent increased risk.²

Immediately sequential bilateral cataract surgery offers potential advantages over DSBCS, including immediate

vision improvement, fewer follow-up visits, and reduced costs for the patient and system.³ However, concerns associated with ISBCS include the inability to adjust the power of the second eye intraocular lens based on the refractive outcome of the first eye⁴ or to address dysphotopsia or other optical symptoms by trying a different intraocular lens type or surgical approach in the second eye and the feared risk of either unilateral or bilateral endophthalmitis.⁵ Although ISBCS is performed with strict aseptic separation between procedures, which includes newly prepping and draping the patient, changing all personal protective equipment, preparing a new sterile field, and obtaining new instruments before the second

procedure,^{6,7} the risk of bilateral endophthalmitis remains. However, only a few cases of bilateral simultaneous postoperative endophthalmitis (BSPOE) after ISBCS have been reported in the literature, and most were associated with failure to achieve proper aseptic separation between 2 eyes.⁸ Other theoretical concerns with ISBCS are the risk of bilateral toxic anterior segment syndrome and increased risk for incorrect intraocular lens placement through fellow-eye confusion.

The coronavirus disease 2019 (COVID-19) pandemic has resulted in unprecedented disruption in medical care, particularly in the field of ophthalmology. Two recent editorials published in *Ophthalmology* highlight the risks and benefits of ISBCS versus DSBSCS in light of the COVID-19 pandemic.^{9,10} Ahmed et al⁹ argue that ISBCS reduces risk of COVID-19 exposure. Considering all risks associated with bilateral surgery, including complications such as endophthalmitis, risks related to anesthesia, and now COVID-19, they argue that ISBCS is safer than DSBSCS. In contrast, according to Masket,¹⁰ cost savings are the main benefit of ISBCS, and COVID-19 considerations are less relevant because cataract surgery primarily is elective. Masket agrees that the risk of bilateral endophthalmitis is very small but points out that cases may be underreported in the literature; thus, all precautions are warranted when blindness is a potential outcome.

Our recent analyses of the refractive outcomes of ISBCS versus DSBSCS using the American Academy of Ophthalmology Intelligent Research in Sight (IRIS[®]) Registry revealed nonclinically significant difference in visual outcome between 2 groups unless patients have multiple risk factors for worse outcome.¹¹ In this study, we evaluated the rate of postoperative endophthalmitis after cataract surgery in the IRIS Registry to determine if there was any difference in risk of endophthalmitis between ISBCS and DSBSCS approaches in this large dataset with nearly 60 million unique patients and 16 000 clinicians reporting from across the United States.¹² The baseline rate of postoperative endophthalmitis is rare regardless of surgical approaches. Given that the number of ISBCS procedures is relatively small in literature, the evaluation of endophthalmitis rate between 2 surgical approaches is difficult with smaller datasets. Thus, we took advantage of the unprecedented size of cataract surgery records within the IRIS Registry to evaluate this challenging question.

Methods

This study was conducted in accordance with the tenets of the Declaration of Helsinki. Given the use of de-identified patient data, the review was exempted from the University of Washington Institutional Review Board. The methods of data collection and aggregation of the IRIS Registry database have been described previously.^{13,14} Version 2020_07_28 of the IRIS Registry, which was last modified on October 23, 2020, was used for this study.

Study Patient Population

Patients in the IRIS Registry with a history of first cataract surgery from 2013 through 2018 were included in the study after reviewing

the entire IRIS Registry dataset for patients who underwent cataract surgery in at least 1 eye. Cataract surgery procedure was defined using Current Procedural Terminology codes 66982 and 66984. Immediately sequential bilateral cataract surgery was defined as both eye cataract extraction procedures occurring on the same date. For the patients who underwent ISBCS, we randomly chose either the left or the right eye to be coded as the first surgery eye. Delayed sequential bilateral cataract surgery was defined by the second eye surgery occurring 1 day or more after the first-eye surgery.

The primary outcome was the rate of endophthalmitis within 4 weeks of cataract surgery in at least 1 eye. We included all patients who underwent unilateral cataract surgery with the DSBSCS group because a significant proportion of patients who experienced postoperative endophthalmitis after the first surgery did not proceed with the second eye; thus, excluding unilateral cases would result in bias toward a lower endophthalmitis rate in the DSBSCS group. In our cohort, 68% of people who had no endophthalmitis diagnosis after the first surgery went on to undergo cataract surgery in their other eye. In comparison, only 33% of patients who had an endophthalmitis diagnosis after the first-eye surgery underwent a cataract surgery in the other eye. Additional secondary analyses were performed with unilateral cases excluded comparing only the ISBCS and DSBSCS groups.

