Incidence of Intraoperative and Early Postoperative Adverse Events in a Large Cohort of Consecutive Refractive Lens Exchange Procedures

JULIE M. SCHALLHORN, STEVEN C. SCHALLHORN, DAVID TEENAN, STEPHEN J. HANNAN, MARTINA PELOUSKOVA, AND JAN A. VENTER

• PURPOSE: To evaluate the incidence of adverse events (AEs) in patients who underwent refractive lens exchange.

• DESIGN: Retrospective case series.

• METHODS: SETTING: Private refractive surgery clinics. PATIENTS/STUDY POPULATION: Patients who underwent refractive lens exchange between July 1, 2014, and June 30, 2016. INTERVENTION/OBSERVATION PROCEDURES: All AEs recorded in the electronic medical record were extracted and retrospectively reviewed. The total incidence of AEs and serious AEs was calculated. Loss of 2 or more lines of corrected distance visual acuity (CDVA) was calculated for the entire cohort of patients that attended a minimum of 3 months follow-up. MAIN OUTCOME MEASURES: AEs.

• RESULTS: The total number of patients included was 10,206 (18,689 eyes). A multifocal intraocular lens (IOL) was implanted in 84.3% of eyes; 15.7% of eyes received a monofocal IOL. A total of 1164 AEs were recorded (1112 eyes of 1039 patients, incidence 6.0% of eyes, 1:17 eyes). The most common AE was posterior capsular opacification (PCO; 748 eyes, incidence 4.0%). Of all AEs, 171 events (occurring in 165 eyes of 151 patients, incidence 0.9%, 1:113 eyes) were classified as serious, potentially sight threatening. Loss of 2 or more lines of CDVA was 0.56% when excluding eyes where the loss of CDVA was due to PCO; the majority of these were due to macular causes.

• CONCLUSION: The incidence of sight-threatening AEs and significant loss of CDVA in elective refractive lens exchange surgery was low. Other than PCO, postoperative macular issues were the most common cause of vision loss in this cohort. (Am J Ophthalmol 2019;208:406–414. © 2019 Elsevier Inc. All rights reserved.)

Accepted for publication Aug 26, 2019.

From the Department of Ophthalmology (J.M.S., S.C.S.) and F.I. Proctor Foundation (J.M.S.), University of California, San Francisco, San Francisco, California, USA; Carl Zeiss, Meditec, Dublin, California, USA (S.C.S.); and Optical Express, Glasgow, United Kingdom (S.C.S., D.T., S.J.H., M.P., J.A.V.).

Inquiries to Julie M. Schallhorn, Department of Ophthalmology, University of California, San Francisco, 10 Koret Way K323, San Francisco, CA 94143, USA; e-mail: Julie.schallhorn@ucsf.edu

CATARACT SURGERY HAS UNDERGONE MULTIPLE technological and medical advances that have yielded a procedure that is safe, is effective, and offers excellent patient outcomes.[1] Many advances, such as an introduction of microincisional surgery, improved intraocular lens (IOL) design, foldable lenses, ability to more precisely measure axial length and keratometry, and new-generation formulae to calculate the lens power have increased both the safety and predictability of outcomes.[1,2] With these superior outcomes evident, surgeon confidence has increased and the procedure is now offered to a wider range of patients. This includes those who would not be good candidates for laser refractive surgery, presbyopic patients,[3] and patients who have reasonable best-corrected vision (20/20 to 20/40) but have significant visual symptoms related to early cataract changes, such as glare and difficulty driving at night.

Compared to laser vision correction, intraocular procedures are more surgically invasive and potential adverse events can be more visually disabling.[4] Refractive lens exchange (RLE) and cataract surgery have a similar spectrum of adverse events (AEs). However, RLE patients are generally younger, have softer crystalline lenses, and have fewer pre-existing medical and ocular comorbidities than patients who undergo the procedure for visually significant cataracts.[1,2,4,5] It has been reported that RLE performed in patients with high axial lengths can increase the risk of certain AEs.[1,4] However, there is a lack of literature specifically reporting AEs of RLE, and the studies have been restricted to a certain group of patients (eg, highly myopic, highly hyperopic).[6,7]

The aim of this study is to report incidence of AEs in a large population of patients who recently underwent phacoemulsification with the implantation of an IOL for refractive indications.

METHODS

THIS STUDY WAS DEEMED EXEMPT FROM FULL REVIEW BY the Committee on Human Research (the institution-specific name for the institutional review board) at the

