REVIEW

A retrospective cohort study of clinical outcomes for intravitreal crystalline retained lens fragments after age-related cataract surgery: a comparison of same-day versus delayed vitrectomy

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Background: This analysis compared outcomes for same-day (under a no-move, no-wait policy) versus delayed vitrectomy for intravitreal crystalline retained lens fragments after surgery for age-related cataract.

Methods: This was a retrospective, nonrandomized treatment comparison cohort study with a consecutive series of 35 eyes (23 same-day, 12 delayed) receiving both cataract surgery and vitrectomy at the Mayo Clinic Florida between 1999 and 2010. Outcome measures included visual acuity (VA), glaucoma progression, visual utility, and complications. Several techniques (bootstrapping, robust confidence intervals, jackknifing, and a homogeneous sample) were used to reduce selection bias and increase confidence in our small sample's results.

Results: No significant baseline treatment group differences. Mean previtrectomy delay (12 eyes) was 40.9 days (median 29.5, range 1–166). Mean postvitrectomy follow-up (35 eyes) was 47.5 months (median 40.5, range 3.1–123.5). Same-day patients had significantly better final VA (adjusted for age [$t = -2.14$, $P = 0.040$] and precataract surgery VA [$t = -2.98$, $P = 0.006$]); a higher rate of good final VA ($\geq$20/40), 78.3% (18/23) versus 58.3% (7/12); a lower rate of bad final VA ($\leq$20/200), 4.3% (1/23) versus 25.0% (3/12); and fewer final retinal conditions, 4.3% (1/23) versus 50.0% (6/12). Same-day patients also had marginally significant better mean final VA in the operated eye (20/40 versus 20/90, $Z = 1.51$, $P = 0.130$) despite poorer initial VA (20/98 versus 20/75) and higher age (3+ years), better final visual utility, and longer survival times for better VA. Among patients with preexisting glaucoma, same-day patients experienced significantly less differential (operated versus nonoperated eye) glaucoma progression.

Conclusion: Results favored same-day patients, who experienced better final VA and visual utility, less differential glaucoma progression, and fewer complications. Results need confirmation with larger samples.

Keywords: intraoperative complications, retained lens fragments, visual acuity, glaucoma, evaluation studies, visual utility, statistics as topic, small nonrandomized sample analysis

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Introduction

Phacoemulsification cataract surgery occasionally results in fragments or the entire crystalline lens dislocating into the vitreous. There is evidence that the clinical course for patients with retained lens fragments (RLF) begins the instant the fragments enter the vitreous and is affected by the cataract surgeon's decisions and actions.[1] Lack of immediate availability of an experienced vitreoretinal surgeon and the necessary equipment usually precludes a same-day vitrectomy, which many suggest might be the optimal time for RLF removal.[2–6]

Studies comparing same-day and delayed vitrectomy show mixed results. Several authors reported better visual acuity (VA)[7–9] and lower rates of complications – retinal detachment (RD),[7–10] corneal edema,[10,11] glaucoma/elevated intraocular pressure (IOP),[7–12] cystoid macular edema (CME),[7,8,10] and intraocular inflammation/infection[7,10,11] – among same-day patients. Lower rates of elevated IOP and/or CME may be related to less intraocular inflammation/infection.[8,10] Others reported no significant differences in VA,[13] RD,[12] and IOP[13] between same-day and delayed vitrectomy patients.

This study compared outcomes of patients with RLF who received a same-day vitrectomy, under the Mayo Clinic Florida (MCF) "no move, no wait" policy, versus a delayed vitrectomy any day after cataract surgery. The MCF policy is that a same-day vitrectomy can be performed only if a vitreoretinal surgeon begins the procedure within 15 minutes of cataract surgery and the patient is not moved from the original operating room. Outcomes included VA, visual utility, new glaucoma cases, differential progression of preexisting glaucoma, and ocular complications. This study received institutional review board approval and an informed consent waiver from the MCF Institutional Review Board.