Postoperative endophthalmitis was determined in 2 ways: (1) any endophthalmitis diagnosis code based on International Classification of Diseases (ICD), Ninth Revision, Clinical Modification, and ICD, Tenth Revision, Clinical Modification, codes (098.42, 360.0*, 360.1*, H44.0*, and H44.1*) within 4 weeks of surgery and (2) a diagnosis code with supporting clinical findings, which were identified programmatically. Supporting clinical findings were defined by the endophthalmitis code occurring with either (1) a best-corrected visual acuity drop to 20/200 or worse or (2) an intraocular tap or injection procedure, or both, on or up to 3 days after the day of endophthalmitis diagnosis in the same eye within 4 weeks of surgery. Analysis with this stricter definition of postoperative endophthalmitis was included to account for the possibility of miscoding or lack of laterality information or that a prior endophthalmitis diagnosis might have been carried forward through patient's records (i.e., the patient did not actually have an active case after cataract surgery). Because bilateral endophthalmitis is rare, we performed a manual check on all suspected bilateral endophthalmitis cases identified within 4 weeks of cataract surgery. Two board-certified ophthalmologists (C.S.L., A.Y.L.) reviewed all available clinical data including visual acuity, intraocular pressure, visit dates, and procedure and diagnosis codes for each eye to confirm both eyes had supporting evidence of endophthalmitis. In addition, to address potential biases in choosing different periods to define endophthalmitis, we performed secondary analyses of postoperative endophthalmitis occurring 2 and 6 weeks after cataract surgery. Supporting clinical evidence for bilateral endophthalmitis in the 2- and 6-week group analyses was evaluated with the same aforementioned criteria.

The following demographic and clinical variables were extracted: age at surgery, sex, race, insurance, history of comorbid ophthalmic disease diagnoses based on ICD, Ninth and Tenth Revisions, Clinical Modification, codes (age-related macular degeneration [AMD], diabetic retinopathy [DR], and glaucoma) in the year leading up to surgery (Table S1, available at www.aaojournal.org), laterality of first surgery, and number of days between bilateral cataract surgeries.

If patients had more than 1 form of insurance, a hierarchical heuristic was used to prioritize insurers in the following order: commercial, Medicare or Medicare Advantage, Medicaid, or other. Date of birth is redacted in the IRIS Registry for patients 87 years of age old or older at the time of data release, and as such, anyone

older than 86 years does not have an age at cataract surgery and is grouped with the individuals in the ninth decade of life.

Statistical Analysis

Baseline demographic features and the outcome measures were summarized by surgery group (ISBCS vs. DSBCS or unilateral), and counts and percentages were reported. The primary outcome of interest was development of postoperative endophthalmitis within 4 weeks of cataract surgery. The number and proportion of patients developing endophthalmitis was reported with Clopper–Pearson confidence intervals (CI) overall and for the 2 surgery groups. Fisher exact tests were performed to determine whether the proportion of patients developing endophthalmitis in either eye in the ISBCS group and the DSBCS or unilateral group were significantly different.

Multivariable logistic regression models were run to estimate odds ratios (OR) for postoperative endophthalmitis developing in the ISBCS group relative to the DSBCS or unilateral group in at least 1 eye, adjusting for decade of life, race, insurance type, and history of AMD, DR, or glaucoma. One model was run for each criterion for postoperative endophthalmitis. Patients missing age (decade of life) or sex were excluded from regression models. For patients in whom postoperative endophthalmitis developed, AMD, DR, and glaucoma status from the affected eye was used. For patients with no postoperative endophthalmitis, the patient was considered to have a history of AMD, DR, or glaucoma if they had a diagnosis code in either eye before surgery.

Secondary analyses were performed to evaluate potential biases in choosing different surgical eye of interest, comparator groups, and follow-up periods. Modeling was repeated for OR of endophthalmitis developing in the first-surgery eye. Further modeling was performed comparing DSBCS alone with ISBCS with odds of endophthalmitis developing in either eye and the second surgery eye as the outcome. All analyses were repeated for endophthalmitis cases within postoperative periods of 2 and 6 weeks. In the cases in which endophthalmitis risk in the first or second eye was examined, AMD, DR, and glaucoma history from the surgery eye was used. Logistic regression models were also fit for odds of confirmed endophthalmitis separately for the ISBCS and DSBCS or unilateral surgery groups to assess the impacts of covariates on endophthalmitis within each group. Ninety-five percent CIs for the OR were computed using the score method. All analyses were performed with R software (R Foundation for Statistical Computing).

Results

Patient Demographic and Baseline Clinical Characteristics

The IRIS Registry database documented 5 573 639 patients who underwent cataract surgery between 2013 and 2018. A total of 165 609 of these patients (3%) underwent ISBCS, and 5 408 030 patients (97%) underwent DSBCS ($n = 3\,695\,440$ [66%]) or unilateral cataract surgery ($n = 1\,712\,590$ [31%]; [Fig 1](#)). Patient demographic factors are reported in [Table 1](#). Most patients in both groups were female (59% and 58%) and White (74% and 73%). Rates of any prior AMD (3% vs. 2.8%), DR (1.5% vs. 1.7%), and glaucoma (4.6% vs. 4.4%) in the year before surgery were similar between the 2 groups.