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2019.08.025

TABLE 1. Definition of Adverse Events in Refractive Lens Exchange

Adverse Event Name	Serious Adverse Event?	Definition
Abrasion	–	Corneal epithelial defect that occurred in immediate postoperative period and likely related to the surgical procedure
Recurrent erosions	–	Repeated postoperative breakdown of corneal epithelium requiring management
Wound leak	Yes	Postsurgical wound leak requiring management
Sterile infiltrate	–	Noninfectious corneal infiltrate(s)
Herpes simplex keratitis	–	Herpes simplex keratitis based on clinical findings
Corneal edema	Yes	Corneal edema persisting for longer than 1 month postoperative
IOP elevated	–	Elevated intraocular pressure (>21 mm Hg) persisting for longer than 1 week
Nonreactive pupil	–	Nonreactive pupil
Aqueous misdirection	Yes	Aqueous misdirection based on clinical findings
Persistent inflammation	–	Anterior uveitis persisting for longer than 1 week postoperative or anterior uveitis that occurred at any time postoperative and required management for longer than 1 month
Toxic anterior segment syndrome	Yes	Significant rapid onset postoperative anterior uveitis (with or without hypopyon, corneal edema, elevated IOP) where endophthalmitis was ruled out
IOL decentered	Yes	IOL complications based on clinical findings
IOL displaced	Yes	
IOL tilted	Yes	
Incorrect treatment	Yes	Incorrect lens power or incorrect lens type
Iris trauma	–	Iris trauma related to procedure
Posterior capsule tear/vitreous loss	Yes	Posterior capsule tear with or without vitreous loss that resulted in inability to implant IOL in the capsular bag
Pigment on IOL	–	Pigment on IOL diagnosed on slit-lamp examination
Retained lens material	Yes	Retained lens material that required subsequent surgical intervention
Posterior capsule opacification	–	Posterior capsule opacification that reduced CDVA by at least 1 Snellen line
Vitreous hemorrhage	Yes	Vitreous hemorrhage that occurred as a result of the procedure
Cystoid macular edema	Yes	Cystoid macular edema diagnosed by clinical examination and confirmed by optical coherence tomography reducing CDVA to ≤20/40 at ≥1 month postoperative
Retinal detachment	Yes	Retinal detachment diagnosed on dilated fundus examination, requiring urgent treatment
Retinal tear	Yes	Retinal tear diagnosed on clinical examination, requiring treatment
Other macular/retinal complication	Yes	Other posterior segment complications diagnosed by clinical examination and confirmed by optical coherence tomography, including pigment epithelium detachment, macular hole, incomplete posterior vitreous detachment with traction forming a macular cyst, epiretinal membrane, or age-related macular degeneration
Endophthalmitis	Yes	Presumptive diagnosis based on clinical examination, including pain, reduced vision, chemosis, conjunctivitis, panuveitis, corneal edema, and/or hypopyon

CDVA = corrected distance visual acuity; IOL = intraocular lens; IOP = intraocular pressure.

University of California San Francisco because it used only retrospective, de-identified patient data. Patients provided informed consent to undergo refractive lens exchange or cataract and agreed to use their de-identified data for statistical analysis.

All AEs following primary RLE of patients treated between July 1, 2014, and June 30, 2016 were extracted from the Optical Express (United Kingdom and Ireland) electronic database. The patients included in this study had either clear lens extraction, in absence of cataract, or mild lens changes (with corrected visual acuity not worse than 20/40) and underwent surgery for refractive reasons. A list of AEs derived from those reported to the Food and Drug Administration during clinical trials was created and each event was clearly defined (Table 1),[8,9] although the list of AEs was expanded and stringent criteria were used for the definition of some of the AEs to ensure that any event that could have a potential negative impact on the patient's outcome was captured. Posterior capsular opacification was treated as an AE, and acuity prior to YAG laser capsulotomy was used in this study, as this was the acuity that patients presented with when the AE was noted.

In addition, a serious adverse event (SAE) was defined as an AE that is potentially sight threatening or likely to result in the loss of corrected visual acuity.[8–11] A comprehensive review was conducted to categorize all AEs according to their definitions.

All surgeries were performed by 1 of 14 surgeons in 1 of 9 surgical centers. Lens fragmentation, capsulorrhexis, and corneal incisions were performed using a femtosecond laser (Catalys Precision Laser System; Johnson & Johnson Vision Care, Inc, Santa Ana, California, USA), and the Whitestar Signature platform (Johnson & Johnson Vision Care, Inc) was used for phacoemulsification. When the corneal astigmatism was between 0.5 and 1.5 diopters (D), incisions were placed on the steepest corneal meridian and/or an intrastromal astigmatic keratotomy was performed with the femtosecond laser, according to surgeon preference and their specific nomogram. A toric IOL was used in patients with corneal astigmatism greater than 1.50 D. Intracameral cefuroxime was used at the end of surgery as a prophylaxis for endophthalmitis, unless the patient was allergic to penicillin. Postoperatively, patients were instructed to instill 1 drop of levofloxacin 0.5%, 4 times daily for 2 weeks; 1 drop of dexamethasone 0.1%, 4 times daily for 2 weeks; and 1 drop of ketorolac trometamol 0.5%, 4 times daily for 1 month.

The preoperative ophthalmic examination included manifest and cycloplegic refraction, monocular and binocular uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA) using a calibrated projected eye chart, low-light pupil diameter, slit-lamp biomicroscopy, dilated fundus examination, noncontact tonometry, corneal topography, ultrasound pachymetry, retinal optical coherence tomography, biometry for lens calculation, endothelial cell count, and wavefront aberrometry measurement. All patients were advised to return for 1 day, 1 week, 1 month, 3 months, 6 months, and 12 months postoperative examination, where manifest refraction (except for day 1), visual acuity, noncontact tonometry, and slit-lamp examination were performed. After this, they were instructed to have yearly follow-up. If patients experienced AEs or side effects that were not resolved by 3 months, they continued with close management until their issues resolved.

All AEs were recorded in the Optical Express Electronic Medical Record (EMR) system. The EMR system is custom built specifically for Optical Express, and consists of both clinical and operating room interfaces. It is designed to enable easy capture of pertinent examination data and operating room specifics, and has special measures built in to comprehensively capture AEs in order to enable rapid analysis of any potential AE issues. All providers that interface with the EMR, including physicians, optometrists, and operating room nurses and technicians, undergo formal training in its use, which includes instruction on capturing AEs. In order to maximize the reporting of AEs, each electronic visit record (operative and postoperative) has a drop-down list of common RLE AEs. The electronic visit cannot be closed without the user first selecting if an AE had occurred or not. Furthermore, the user is able to select more than 1 AE for either eye of a given patient, and there is a field for free-text entries if the encountered AE does not exist in the prespecified list. Continuous quality monitoring of the EMR data is also undertaken to ensure data integrity. Postoperative variables are analyzed on a per-examiner basis and compared with expected norms. Any substantial outliers trigger a review process, with retraining if necessary. Patients who were treated at a different institution for any AE were instructed to submit bills for reimbursement, and the AE was logged into the EMR.