Methods
Patients, study design, and setting
This was a retrospective cohort study with a consecutive series of 34 patients (35 eyes) who had received both cataract surgery and vitrectomy at MCF (1999–2010). Inclusion criteria were scheduled phacoemulsification cataract surgery for an age-related cataract and intravitreal crystalline RLF managed surgically with a standard three-port pars plana vitrectomy. Twelve eyes (exposed to RLF for 1+ days) received a delayed vitrectomy (1999–2004) with mean delay of 40.9 days (median 29.5, range 1–166). Indications for vitrectomy in this delayed group included elevated IOP, excessive inflammation, CME, and/or decreased VA. Same-day vitrectomy (1999–2010) was successfully performed on 22 eyes and attempted on the remaining eye, but not completed due to an equipment problem. This patient's data were analyzed in the same-day group, according to intention-to-treat,[14] yielding an unexposed group with 23 eyes. All patients returned for follow-up visits (mean postvitrectomy follow up 47.5 months [median 40.5, range 3.1–123.5]) as per the standard of care, and data was abstracted from patients' medical records.

Variables
All variables pertain to the operated eye unless otherwise noted. Snellen VA, measured during all visits, was converted

to logarithm of the minimum angle of resolution (logMAR) for statistical analysis.[15] Total elapsed time was from cataract surgery to final visit. The following were considered final retinal conditions: CME, RD, background diabetic retinopathy with focal laser photocoagulation, macular scar, and/or drusen; and we included the following as final corneal conditions: superficial scar, mild edema, and/or mild haze. We defined good VA as ≥20/40, bad VA as ≤20/200, and ocular inflammation as the presence of cells in the anterior chamber.

New glaucoma cases included patients requiring long-term pressure-lowering drops (in the operated eye) after vitrectomy who did not require this before cataract surgery. Glaucoma progression was defined as the exacerbation of visual field abnormalities, calculated by subtracting precataract surgery mean deviation (MD) from final MD and precataract surgery pattern-specific deviation (PSD) from final PSD. Differential glaucoma progression was calculated (separately for MD and PSD) by subtracting glaucoma progression in the nonoperated (fellow) eye from glaucoma progression in the operated eye.

Two scales were used for final visual utility: visual utility – better eye (based mainly on VA in the better eye)[16] and visual utility – both eyes (adapted to use only VA data but from both eyes[17] because RLF typically occur only in a single eye, often the one with worse VA). Because it is patient-specific (not eye-specific), the visual utility analyses contained only 22 same-day patients because one patient received a same-day vitrectomy in both eyes.

Data analyses
All analyses compared results for patients' operated eyes by treatment group (same-day versus delayed) and were preformed using Stata/IC version 11.1 (StataCorp, College Station, TX, USA). When doing the analyses, exact tests (which do not rely on large-sample assumptions of asymptotic normality) were used whenever possible.[18] In addition, model adjustment for potential confounding variables was limited because, in a small dataset, including too many variables in a model might result in overfitting.[19] However, it was important to adjust these analyses for potential confounding variables to reduce the effects of selection bias, which is inherent when comparing nonrandomized samples.[14,20] Potential confounding variables included patient age (at final visit), VA precataract surgery (the best proxy available for ocular health and vision before the RLF), and total elapsed time. See the appendix, which describes additional steps taken to reduce effects of selection bias and increase confidence in our small sample results.

Continuous variables were assessed for normal distributions. Three types of models were built: analysis of covariance (ANCOVA) for final VA and final visual utility – better eye, ordinal logistic regression for final visual utility – both eyes, and exact Cox proportional-hazards regression for time from vitrectomy until VA decreased to and remained <20/40 and ≤20/200. An independent-samples t-test compared differential MD glaucoma progression, a Mann–Whitney test compared differential PSD glaucoma progression, and Fisher's exact tests compared complication rates.