Postoperative Endophthalmitis

Overall, 3703 patients (0.066%) had a diagnosis of endophthalmitis within 4 weeks of cataract surgery, and of these, 3102 patients (0.056%) had a diagnosis of endophthalmitis with supporting clinical results. Rates of endophthalmitis within 4 weeks of surgery were similar between the 2 surgery groups, with 116 cases (0.070%; 95% CI, 0.058%–0.084%) in the group of patients who underwent ISBCS and 3587 cases (0.066%; 95% CI, 0.064%–0.069%) in the group of patients who underwent either DSBCS or unilateral cataract surgery ($P = 0.56$). For endophthalmitis diagnosis with supporting clinical findings, 98 cases (0.059%; 95% CI, 0.048%–0.072%) were identified in the ISBCS group, and 3004 cases (0.056%; 95% CI, 0.054%–0.058%) were identified in the DSBCS or unilateral group ($P = 0.53$). After expert review of examination findings, intraocular pressure results, diagnosis records, and procedure records by an established criteria mentioned in “Methods,” a total of 7 patients (0.00013%) were found to have had bilateral endophthalmitis within 4 weeks of cataract surgery, all of whom had undergone DSBCS. None of 4 patients with bilateral endophthalmitis identified by diagnosis in the ISBCS group (3 during the 4-week period and 1 during the 6-week period of follow-up) were found to have clinical findings that met our confirmation criteria, which was upheld on manual review ([Table 2](#); [Table S2](#), [Table S3](#) and [Supplemental Appendix](#), available at www.aaojournal.org).

Secondary analyses failed to show a statistically significant difference in the rate of endophthalmitis between different groups. The OR of any diagnosis of postoperative endophthalmitis in either eye adjusted for decade of life, sex, race, and insurance type was 1.07 (95% CI, 0.88–1.08) for the ISBCS group compared with the DSBCS or unilateral surgery group; however, this was not statistically significant ($P = 0.49$). Results were similar in the subset of patients with supporting clinical findings with the OR of 1.08 (95% CI, 0.87–1.31), which also was not statistically significant ($P = 0.47$; [Table 3](#)). The OR of a diagnosis of postoperative endophthalmitis in the first surgery eye adjusted for decade of life, sex, race, and insurance type was 0.91 (95% CI, 0.68–1.18) for the ISBCS group compared with the DSBCS or unilateral surgery group; however, this was not statistically significant ($P = 0.48$). Results were similar in the subset of these patients with supporting clinical findings with the OR of 0.88 (95% CI, 0.64–1.17), which was not statistically significant ($P = 0.40$; [Table 3](#)).

[Figure 2](#) summarizes OR and 95% CIs associated with each covariate for development of endophthalmitis by surgery group. For the DSBCS or unilateral group, endophthalmitis odds were lowest for those 69 years of age and younger, with OR increasing for those 70 to 79 years of age (OR, 1.23; 95% CI, 1.08–1.40) and highest for those 80 years of age and older (OR, 1.56; 95% CI, 1.35–1.80) relative to those 0 to 59 years of age. Men showed higher odds of endophthalmitis developing relative to women (OR, 1.33; 95% CI, 1.24–1.43). No significant differences were found in OR for endophthalmitis based