Specific to the operating room, the clinical personnel are trained to record all intraoperative AEs that were evident during a procedure, such as capsular tear, vitreous loss, and IOL positioning issues. The operating room nurses or healthcare assistants (surgical technicians) were trained to enter any AE encountered, and separately the treating physician also was required to input a free-text explanation of the situation leading to the AE. Postoperatively, patients were seen by qualified and experienced refractive optometrists, the only exception to this being that patients who experienced an intraoperative AE were generally seen by their treating physicians. Any postoperative AE was recorded into the EMR in the process specified above. The refractive optometrists are provided with and instructed in a protocol regarding the engagement of the treating ophthalmic surgeon for management of AEs. Depending on the nature and severity of the AE, the patient was either managed by the optometrist in close communication with the treating surgeon or the patient was immediately referred to the surgeon. All severe AEs were managed by the treating surgeon. Every refractive optometrist undergoes a program of annual education and training to identify and manage AEs.

• **STATISTICAL ANALYSIS:** The AEs were summarized and the incidence rate was calculated based on the total number of eyes treated in the time period between July 1, 2014, and June 30, 2016. All percentages were calculated on "per eye" basis. Separate calculations were performed for serious, potentially vision-threatening AEs, defined in Table 1. Clinical data of the last available postoperative examination were used for all visual acuity and refractive predictability calculations. A Cox proportional hazards model was created to find factors predicting the incidence of AEs and SAEs; the model was clustered on a per-patient basis to account for the interrelatedness of 2 eyes from the same patient. Data tabulation was performed with Microsoft Office Excel (Microsoft Corporation, Redmond, Washington, USA) software and with STATA (Stata Corp, College Station, Texas, USA).

RESULTS

THE TOTAL NUMBER OF PATIENTS TREATED BETWEEN July 1, 2014, and June 30, 2016 was 10,206 (18,689 eyes). The mean follow-up of the entire study group was

TABLE 2. Refractive Lens Exchange/Cataract Adverse Events

Total Consecutive Treatments			18,689 Eyes of 10,206 Patients				
Total AE			1164 (1112 Eyes of 1039 Patients): 6.0% or 1:17 Eyes				
Total SAE			171 (165 Eyes of 151 Patients): 0.9% or 1:113 Eyes				
AE	SAE	Eyes	Incidence	1:__ Eyes	Last CDVA ≤20/20[a]	Last CDVA ≤20/40	Lost ≥2 Lines CDVA[b]
Posterior capsule opacification	–	748	4.00%	1:25	64.9%	94.3%	22.9%
Abrasion	–	81	0.43%	1:231	88.6%	100.0%	2.7%
IOP elevated	–	76	0.41%	1:246	96.8%	100.0%	2.8%
Cystoid macular edema	Yes	54	0.29%	1:346	68.9%	92.6%	19.2%
Persistent inflammation	–	48	0.26%	1:389	92.5%	93.8%	9.3%
Other macular/retinal complication	Yes	26	0.14%	1:719	4.0%	88.5%	88.5%
Corneal edema	Yes	19	0.10%	1:984	66.7%	100.0%	10.5%
Recurrent erosions	–	19	0.10%	1:984	93.8%	100.0%	0.0%
Posterior capsule tear/vitreous loss	Yes	16	0.09%	1:1168	100.0%	100.0%	0.0%
IOL displaced	Yes	11	0.06%	1:1699	100.0%	100.0%	0.0%
Wound leak	Yes	11	0.06%	1:1699	90.9%	100.0%	0.0%
Nonreactive pupil	–	10	0.05%	1:1869	71.4%	100.0%	10.0%
Aqueous misdirection	Yes	6	0.03%	1:3115	100.0%	100.0%	0.0%
Incorrect treatment	Yes	6	0.03%	1:3115	100.0%	100.0%	0.0%
Sterile infiltrates	–	6	0.03%	1:3115	100.0%	100.0%	0.0%
IOL decentered	Yes	4	0.02%	1:4672	75.0%	100.0%	0.0%
Iris trauma	–	4	0.02%	1:4672	50.0%	100.0%	25.0%
IOL tilted	Yes	3	0.02%	1:6230	50.0%	100.0%	0.0%
Retinal detachment	Yes	3	0.02%	1:6230	0.0%	33.3%	100.0%
Retinal tear	Yes	3	0.02%	1:6230	66.7%	100.0%	0.0%
Toxic anterior segment syndrome	Yes	3	0.02%	1:6230	100.0%	100.0%	0.0%
Retained lens material	Yes	2	0.01%	1:9345	100.0%	100.0%	0.0%
Vitreous hemorrhage	Yes	2	0.01%	1:9345	100.0%	50.0%	50.0%
Endophthalmitis	Yes	1	0.01%	1:18,689	–	0.0%	100.0%
Herpes simplex keratitis	Yes	1	0.01%	1:18,689	100.0%	100.0%	0.0%
Pigment on IOL	–	1	0.01%	1:18,689	100.0%	100.0%	0.0%

AE = adverse event; CDVA = corrected distance visual acuity; IOL = intraocular lens; IOP = intraocular pressure; SAE = serious adverse event.

[a]Last available CDVA 20/20 or better was calculated only for eyes that had preoperative CDVA 20/20 or better.

[b]Loss of ≥2 lines of CDVA calculated only for eyes that reached a minimum of 3 months follow-up.

8.9 ± 6.4 months (range: 1 week to 36 months). The percentage of patients that attended a minimum of 1 month, 3 months, 6 months, and 12 months follow-up visit was, respectively, 97.6%, 87.4%, 74.5%, and 46.8%.

A multifocal IOL was used in 84.3% of eyes, and 15.7% of eyes had a monofocal IOL. The most common types of multifocal lenses were split bifocal refractive lenses, used in 41.9% of all eyes. The following split bifocal lenses were implanted: Lentis Mplus (Oculentis GmbH, Berlin, Germany) with +3.0 near addition, 27.6% of all eyes; Lentis Mplus with +2.00 D near addition, 3.8%; Lentis Mplus with +1.50 near addition, 6.5%; and SBL-3 (Lenstec Inc, Christ Church, Barbados) with 3.0 D near addition, 4.1%.