Results were considered statistically significant with P-values ≤ 0.05.[21,22] When appropriate, marginally significant differences (P ≤ 0.15) were noted because small samples are often underpowered to detect significant differences, even when treatment effects are real.[14] Noting marginally significant results is as appropriate as a multiplicity of post hoc power analyses, and probably more informative, since it is specifically the marginally significant results which should be included in the hypotheses of larger studies to verify the small sample's results. Discussing marginally significant results attempts to reduce the effect of type II errors (the failure of a statistical test to detect actual treatment group differences, when they exist), which are a problem associated with small-sample studies.[14]

Results

During the study period (1999–2010), 7565 patients had scheduled age-related cataract surgery at MCF, so these 35 cases indicate an RLF incidence rate of 0.46%. All 35 RLF cases were included in this study. Table 1 contains descriptive statistics and treatment group comparisons. There were no significant (or marginally significant) baseline group differences in any precataract surgery variable. There was a significant difference in the volume of RLF (same-day patients having larger amounts, $P < 0.001$) and a marginally significant difference in intraocular lens (IOL) type (more same-day patients had anterior-chamber IOLs, $P = 0.084$). For postvitrectomy variables, there were significant differences in both MD and PSD differential glaucoma progression (discussed below) and final retinal conditions (same-day = 4.3%, delayed = 50.0%; $P = 0.003$). There were also marginally significant differences in unadjusted final VA in the operated eye (same-day = 0.30, delayed = 0.65; $Z = 1.51$, $P = 0.130$), age at final visit (same-day = 84.43, delayed = 81.37; $Z = -1.53$, $P = 0.126$), bad final VA (same-day = 4.3% [1/23], delayed = 25.0% [3/12]; $P = 0.106$), and final visual utility – both eyes (same-day = 0.94, delayed = 0.91; $Z = 1.54$, $P = 0.124$). For all postvitrectomy

clinical variables with significant or marginally significant differences, same-day patients had better results. Figure 1 compares precataract surgery and final VA (operated eye) and differential glaucoma progression (operated versus nonoperated eye) by treatment group.

Table 2 displays descriptive statistics and normal distribution test results. For three dependent variables, final logMAR VA in the operated eye, visual utility – both eyes, and differential PSD glaucoma progression, a normal distribution could not be assumed. Analogous ANCOVA models, built with Snellen (normally distributed) and logMAR final VA, produced similar results. We report only the logMAR final VA models' results, because it is a continuous variable,[15] as required by ANCOVA. Attempts to transform the other two variables to normal distributions were unsuccessful.

The models' results are summarized in Table 3. ANCOVA (Table 4) indicated that same-day patients had significantly better adjusted final VA (models 1A and 1B) (age-adjusted difference = −0.42, 95% confidence interval [CI] = −0.83, −0.02, $t = −2.14$, $P = 0.040$ and precataract surgery VA-adjusted difference = −0.45, 95% CI = −0.75, −0.14, $t = −2.98$, $P = 0.006$) and marginally significant higher adjusted visual utility – better eye (models 2A and 2B), approximately the difference between 20/25 and 20/30 (age-adjusted difference = 0.04, 95% CI = −0.01, 0.10, $t = 1.62$, $P = 0.116$ and precataract surgery VA-adjusted difference = 0.04, 95% CI = −0.01, 0.09, $t = 1.48$, $P = 0.149$). Table 3 shows the results of using these ANCOVA models to estimate the patients' mean final VA and visual utility – better eye if the patients had been in the other treatment group.

Ordinal logistic regression (Table 4, models 3A and 3B) indicated that same-day patients had significantly higher odds of better adjusted visual utility – both eyes (age-adjusted odds ratio = 7.38, 95% CI = 1.12, 48.78, $Z = 2.07$, $P = 0.038$ and precataract surgery VA-adjusted odds ratio = 7.26, 95% CI = 1.06, 49.66, $Z = 2.02$, $P = 0.043$). Cox regressions (Table 5) indicated that same-day patients had lower hazards for VA decreases for both time-to-VA < 20/40 (models 4A and 4B) (age-adjusted hazard ratio = 0.34, 95% CI = 0.01, 1.19, $Z = −1.69$, $P = 0.092$, marginally significant, and precataract surgery VA-adjusted hazard ratio = 0.17, 95% CI = 0.03, 0.87, $Z = −2.13$, $P = 0.033$, significant) and time-to-VA ≤ 20/200 (models 5A and 5B) (age-adjusted hazard ratio = 0.16, 95% CI = 0.02, 1.67, $Z = −1.53$, $P = 0.126$ and precataract surgery VA-adjusted hazard ratio = 0.07, 95% CI = 0.00, 1.06, $Z = −1.92$, $P = 0.055$, both marginally significant). Figure 2 compares precataract surgery VA-adjusted survival functions by treatment group.