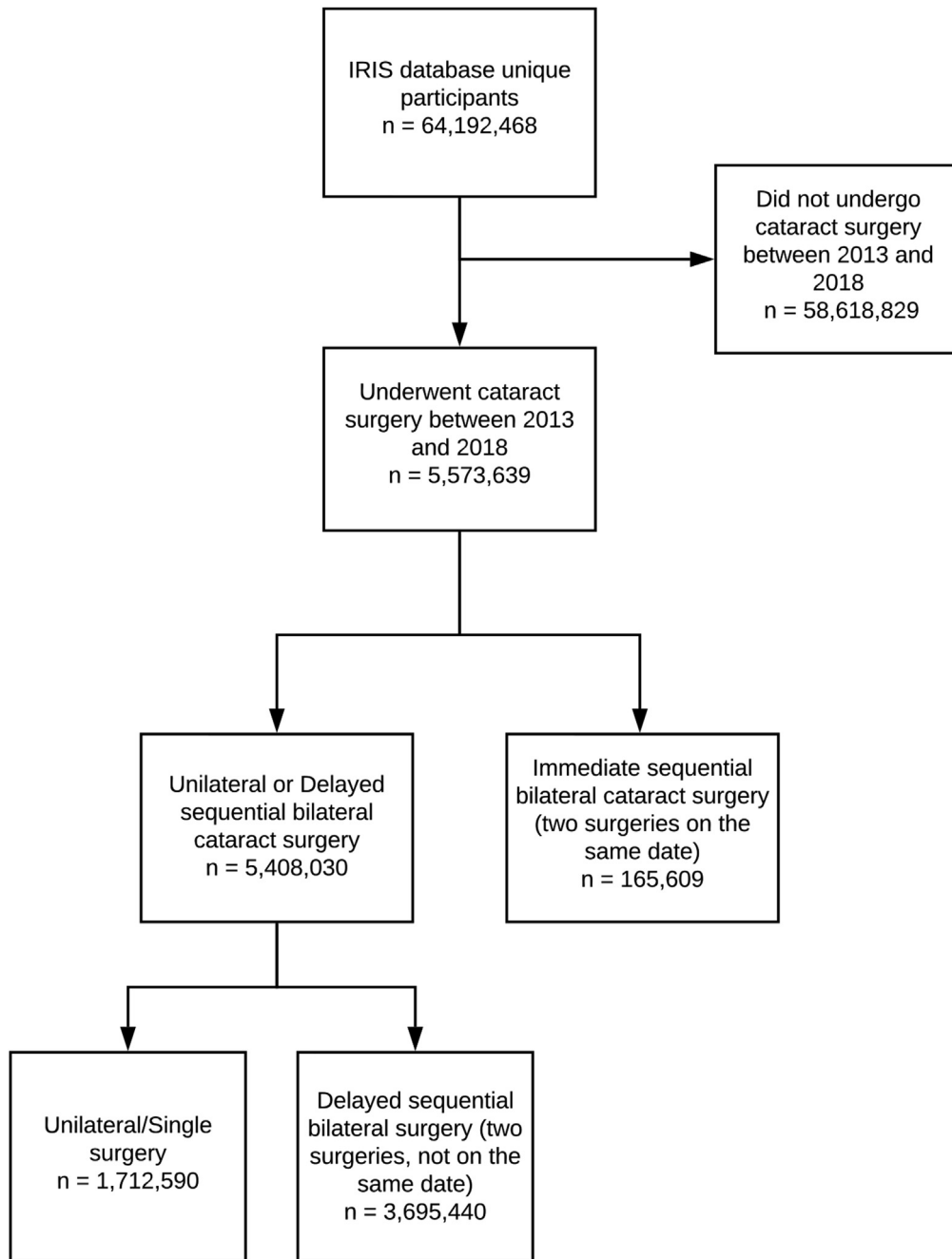


Figure 1. Flow diagram of study participants.

on race. Patients with commercial insurance showed a higher OR of endophthalmitis relative to those with Medicare (OR, 1.11; 95% CI, 1.02–1.21), and patients with prior history of glaucoma showed a higher odds of endophthalmitis (OR, 1.46; 95% CI, 1.26–1.68) relative to those without prior glaucoma.

Secondary Analyses

No significant differences in estimated odds of endophthalmitis developing after cataract surgery within 2 or 6

weeks were found between the ISBCS group and the combined DSBCS or unilateral group. Endophthalmitis rates based on diagnosis with supporting clinical findings in either eye in the ISBCS group were 0.037% at 2 weeks and 0.065% at 6 weeks, and in the combined DSBCS or unilateral group, they were 0.047% at 2 weeks (OR, 0.79; 95% CI, 0.61–1.01) and 0.060% at 6 weeks (OR, 1.11; 95% CI, 0.91–1.33). Endophthalmitis rates by diagnosis with supporting clinical findings in the first-surgery eye in the ISBCS group were 0.019% at 2 weeks and 0.028% at 6 weeks, and the rates in the combined DSBCS or unilateral group were

Table 1. Demographic and Baseline Clinical Factors of Study Populations by Surgery Group

	Unilateral (n = 1 712 590)	Delayed Sequential Bilateral Cataract Surgery (n = 3 695 440)	Delayed Sequential Bilateral Cataract Surgery and Unilateral Surgery (n = 5 408 030)	Immediate Sequential Bilateral Cataract Surgery (n = 165 609)	Total (n = 5 573 639)
Decade of life at first surgery (yrs)					
0–9	1133 (< 0.1)	689 (< 0.1)	1822 (< 0.1)	101 (< 0.1)	1923 (< 0.1)
10–19	2097 (0.1)	1271 (< 0.1)	3368 (< 0.1)	166 (0.1)	3534 (< 0.1)
20–29	4760 (0.3)	3008 (< 0.1)	7768 (0.1)	334 (0.2)	8102 (0.1)
30–39	12 196 (0.7)	8604 (0.2)	20 800 (0.4)	839 (0.5)	21 639 (0.4)
40–49	46 164 (2.7)	46 021 (1.2)	92 185 (1.7)	3078 (1.9)	95 263 (1.7)
50–59	190 144 (11)	282 911 (7.7)	473 055 (8.7)	15 371 (9.3)	488 426 (8.8)
60–69	519 982 (30)	1 186 682 (32)	1 706 664 (32)	53 232 (32)	1 759 896 (32)
70–79	615 410 (36)	1 589 310 (43)	2 204 720 (41)	67 046 (40)	2 271 766 (41)
80+	320 321 (19)	576 623 (16)	896 944 (17)	25 398 (15)	922 342 (17)
Missing age	383	321	704	44	748
Gender					
Female	905 774 (53)	2 225 135 (60)	3 130 909 (58)	97 351 (59)	3 228 260 (58)
Male	800 072 (47)	1 459 533 (39)	2 259 605 (42)	67 790 (41)	2 327 395 (42)
Not reported	6744 (0.4)	10 772 (0.3)	17 516 (0.3)	468 (0.3)	17 984 (0.3)
Race					
White	1 207 426 (71)	2 816 202 (76)	4 023 628 (74)	120 224 (73)	4 143 852 (74)
Black or African American	139 019 (8.1)	211 521 (5.7)	350 540 (6.5)	11 860 (7.2)	362 400 (6.5)
Asian	48 297 (2.8)	73 758 (2.0)	122 055 (2.3)	3774 (2.3)	125 829 (2.3)
Other	19 544 (1.1)	31 870 (0.9)	51 414 (1.0)	2054 (1.2)	53 468 (1.0)
Unknown	298 304 (17)	562 089 (15)	860 393 (16)	27 697 (17)	888 090 (16)
Insurance					
Medicare	431 429 (25)	1 108 236 (30)	1 539 665 (28)	50 655 (31)	1 590 320 (29)
Medicaid	23 501 (1.4)	42 490 (1.1)	65 991 (1.2)	5267 (3.2)	71 258 (1.3)
Commercial	928 930 (54)	2 161 988 (59)	3 090 918 (57)	87 356 (53)	3 178 274 (57)
Other	36 090 (2.1)	62 335 (1.7)	98 425 (1.8)	4915 (3.0)	103 340 (1.9)
Unknown	292 640 (17)	320 391 (8.7)	613 031 (11)	17 416 (11)	630 447 (11)
Prior eye disease					
First surgery eye					
AMD	46 985 (2.7)	73 777 (2.0)	120 762 (2.2)	3208 (1.9)	123 970 (2.2)
DR	27 983 (1.6)	35 539 (1.0)	63 522 (1.2)	2040 (1.2)	65 562 (1.2)
Glaucoma	88 323 (5.2)	109 414 (3.0)	197 737 (3.7)	4928 (3.0)	202 665 (3.6)
Second surgery eye*					
AMD	—	79 145 (2.1)	79 145 (2.1)	3147 (1.9)	82 292 (2.1)
DR	—	40 264 (1.1)	40 264 (1.1)	2031 (1.2)	42 295 (1.1)
Glaucoma	—	121 037 (3.3)	121 037 (3.3)	4913 (3.0)	125 950 (3.3)
Either eye					
AMD	46 985 (2.7)	117 925 (3.2)	164 910 (3.0)	4711 (2.8)	169 621 (3.0)
DR	27 983 (1.6)	54 432 (1.5)	82 415 (1.5)	2755 (1.7)	85 170 (1.5)
Glaucoma	88 323 (5.2)	158 059 (4.3)	246 382 (4.6)	7283 (4.4)	253 665 (4.6)