The second most commonly implanted IOL was Tecnis Symfony (Johnson & Johnson Vision Care, Inc, Santa Ana, California, USA), used in 29.7% of all eyes, followed by Tecnis multifocal +2.75 (6.5%) and Tecnis multifocal +3.25 D lens (3.5%). Other types of multifocal lenses were used in 2.6% of eyes (FineVision IOL, PhysIOL, Liège, Belgium; the ReSTOR +3.0 D and +2.5 D multifocal IOLs, Alcon Laboratories, Inc., Fort Worth, Texas, USA; or the AT LISA, Carl Zeiss Meditec AG, Jena, Germany).

Table 2 summarizes the incidence of all postoperative AEs. The total number of AEs was 1164 and the total number of eyes with AEs was 1112 (1039 patients, incidence 6.0%, 1:17 eyes; note some eyes experienced 2 independent AEs). The total number of SAEs was 171 (165 eyes of 151 patients, incidence 0.9%, 1:113 eyes).

The clinical and demographic characteristics of patients with and without AEs are presented in Table 3. Overall, patients with AEs were more likely to have preoperative myopia, but there was a great variation between types of AEs.

Of all eyes with AEs (regardless of preoperative CDVA) (1112 eyes of 1039 patients), 94.9% achieved

TABLE 3. Clinical Data for Eyes With and Without Adverse Events After Refractive Lens Exchange

Event	N Eyes	Age ± SD (Years)	% Female (N Patients)	% Myopic (N Eyes)	Preop MSE ± SD Myopic [D]	Preop MSE ± SD Hyperopic [D]	Postop Sphere ± SD [D]	Postop Cylinder ± SD [D]	Postop UDVA ± SD [logMAR]	Postop CDVA ± SD [logMAR]	Axial Length ± SD[a] [mm] (Number of Eyes)
Cohort without AEs	17,577	57.5 ± 7.6	49.9 (8771)	15.4 (2707)	−3.24 ± 3.07	2.50 ± 1.72	0.06 ± 0.57	−0.44 ± 0.42	0.05 ± 0.17	−0.04 ± 0.08	23.3 ± 1.5 (6070)
Posterior capsule opacification	748	56.8 ± 7.3	54 (404)	21.3 (159)	−4.48 ± 3.55	1.82 ± 1.5	0.11 ± 0.63	−0.57 ± 0.43	0.14 ± 0.21	0.05 ± 0.16	23.6 ± 1.7 (113)
Abrasion	81	57.0 ± 6.4	40.7 (33)	17.3 (14)	−3.38 ± 2.3	2.17 ± 1.48	0.15 ± 0.66	−0.56 ± 0.38	0.08 ± 0.17	−0.03 ± 0.09	23.5 ± 1.1 (28)
IOP elevated	76	58.2 ± 8.3	40.8 (31)	13.2 (10)	−3.45 ± 2.88	2.29 ± 1.99	0.10 ± 0.54	−0.56 ± 0.43	0.07 ± 0.22	−0.04 ± 0.07	23.9 ± 1.1 (9)
Cystoid macular edema	54	59.7 ± 6.7	42.6 (23)	13.0 (7)	−1.25 ± 0.94	1.86 ± 1.02	0.24 ± 0.59	−0.67 ± 0.46	0.16 ± 0.21	0.04 ± 0.18	23 ± 0.9 (17)
Persistent inflammation	48	57.6 ± 7.5	50 (24)	8.3 (4)	−1.16 ± 1.65	2.08 ± 1.53	0.23 ± 0.52	−0.49 ± 0.4	0.07 ± 0.18	0 ± 0.15	22.7 ± 1.1 (10)
Other macular/retinal complication	26	58.2 ± 5.4	57.7 (15)	26.9 (7)	−3.96 ± 2.21	1.65 ± 0.78	0.13 ± 0.83	−0.57 ± 0.5	0.39 ± 0.2	0.25 ± 0.12	23.4 ± 1.2 (7)
Corneal edema	19	61.9 ± 8.4	42.1 (8)	5.3 (1)	−17.25	1.86 ± 1.29	0.19 ± 0.58	−0.81 ± 0.57	0.31 ± 0.32	0.04 ± 0.09	22.5 ± 1.1 (4)
Recurrent erosions	19	58.6 ± 7.8	31.6 (6)	10.5 (2)	−4.63 ± 1.94	1.43 ± 0.81	0.17 ± 0.46	−0.60 ± 0.46	0.05 ± 0.17	−0.03 ± 0.06	23.6 ± 1.1 (8)
Vitreous loss/posterior capsule tear	16	61.1 ± 6.7	56.3 (9)	12.5 (2)	−10.44 ± 11.23	1.78 ± 0.97	0.06 ± 0.52	−0.89 ± 1.1	0.14 ± 0.29	−0.04 ± 0.06	23.7 ± 0.8 (10)
IOL displaced	11	60.3 ± 10.1	45.5 (5)	0.0 (0)	–	1.78 ± 2.43	0.18 ± 0.40	−0.53 ± 0.32	0.05 ± 0.13	−0.03 ± 0.06	22.8 ± 1 (5)
Wound leak	11	55.9 ± 7.7	18.2 (2)	18.2 (2)	−1.25 ± 0.18	1.71 ± 0.65	−0.09 ± 0.48	−0.65 ± 0.57	0.14 ± 0.4	−0.05 ± 0.08	23.2 ± 0.9 (8)
Nonreactive pupil	10	60.2 ± 8.3	80 (8)	20.0 (2)	−0.63 ± 0.18	1.39 ± 1.23	0.10 ± 0.60	−1.00 ± 0.68	0.33 ± 0.42	0 ± 0.11	23 ± 1.7 (3)
Aqueous misdirection	6	54.5 ± 10.7	50 (3)	0.0 (0)	–	1.58 ± 1.07	0.17 ± 0.30	−0.69 ± 0.40	0.03 ± 0.12	−0.04 ± 0.04	23.6 ± 0 (2)
Incorrect treatment	6	54.0 ± 4.1	83.3 (5)	16.7 (1)	−5.5	2.95 ± 1.57	−0.17 ± 0.89	−0.35 ± 0.29	0.11 ± 0.25	−0.07 ± 0.04	22.3 ± 1.3 (2)
Sterile infiltrates (not infectious)	6	59.5 ± 2.8	83.3 (5)	16.7 (1)	−0.25	1.43 ± 0.07	−0.21 ± 0.29	−0.29 ± 0.10	−0.02 ± 0.12	−0.05 ± 0.04	–
IOL decentered	4	59.5 ± 11.5	25 (1)	25.0 (1)	−1	1.17 ± 2.27	−0.38 ± 0.78	−1.31 ± 0.69	0.48 ± 0.57	0.01 ± 0.07	24.8 ± 0.5 (2)
Iris trauma	4	65.0 ± 14.3	100 (4)	25.0 (1)	−0.75	2.08 ± 0.63	−0.50 ± 1.08	−1.13 ± 0.88	0.41 ± 0.34	0.04 ± 0.15	23 ± 0.8 (3)
IOL tilted	3	57.7 ± 5.5	33.3 (1)	66.7 (2)	−5.31 ± 1.86	7.63	0.33 ± 0.38	−1.25 ± 1.15	0.11 ± 0.19	−0.02 ± 0.1	24.5 ± 3.9 (2)
Retinal detachment	3	65.7 ± 7.4	33.3 (1)	100 (3)	−2.71 ± 1.95	–	0.25 ± 0.43	−0.17 ± 0.29	0.71 ± 0.55	0.71 ± 0.55	–
Retinal tear	3	60.0 ± 6.1	33.3 (1)	66.7 (2)	−4.88 ± 5.66	0.88	−1.00 ± 1.52	−0.75 ± 0.43	0.24 ± 0.41	−0.02 ± 0.1	–
Toxic anterior segment syndrome	3	57.3 ± 9.0	33.3 (1)	0.0 (0)	–	2.54 ± 1.45	0.13 ± 0.14	−0.75 ± 0.50	0.03 ± 0.06	0.0	–
Retained lens material	2	64.5 ± 20.5	100 (2)	0.0 (0)	–	1.56 ± 0.62	−0.63 ± 0.88	−1.00 ± 0.71	0.3 ± 0.42	0.11 ± 0.16	–
Vitreous hemorrhage	2	56.5 ± 7.8	50 (1)	0.0 (0)	–	3.69 ± 3.27	−0.63 ± 2.65	−1.13 ± 0.18	0.8 ± 0.14	0.31 ± 0.55	21.9 ± 2 (2)
Endophthalmitis	1	67	0 (0)	0.0 (0)	–	2.50	0.00	−0.50	0.52	0.4	–
Herpes simplex virus keratitis	1	48	0 (0)	100 (1)	−0.25	–	0.25	−0.75	0.1	−0.08	–
Pigment on IOL	1	63	100 (1)	0.0 (0)	–	0	0.00	−0.25	−0.08	−0.08	–