AMD = age-related macular degeneration; DR = diabetic retinopathy; — = not applicable.

Data are presented as no. (%).

*Percentages taken from the number of participants who underwent bilateral cataract surgery (n = 3 695 440, n = 165 609, and n = 3 861 049, respectively).

0.025% (OR, 0.74; 95% CI, 0.50–1.04) at 2 weeks and 0.033% at 6 weeks (OR, 0.84; 95% CI, 0.62–1.12), respectively (Table 3).

When comparing the ISBCS group with the DSBCS patients only, the odds of endophthalmitis developing by diagnosis with supporting clinical findings in the second eye were slightly lower at 2 weeks (OR, 0.59; 95% CI, 0.40–0.83) but similar when looking at endophthalmitis within 4 weeks (OR, 0.91; 95% CI, 0.68–1.18) and 6 weeks (OR, 0.99;

95% CI, 0.76–1.26) of surgery (Table S4, available at www.aaojournal.org).

Discussion

In analyses of 5 408 030 DSBCS or unilateral cataract surgeries and 165 609 ISBCS included in the IRIS Registry from 2013 through 2018, no significant difference in the

Table 2. Cases of Postoperative Endophthalmitis within 4 Weeks after Cataract Surgery Diagnosed with or without Supporting Clinical Findings

Diagnosis	Eye	Delayed Sequential Bilateral Cataract Surgery and Unilateral Surgery			Immediate Sequential Bilateral Cataract Surgery	
		Unilateral Surgery (n = 1 712 590)	Delayed Sequential Bilateral Cataract Surgery (n = 3 695 440)	Total (n = 5 408 030)	Bilateral Cataract Surgery (n = 165 609)	Total (n = 5 573 639)
Endophthalmitis diagnosis	Either eye*	1311 (0.077)	2276 (0.062)	3587 (0.066)	116 (0.070)	3703 (0.066)
	First eye	1311 (0.077)	690 (0.019)	2001 (0.037)	55 (0.033)	2056 (0.037)
	Second eye†	—	1623 (0.044)	1623 (0.044)	64 (0.039)	1687 (0.044)
	Both eyes†	—	37 (0.001)	37 (0.001)	3 (0.002)	40 (0.001)
Diagnosis with supporting clinical findings	Either eye*	1118 (0.065)	1886 (0.051)	3004 (0.056)	98 (0.059)	3102 (0.056)
	First eye	1118 (0.065)	524 (0.014)	1642 (0.030)	44 (0.027)	1686 (0.030)
	Second eye†	—	1369 (0.037)	1369 (0.037)	54 (0.033)	1423 (0.037)
	Both eyes†	—	7 (0.0002)	7 (0.0001)	0 (0.0)	7 (0.0001)

— = not applicable.

Data are presented as no. (%).

*Patients demonstrated postoperative endophthalmitis in either the first or second surgery eye, or both.

†Percentages taken from the number of participants who underwent bilateral cataract surgery (n = 3 695 440, n = 165 609, and n = 3 861 049).

odds of postoperative endophthalmitis between the ISBCS and DSBSCS or unilateral groups were found after controlling for age, sex, race, insurance status, and comorbid eye diseases. Bilateral endophthalmitis was extremely rare in general, and all 7 cases of bilateral postoperative endophthalmitis (BPOE), confirmed by clinical review, occurred in the DSBSCS group.

Endophthalmitis is one of the most serious complications associated with cataract surgery and is rare in the United States. Previous smaller studies in the United States have reported rates of postoperative endophthalmitis ranging from 0.04% to 0.215%.^{15–18} The difference in the observed postoperative period after cataract surgery may have contributed to the varying rates. For example, researchers at the Shandong Eye Institute defined the study period as 1 to 37 days and found an endophthalmitis rate of 0.13%, which was much higher than our rate of approximately 0.05% over

6 years.¹⁹ Another recent retrospective study of more than 8 million eyes in the IRIS Registry undergoing unilateral cataract surgery between 2013 and 2017 estimated an overall incidence of endophthalmitis occurring within 30 days after surgery to be 0.04% based on the ICD, Ninth and Tenth Revisions, Clinical Modification, diagnosis codes, the Current Procedural Terminology codes for intravitreal antibiotics, or both.²⁰ Unlike our study, Pershing et al²⁰ excluded patients undergoing ISBCS but included patients who underwent cataract surgery combined with other ocular procedures and found a higher rate of endophthalmitis in this group. Using the most recent version of the IRIS Registry, we found a slightly higher overall rate of endophthalmitis (0.056%) when we restricted our endophthalmitis definition within 4 weeks after cataract surgery using a stricter criterion (ICD code diagnosis combined with clinical results in patients

Table 3. Comparison of Odds Ratios for Risk of Postoperative Endophthalmitis between the Immediate Sequential Bilateral Cataract Surgery and Delayed Sequential Bilateral Cataract Surgery or Unilateral Surgery Groups

Duration of Postoperative Follow-up for Endophthalmitis Diagnosis (wks)	Diagnosis	Eye	Odds Ratio* (95% Confidence Interval) and P Value
2	Endophthalmitis diagnosis	Either eye†	0.81 (0.64–1.01), 0.08
		First eye	0.78 (0.56–1.06), 0.14
	Diagnosis with supporting clinical findings	Either eye†	0.79 (0.61–1.01), 0.07
		First eye	0.74 (0.50–1.04), 0.10
4	Endophthalmitis diagnosis	Either eye†	1.07 (0.88–1.28), 0.49
		First eye	0.91 (0.68–1.18), 0.48
	Diagnosis with supporting clinical findings	Either eye†	1.08 (0.87–1.31), 0.47
		First eye	0.88 (0.64–1.17), 0.40
6	Endophthalmitis diagnosis	Either eye†	1.11 (0.93–1.32), 0.34
		First eye	0.88 (0.67–1.13), 0.25
	Diagnosis with supporting clinical findings	Either eye†	1.11 (0.91–1.33), 0.31
		First eye	0.84 (0.62–1.12), 0.25

*For endophthalmitis developing after immediately sequential bilateral cataract surgery relative to delayed sequential bilateral cataract surgery or unilateral surgery based on logistic regression model adjusted for decade of life, sex, race, insurance, and history of age-related macular degeneration, diabetic retinopathy, and glaucoma.

†Patients demonstrated postoperative endophthalmitis in either the first or second surgery eye, or both.

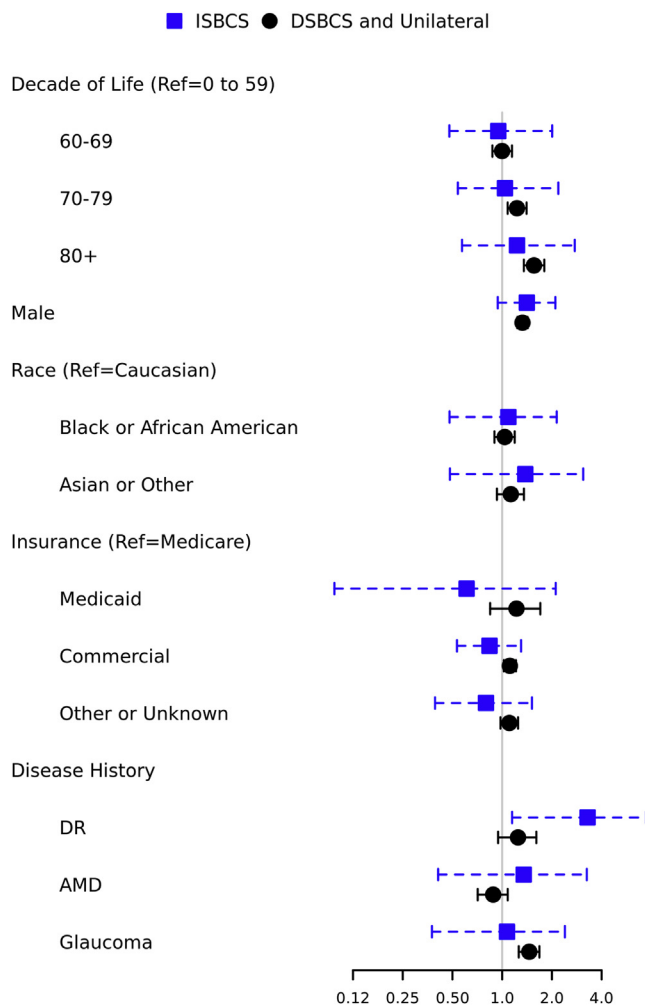


Figure 2. Forest plot showing risk of endophthalmitis associated with covariates for immediately sequential bilateral cataract surgery group (ISBCS; $n = 165\,609$) versus delayed sequential bilateral cataract surgery (DSBCS) or unilateral surgery ($n = 5\,408\,030$). AMD = age-related macular degeneration; DR = diabetic retinopathy.

undergoing unilateral surgery, DSBCS, and ISBCS). When we extended the postoperative period in question after cataract surgery, the overall rate of endophthalmitis increased slightly (0.060% at 6 weeks).