AE = adverse event; CDVA = best spectacle-corrected monocular distance visual acuity; D = diopter; IOL = intraocular lens; IOP = intraocular pressure; MSE = manifest spherical equivalent; Postop = postoperative; Preop = preoperative; UDVA = uncorrected monocular distance visual acuity.

[a]Axial length available only in 33.7% of records.

postoperative CDVA 20/40 or better, 87.2% had postoperative UDVA 20/40 or better, and 98.2% had binocular UDVA 20/40 or better.

Of all eyes with AEs that had preoperative CDVA 20/20 or better (985 eyes of 918 patients), 70.8% achieved postoperative CDVA 20/20 or better, 43.7% had postoperative monocular UDVA 20/20 or better, and 73.0% had binocular UDVA 20/20 or better on the last available examination. When eyes that had preoperative CDVA 20/20 or better and posterior capsule opacification as the cause of reduced CDVA (n = 658 eyes with an AE) were excluded, 82.6% of eyes had a postoperative CDVA of 20/20 or better, 48.6% had a UDVA of 20/20 or better, and 78.8% had postoperative binocular UDVA 20/20 or better on the last available examination. In the whole cohort of patients without any AEs, of all patients that had preoperative CDVA 20/20 or better, 94.8% achieved postoperative CDVA 20/20 or better, 70.0% had postoperative monocular UDVA 20/20 or better, and 89.1% of patients had binocular UDVA 20/20 or better.

Manifest spherical equivalent on the last postoperative visit (in eyes targeted for emmetropia) was within 0.50 D of emmetropia in 74.2% of all eyes with AEs, and within 1.0 D in 91.8%. In the cohort of patients without AEs, 81.7% of eyes were within 0.50 D and 96.7% were within 1.00 D of emmetropia on the last available visit.

• **SERIOUS ADVERSE EVENTS:** The incidence of SAE was 0.9% (1:113 eyes) and they were present in 165 eyes of 151 patients (Table 2). The most common SAE was cystoid macular edema (CME), occurring in 54 eyes (0.29%), followed by other macular pathology such as macular hole, epiretinal membrane, vitreous traction, and age-related macular degeneration (n = 26 eyes, 0.14%).

Of all eyes with SAE that had preoperative CDVA 20/20 or better (139 eyes of 126 patients), 66.2% achieved postoperative CDVA 20/20 or better, 33.8% had postoperative UDVA 20/20 or better, and 68.3% had binocular UDVA 20/20 or better. Of all eyes with SAEs (regardless of preoperative CDVA), 93.3% achieved postoperative CDVA 20/40 or better, 78.8% had postoperative UDVA 20/40 or better, and 94.0% had binocular UDVA 20/40 or better.