Previous studies also compared the rates of postoperative endophthalmitis between ISBCS and DSBCS. However, all were limited by relatively small sample sizes ranging from 980 to 125 188 eyes.^{8,21,22} Two smaller randomized control trials in Europe analyzing visual acuity outcomes found no cases of postoperative endophthalmitis in either ISBCS patients (480–834 eyes) or DSBCS patients.^{21,22} A larger cohort study involving 125 188 eyes (ISBCS, $n = 95\,606$ eyes; DSBCS, $n = 29\,582$ eyes) in 10 countries found the incidence of postoperative endophthalmitis after ISBCS to be 0.017% overall and a reduced incidence of 0.00696% with intracameral antibiotics.⁸ These endophthalmitis rates were based on self-reported data from members of the International Society of Bilateral Cataract Surgeons; thus, the true rates may have been different. In comparison, our study

relied on anonymized electronic health record data information from more than 16 000 clinicians in the IRIS Registry.¹² We also performed an analysis using a stricter definition for endophthalmitis that assessed for clinical supporting evidence, including antibiotic injection codes and visual acuity measurements, and found no statistically significant difference in the rate of endophthalmitis between ISBCS and DSBCS with or without unilateral surgery groups.

One of the primary concerns with performing ISBCS is the risk of BSPOE,²³ which could result in profound blindness in both eyes, although the risk of bilateral endophthalmitis exists with either ISBCS or DSBCS. The existing literature shows the risk of BSPOE after ISBCS to be extremely small.^{23,24} Only 5 cases of BSPOE after ISBCS have been reported to the best of our knowledge, making the overall rate prediction difficult.^{25–29} In addition, the first 4 cases were believed to be the result of a breach in the aseptic protocol published by the International Society of Bilateral Cataract Surgeons.^{23,24,30} Operating room protocol preparation and instrumentation protocol were unknown for the fifth and most recent case.²⁹ Moreover, no cases of bilateral endophthalmitis were reported among studies comparing outcomes between ISBCS and DSBCS.^{8,21,22,31} The lack of bilateral endophthalmitis in the ISBCS group in our study suggests that an aseptic protocol between the 2 surgery eyes was likely followed strictly in the IRIS Registry population. The absence of BPOE cases in the DSBCS group in previous literature could have been the result of having a smaller sample size overall, because we found several BPOE cases in the DSBCS group. Nevertheless, immediately sequential bilateral surgery in other specialties such as orthopedics have been performed routinely and continue to be the standard or a viable choice.^{32–34}

Endophthalmitis is a rare surgical occurrence, and BPOE is extremely rare.^{15–18,20} When evaluating studies in this topic, it is critical to consider whether the sample size was sufficient to have observed any cases of endophthalmitis. To our best knowledge, our analysis is the largest and most current analysis of endophthalmitis risk in both ISBCS and DSBCS populations in the United States or in the existing literature, with 3.5 times more ISBCS patients than other similar studies.^{8,21,22,31} However, based on the rate of unilateral endophthalmitis detected in the ISBCS group (0.070%) and assuming that endophthalmitis risk is independent between the 2 eyes, we would need roughly 2 million patients (more than 10 times the number of patients that we included in this group) before we would expect to see any bilateral endophthalmitis. Thus, even a larger amount of data from diverse populations is needed to confirm this rate. It is noteworthy that the only other study in the United States to evaluate the endophthalmitis risk in the ISBCS versus DSBCS groups was restricted to patients from Northern California from 2013 through 2015.³¹ Thus, the current study results using the IRIS Registry, which come from a wide distribution of geographic locations throughout the entire United States, may be more generalizable.

It is important to note that we included unilateral cases in the DSBCS group in our primary analysis because patients who had endophthalmitis after the first cataract surgery were less likely to have proceeded to a second surgery. By excluding patients who underwent surgery in only 1 eye, we may have missed a small number of patients who did not undergo second-eye cataract surgery because of endophthalmitis after the first surgery, thus biasing our results toward less endophthalmitis in the DSBCS group and making the odds of any endophthalmitis developing in the ISBCS group seem deceptively higher in comparison. It is also possible that these patients could have undergone 2 surgeries, with only 1 surgery reported in the IRIS Registry. However, at the same time, our inclusion of unilateral cases with DSBCS also could have biased the results toward a higher endophthalmitis rate in this group, because the sample of patients who undergo unilateral surgery may overrepresent those in whom endophthalmitis developed after the first-eye surgery, may have more underlying systemic or ocular comorbidities that might increase odds for endophthalmitis, or both.

We did not find a significant difference in OR for endophthalmitis between the ISBCS and DSBCS or unilateral groups in our study. We performed multiple secondary analyses such as evaluating the risks of endophthalmitis in either eye or specifically in the first eye, excluding all unilateral cases from the DSBCS or unilateral group, comparing the first-eye rates of endophthalmitis in the combined group with the ISBCS group, and repeating all analyses for 2 and 6 weeks of postoperative follow-up to address any potential biases. Nevertheless, results were consistent for all analytic approaches, that is, none of these analyses revealed a significant difference in the rate of endophthalmitis between ISBCS and DSBCS with or without unilateral surgery groups.

The COVID-19 pandemic has presented many challenges to outpatient elective surgeries. Most notable is the fear of COVID-19 transmission in a medical setting, because hospitals are thought to be possible hot zones of potential COVID-19 transmission.^{35,36} As a result, patients are less likely to elect to undergo cataract surgery because of concerns of COVID-19 exposure in hospital or during travel to the hospital.³⁷ In addition to decreased patient burden and recovery time,³⁸ proponents of ISBCS⁹ also have highlighted the overall reduced COVID-19 exposure risk with ISBCS because of the decrease of patient visits and contact exposures by half, which is especially significant for the elderly population, who are at higher risk of death resulting from COVID-19.^{9,39}

Several limitations exist in our study. First, we can measure only associations of various exposure and not causality. Second, we used ICD and Current Procedural Terminology codes and electronic health records to obtain patient information, which may have included misclassified

or missing data. Coding error in particular would have resulted in a higher rate of endophthalmitis. However, we had strict criteria for defining endophthalmitis using the available clinical data such as 20/200 vision or worse, thus missing less severe cases and underrepresenting the true rate. Therefore, we believe that the true rate of endophthalmitis will be close to these 2 estimates of the endophthalmitis rate. Third, we did not have access to operative complications, and the cases that resulted in complications likely had a higher rate of endophthalmitis. Fourth, we included only patients who had undergone the first surgery between 2013 and 2018 after evaluating the records of patients who underwent cataract surgery in the entire dataset, including the years before 2013. However, it is possible that only 1 surgery that a patient underwent may have been reported in the IRIS Registry or that a patient underwent the second surgery after 2018, such that only 1 surgery would have been included in our dataset. Therefore, we focused on the patient-level data and analyzed primarily the rate of endophthalmitis in either eye. Fifth, we cannot account for many ocular or systemic factors that would contraindicate ISBCS in our dataset. However, ruling out these factors likely would occur by any clinicians before balancing the risks of endophthalmitis, and this may not have been a critical consideration because the number of DSBCS cases are overwhelmingly higher than that of ISBCS in the United States. A future randomized clinical trial likely would not be possible given the power needed to study this question, forcing us to rely on a large retrospective data analysis with important caveats. Therefore, despite these limitations, we believe our results are still likely applicable to routine clinical settings. Finally, our dataset may not represent other patient populations in the United States such as patients within the Veterans Affairs health care system or at other sites not participating in the IRIS Registry.

Based on data of over 5 million patients who underwent cataract surgery in a routine clinical setting, we found no statistically significant difference in the rates of postoperative endophthalmitis for patients who underwent ISBCS and those who had DSBCS or unilateral cataract surgery. Bilateral postoperative endophthalmitis is extremely rare, and it is possible that surgery center-related confounders may have a greater influence than surgical timing. Additionally, the lack of BSPOE in the ISBCS group may be the result of its significantly smaller sample size compared with the DSBCS and unilateral group. As ISBCS increases in popularity, expansion of the present study will be valuable to confirm our findings, and we hope to see progressive decline in endophthalmitis frequencies in all groups. In conclusion, our results suggest that the risk of postoperative endophthalmitis is similarly low for ISBCS and DSBCS. We were unable to validate it as a significant factor for patients choosing between these 2 approaches.

Footnotes and Disclosures

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¹ Department of Ophthalmology, University of Washington, Seattle, Washington.

² Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, The State University of New York, Buffalo, New York.

³ Department of Ophthalmology, Byers Eye Institute, Stanford University, Palo Alto, California.

⁴ Veterans Affairs Palo Alto Health California System, Palo Alto, California.

⁵ The Vision Research Center, Wills Eye Hospital, Philadelphia, Pennsylvania.

⁶ Roger and Angie Karalis Johnson Retina Center, Seattle, Washington.

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*Both authors contributed equally as senior authors.

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MPH (Department of Ophthalmology, Mass Eye and Ear, Harvard Medical School, Boston, MA), Joan W. Miller, MD (Department of Ophthalmology, Mass Eye and Ear, Harvard Medical School, Boston, MA).

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Author Contributions:

Conception and design: Lacy, A.Y.Lee, C.S.Lee

Analysis and interpretation: Lacy, Kung, Owen, Yanagihara, Blazes, Pershing, Hyman, Van Gelder, A.Y.Lee, C.S.Lee

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Overall responsibility: Lacy, Kung, Owen, Yanagihara, Blazes, Pershing, Hyman, Van Gelder, A.Y.Lee, C.S.Lee

Abbreviations and Acronyms:

AMD = age-related macular degeneration; **BPOE** = bilateral postoperative endophthalmitis; **BSPOE** = bilateral simultaneous postoperative endophthalmitis; **CI** = confidence interval; **COVID-19** = coronavirus disease 2019; **DR** = diabetic retinopathy; **DSBCS** = delayed sequential bilateral cataract surgery; **ICD** = International Classification of Diseases; **IRIS** = Intelligent Research in Sight; **ISBCS** = immediately sequential bilateral cataract surgery; **OR** = odds ratio.

Keywords:

Complications, COVID-19, Delayed sequential bilateral cataract surgery (DSBCS), Immediately sequential bilateral cataract surgery (ISBCS), Intelligent Research in Sight Registry (IRIS® Registry), Outcomes, Post-operative endophthalmitis, Same-day bilateral cataract surgery, SARS-CoV-2, Simultaneous bilateral cataract surgery.

Correspondence:

Cecilia S. Lee, MD, MS, Department of Ophthalmology, University of Washington, Box 359608, 325 Ninth Avenue, Seattle, WA 98104. E-mail: leecs2@uw.edu.

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