• **LOSS OF 2 OR MORE LINES OF CORRECTED DISTANCE VISUAL ACUITY:** The loss of ≥2 lines of CDVA was calculated for all patients who underwent clear lens extraction (corrected preoperative visual acuity of ≥20/20) and completed a minimum of 3 months follow-up (15,850 eyes of 9769 patients). The loss of 2 or more lines of CDVA was present in 263 (1.66%) eyes of 233 patients.

The most common reason for CDVA loss was posterior capsule opacification (175 eyes, 1.10% of the cohort), followed by postoperative posterior segment complications (38 eyes, 0.24%), such as CME, macular hole, epiretinal membrane, age-related macular degeneration, and endophthalmitis. Other reasons for CDVA loss were ocular surface issues and dry eyes (15 eyes, 0.09%), persistent postoperative inflammation (2 eyes, 0.01%), and corneal edema (2 eyes, 0.01%). In 31 eyes (0.20%), the loss of CDVA was unexplained. When excluding eyes that had CDVA reduced owing to posterior capsular opacification (PCO), the total loss of ≥2 lines of CDVA on the last available follow-up was 0.56%.

Of all eyes that lost 2 or more lines of CDVA, 73.4% (193 eyes) had postoperative CDVA 20/40 or better. There were only 2 patients in the study that had postoperative CDVA reduced to less than 20/40 in both eyes, and in both cases it was owing to dense PCO.

• **REGRESSION ANALYSIS:** Outcomes of the Cox proportional hazards model for predicting the occurrence of an AE or an SAE are shown in Table 4 (all AEs excluding PCO). Of all variables, older age and surgical volumes were the only factors affecting the incidence of AEs and SAEs. Surgeons performing higher numbers of surgeries per week were less likely to have their patient develop an AE or SAE.

A sensitivity analysis was conducted to look at preoperative spherical equivalent. Neither a myopic spherical equivalent nor a hyperopic spherical equivalent was significant in the sensitivity model ($P = .85$ for SAEs, $P = .81$ for all AEs). Models were also constructed to look specifically at myopic or hyperopic patients. Increasing amounts of myopia or hyperopia were not associated with an increased risk for non-PCO AEs or SAEs ($P > .1$ for all comparisons).

DISCUSSION

WITH THE GROWTH IN THE NUMBER OF RLE PROCEDURES performed worldwide, patients' expectations of achieving "perfect" vision with minimal side effects has increased.[1–3] Minimizing risks and potential adverse events is one of the main goals of modern refractive lens exchange, especially because the procedure is elective and performed for refractive indications.[1,2,5] In this review, the total rate of AEs was 6.0%, but the incidence of potentially serious, vision-threatening AEs was 0.9%. Fortunately the majority of patients that had these SAEs were able to achieve a postoperative binocular UDVA 20/20 or better. There were only 2 patients in the study that had postoperative CDVA reduced to less than 20/40 in each eye, and in both cases it was owing to PCO, and acuity in both cases improved after treatment.

Intraoperative AEs were rare in this study. The most commonly reported intraoperative AE in the literature is capsular tear with or without vitreous loss, with the rates ranging between 1% and 2% for modern cataract surgery in developed countries.[11] The incidence in this study was much lower (0.09%), which could be attributed to the minimal nuclear sclerotic change, which made the surgery

TABLE 4. Multivariable Cox Proportional Hazards Model of All Adverse Events and Serious Adverse Events, Excluding Posterior Capsule Opacification

	All Adverse Events			Serious Adverse Events		
Variable	Hazard Ratio	95% CI	*P* Value	Hazard Ratio	95% CI	*P* Value
Age (per year)	1.02	1.00-1.03	.018	1.02	1.01-1.05	.008
Spherical equivalent (per diopter)	0.99	0.95-1.03	.15	0.97	0.92-1.03	.37
Sex						
Female (ref)	1.0	–	.083	1	–	.23
Male	1.22	0.97-1.54		1.24	0.92-1.03	
Surgeon cases per week	0.98	0.97-0.99	.001	0.97	0.96-0.99	.004

Ref = reference value.

technically easier to perform; surgeon experience; the use of femtosecond laser; and fewer ocular and medical comorbidities. One of the most important factors for capsular tear events is surgeon experience. Each surgeon included in this study performed in excess of 5000 cataract or refractive lens exchange procedures, which could be another reason for such low rates. Other rare surgery-related AEs included iris trauma, displaced/decentered IOL, or retained lens material, with the total incidence of 0.11%, although some of the lens complications can also happen in the postoperative period.

Anterior segment complications are not uncommon after intraocular procedures, but the incidence of significant complications was very low in this study. Corneal complications (wound leak, corneal edema, corneal abrasion, recurrent erosions, and sporadic cases of sterile infiltrates) usually manifest in the early postoperative period and were found in 0.73% of all eyes, and in all cases resulted in the final CDVA 20/40 or better.

Some amount of inflammation in anterior structures of the eye is expected in the early postoperative time period after intraocular surgery.[4] In this review, we only included cases of persistent anterior chamber inflammation that persisted for longer than 1 week postoperatively, or occurred at any time postoperatively and required management for longer than 1 month. The total incidence was 0.26%. There were only 3 cases of intense anterior chamber reaction associated with toxic anterior segment syndrome and all of them were successfully managed with no loss of CDVA.

Although cataract surgery has been shown to reduce intraocular pressure (IOP) in the long term,[12,13] some patients experience IOP elevation in the immediate postoperative period and might need urgent attention to avoid serious consequences. This is most likely related to the actual surgery (typically retained viscoelastic agent), postoperative use of steroids, or postoperative inflammation. Some patients are also simply more prone to postoperative IOP complications owing to the structure of their eye (nanophthalmos, high hyperopia, history of previous angle closure), although no patients in this study were nanophthalmic or had a history of angle closure.[14] In our study, 0.41% of patients had elevated IOP that persisted for longer than 1 week postoperative and 6 eyes (0.03%) presented with aqueous misdirection. The loss of CDVA owing to IOP complications was, however, minimal. For the most serious IOP complication, aqueous misdirection, all patients achieved postoperative CDVA of 20/20 or better.

The most common complication in this study was PCO, which was present in 4% of eyes (incidence 1:25); however, it is debatable whether PCO is an AE or rather a consequence of an uneventful extracapsular surgery. In our dataset, PCO was also the most common reason for CDVA loss, although the vision was very likely to improve following YAG laser capsulotomy. As there were data available on 46.8% at 1 year follow-up, the incidence of PCO in our study group is likely to increase. There is a great variation in the literature in reported PCO rates, ranging from less than 5% to as high as 50%.[15] Several contributing factors for PCO development have been described, most commonly surgical technique, IOL design, and material.[15] All patients in this study had either a hydrophobic IOL or an IOL with hydrophobic surface, and this material may lower rates of PCO.[16,17]

Postoperative AEs related to posterior segment in this study included rare cases of retinal tear, retinal detachment, epiretinal membrane, age-related macular degeneration, macular hole, pigment epithelium detachment, or vitreous hemorrhage, with a total incidence of 0.18% (1:550). Although these AEs had a low occurrence, they were very likely to result in the loss of corrected vision, with the majority of eyes losing 2 or more lines of CDVA. For some of these AEs, it is difficult to establish whether they were related to surgery or would have occurred without the surgical procedure. The most significant of the above-listed AEs, retinal detachment, is usually associated with refractive lens exchange in younger patients with higher axial lengths, where the incidence is ranging between 1.5% and 8.1%.[18,19] In this study, we had 3 unilateral cases, and all occurred in patients older than 60 years: 1 in a patient with low hyperopia (axial

length 23.05 mm) 9 months after surgery and 2 in patients with low/moderate myopia (axial length 25.58 mm and 25.69 mm) at 3 and 8 months after surgery. With the relatively short follow-up, we were unable to evaluate long-term incidence of this sight-threatening AE. Retinal detachment has been reported to be more common in eyes that have undergone cataract surgery, and this risk remains elevated for some time after surgery, especially in subjects with high myopia.[20,21] It is possible that the prevalence of retinal detachment will increase with time in this cohort. As such, this possibility needs to be discussed with patients prior to intraocular surgery, and patients should be alerted to the signs/symptoms of retinal detachment should it occur postoperatively.

The most common retina complication of cataract surgery, CME, had an incidence of 0.29% in this study. Only cases confirmed by optical coherence tomography were included in this review. Following modern cataract surgery, the reported incidence of CME ranges between 0.1% and 2.35%.[22,23] Although the mechanism of postsurgical CME is not completely understood, the reported risk factors associated with its development are older age, male sex, pre-existing conditions such as diabetes mellitus, uveitis, epiretinal membrane, previous retinal detachment repair, and intraoperative complications.[23] The reason for a low incidence of CME in this study could be the younger age of our study population and absence of retinal pathology in the patients that underwent procedure for refractive reasons.

The most feared complication following intraocular surgery remains endophthalmitis. Incidence rate after cataract surgery ranges between 0.04% and 0.20%[24,25] and it has been reported to permanently reduce corrected vision below 20/40 in two-thirds of cases.[26] There has been a decline in endophthalmitis cases since the widespread use of intracameral antibiotics.[26,27] In our study, we had only 1 unilateral case (incidence 0.01%) where vision remained permanently reduced from 20/25 preoperative to 20/50 postoperative. The reasons for such low endophthalmitis rate might have been the relatively young and healthy study population (age greater than 80-85 years is a commonly reported endophthalmitis risk factor[24]), use of intracameral cefuroxime,[26,27] and a low incidence of intraoperative complications, which are also associated with an increased endophthalmitis rate.[24]

When looking at the entire population of RLE patients and AEs excluding PCO, increasing age and surgeon caseload were significant factors. Age has been previously implicated as a risk factor for complications in patients undergoing cataract surgery,[28] and it seems to be a risk factor in RLE as well. Surgeon caseload also has been reported to be a factor in cataract surgery complications, with surgeons performing more cases having a lower risk of complications.[29] We found this in the RLE population as well, with each additional case per week conferring a 2% decreased hazard of both AEs and SAEs.

This study had a few important limitations. One of the most notable is the retrospective nature of this study and inability to evaluate long-term (beyond 12 months) complications. However, most of the serious complications are known to manifest in the early postoperative period, and in our study population 97.6% of patients attended 1 month postoperative and 87.4% 3 months postoperative aftercare. There is also a possibility some of the AEs might have been underreported. To counter this, the EMR is designed to capture reporting of AEs, and requires AE information to be input prior to closing the electronic record. There is also a possibility that patients sought postoperative care at other clinics. However, patients who were seen at other clinics were instructed to submit reimbursement claims and were thus more likely to be captured. Despite this, the possibility does remain that some AEs are underrepresented in this study.

In conclusion, cataract/refractive lens exchange surgery with modern surgical methods is safe. Although the total complication rate in this study was 6.0% (2.0% when excluding PCO), most of the complications were relatively minor and had minimal impact on the final outcome. Macular pathology was the most common cause of corrected vision loss.

FUNDING/SUPPORT: THE DEPARTMENT OF OPHTHALMOLOGY AT UCSF IS SUPPORTED BY AN UNRESTRICTED DEPARTMENTAL grant from Research to Prevent Blindness as well as the NIH-NEI EY002162 core grant for vision research. Financial Disclosures: Julie M. Schallhorn is a consultant for Zeiss and Avedro. Steven C. Schallhorn is a chief medical officer for Zeiss, consultant for Acufocus, and a chairman of the medical advisory board for Optical Express. None of the other authors has a financial or proprietary interest in the products and materials presented in this paper. All authors attest that they meet the current ICMJE criteria for authorship.

REFERENCES

1. Alio JL, Grzybowski A, El Aswad A, Romaniuk D. Refractive lens exchange. *Surv Ophthalmol* 2014;59(6):579–598.
2. Alió JL, Grzybowski A, Romaniuk D. Refractive lens exchange in modern practice: when and when not to do it? *Eye Vis (Lond)* 2014;1:10.
3. Lundström M, Manning S, Barry P, Stenevi U, Henry Y, Rosen P. The European registry of quality outcomes for cataract and refractive surgery (EUREQUO): a database study of trends in volumes, surgical techniques and outcomes of refractive surgery. *Eye Vis (Lond)* 2015;2:8.
4. Kook D, Kampik A, Kohnen T. Complications after refractive lens exchange. *Ophthalmologe* 2008;105(11):1005–1012.

5. Westin O, Koskela T, Behndig A. Epidemiology and outcomes in refractive lens exchange surgery. *Acta Ophthalmol* 2015;93(1):41–45.
6. Srinivasan B, Leung HY, Cao H, Liu S, Chen L, Fan AH. Modern phacoemulsification and intraocular lens implantation (refractive lens exchange) is safe and effective in treating high myopia. *Asia Pac J Ophthalmol (Phila)* 2016;5(6):438–444.
7. Siganos DS, Pallikaris IG. Clear lensectomy and ocular lens implantation for hyperopia from +7 to +14 diopters. *J Refract Surg* 1998;14:105–113.
8. International Organization for Standardization. Ophthalmic Implants - Intraocular Lenses - Part 7: Clinical Investigations. 2014. ISO Standard 11979-7. Available at: https://www.iso.org/standard/69038.html.
9. Masket S, Rorer E, Stark W, et al. Special Report: The American Academy of Ophthalmology Task Force Consensus Statement on Adverse Events with Intraocular Lenses. *Ophthalmology* 2017;124(1):142–144.
10. Stein JD. Serious adverse events after cataract surgery. *Curr Opin Ophthalmol* 2012;23(3):219–225.
11. Yorston D. Cataract complications. *Community Eye Health* 2008;21(65):1–3.
12. Nganga Ngabou CG, Makita C, Ndalla SS, Nkokolo F, Madzou M. Intraocular pressure decrease after manual small incision cataract surgery. *J Fr Ophtalmol* 2017;40(5):397–402.
13. Armstrong JJ, Wasiuta T, Kiatos E, Malvankar-Mehta M, Hutnik CM. The effects of phacoemulsification on intraocular pressure and topical medication use in patients with glaucoma: a systematic review and meta-analysis of 3-year data. *J Glaucoma* 2017;26(6):511–522.
14. Shahid H, Salmon JF. Malignant glaucoma: a review of the modern literature. *J Ophthalmol* 2012;2012:852659.
15. Raj SM, Vasavada AR, Johar SR, Vasavada VA, Vasavada VA. Post-operative capsular opacification: a review. *Int J Biomed Sci* 2007;3(4):237–250.
16. Kugelberg M, Wejde G, Jayaram H, Zetterström C. Two-year follow-up of posterior capsule opacification after implantation of a hydrophilic or hydrophobic acrylic intraocular lens. *Acta Ophthalmol* 2008;86:533–536.
17. Saeed MU, Jafree AJ, Saeed MS, Zia R, Sheikh IM, Heravi M. Intraocular lens and capsule opacification with hydrophilic and hydrophobic acrylic materials. *Semin Ophthalmol* 2012;27(1-2):15–18.
18. Colin J, Robinet A, Cochener B. Retinal detachment after clear lens extraction for high myopia. *Ophthalmology* 1999;106:2281–2285.
19. Neuhann IM, Neuhann TF, Heimann H, Schmickler S, Gerl RH, Foerster MH. Retinal detachment after phacoemulsification in high myopia: analysis of 2356 cases. *J Cataract Refract Surg* 2008;34:1644–1657.
20. Bjerrum SS, Mikkelsen KL, La Cour M. Risk of pseudophakic retinal detachment in 202,226 patients using the fellow nonoperated eye as reference. *Ophthalmology* 2013;120(12):2573–2579.
21. Daien V, Le Pape A, Heve D, Carriere I, Villain M. Incidence, risk factors, and impact of age on retinal detachment after cataract surgery in France: a national population study. *Ophthalmology* 2015;122(11):2179–2185.
22. Zur D, Loewenstein A. Postsurgical cystoid macular edema. *Dev Ophthalmol* 2017;58:178–190.
23. Chu CJ, Johnston RL, Buscombe C, Sallam AB, Mohamed Q, Yang YC, United Kingdom Pseudophakic Macular Edema Study Group. Risk factors and incidence of macular edema after cataract surgery: a database study of 81984 eyes. *Ophthalmology* 2016;123(2):316–323.
24. Hashemian H, Mirshahi R, Khodaparast M, Jabbarvand M. Post-cataract surgery endophthalmitis: brief literature review. *J Curr Ophthalmol* 2016;28(3):101–105.
25. Packer M, Chang DF, Dewey SH. Prevention, diagnosis, and management of acute postoperative bacterial endophthalmitis. *J Cataract Refract Surg* 2011;37:1699–1714.
26. Friling E, Lundstrom M, Stenevi U, Montan P. Six-year incidence of endophthalmitis after cataract surgery: Swedish national study. *J Cataract Refract Surg* 2013;39:15–21.
27. Barry P. Adoption of intracameral antibiotic prophylaxis of endophthalmitis following cataract surgery: update on the ESCRS Endophthalmitis Study. *J Cataract Refract Surg* 2014;40(1):138–142.
28. Kim BZ, Patel DV, Sherwin T, McGhee CNJ. The Auckland Cataract Study: assessing preoperative risk stratification systems for phacoemulsification surgery in a teaching hospital. *Am J Ophthalmol* 2016;171(11):145–150.
29. Campbell RJ, El-Defrawy SR, Gill SS, et al. New surgeon outcomes and the effectiveness of surgical training. *Ophthalmology* 2017;124(4):532–538.