Table 1 Patient characteristics and univariate tests of between-group differences

Means (M) and standard deviations (SD)	Delayed (N = 12)		Same-day (N = 23)		Test	Statistic	*P*-value
	M	SD	M	SD			
Age at Final Visit	81.37	9.21	84.43	8.41	MW	−1.53	0.126†
logMAR VA OP pre-CS	0.57	0.40	0.69	0.56	MW	−0.33	0.739
logMAR VA non-OP pre-CS	0.26	0.19	0.30	0.24	MW	−0.21	0.832
FU post-vitrectomy (months)	54.82	37.74	43.70	33.26	IS-t	0.90	0.376
Total elapsed time (months)	56.18	38.32	43.70	33.26	IS-t	1.00	0.324
logMAR VA OP final	0.65	0.74	0.30	0.47	MW	1.51	0.130†
logMAR VA non-OP final	0.21	0.18	0.28	0.33	MW	−0.04	0.972
Visual Utility-better eye[a]	0.85	0.07	0.89	0.08	IS-t	−1.28	0.210
Visual Utility-both eyes[a]	0.91	0.07	0.94	0.05	MW	−1.54	0.124†
Diff MD glaucoma progression	−5.62	2.96	0.17	3.41	IS-t	−2.88	0.016*
Diff PSD glaucoma progression	2.00	2.76	−1.20	1.11	MW	2.55	0.011*
Counts (n) and proportions	**n**	**Prop**	**n**	**Prop**	**Test**		***P*-value**
# right eye	6	50.0%	13	56.5%	Fischer exact		0.736
# w/pseudo. pre-CS	3	25.0%	7	30.4%	Fischer exact		1.000
# w/polar cataract pre-CS	1	8.3%	0	0.0%	Fischer exact		0.343
# w/cortical lens pre-CS	1	8.3%	4	17.4%	Fischer exact		0.640
# w/glaucoma pre-CS	4	33.3%	11	47.8%	Fischer exact		0.489
Cataract nuclear sclerosis (NS)							
NS = 4+	0	0.0%	3	13.0%	Kendall's tau		0.813
NS = 3+	6	50.0%	9	39.1%			
NS = 2+	5	41.7%	8	34.8%			
NS = 1+	0	0.0%	2	8.7%			
None	1	8.3%	1	4.3%			
Posterior subcapsular cataract (PSC)							
PSC = 3+	1	8.3%	2	8.7%	Kendall's tau		0.531
PSC = 2+	2	16.7%	1	4.4%			
PSC = 1+	0	0.0%	2	8.7%			
None	9	75.0%	18	78.3%			
Intraocular lens type							
posterior chamber	4	33.3%	1	4.6%	Fischer exact		0.084†
anterior chamber	4	33.3%	13	59.1%			
posterior sulcus	4	33.3%	8	36.4%			
Volume of retained lens fragments							
Large	1	11.1%	19	100.0%	Kendall's tau		0.000***
Moderate	5	55.6%	0	0.0%			
Small	3	33.3%	0	0.0%			
missing data	3		4				
# new glaucoma cases	1	12.5%	2	15.4%	Fischer exact		1.000
# w/final retinal condition	6	50.0%	1	4.3%	Fischer exact		0.003**
# w/retinal detachment	2	16.7%	1	4.3%	Fischer exact		0.266
# w/cystoid macular edema	3	25.0%	3	13.0%	Fischer exact		0.391
# w/final anterior chamber cells	0	0.0%	2	8.7%	Fischer exact		0.536
# w/final corneal condition	2	16.7%	1	4.3%	Fischer exact		0.266
# w/VA Snellen final < 20/40	5	41.7%	5	21.7%	Fischer exact		0.258
# w/VA Snellen final ≤ 20/200	3	25.0%	1	4.3%	Fischer exact		0.106†

Notes: *$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$, †$P \leq 0.15$. All data are for the operated eye unless noted. [a]Visual utility analyses included 22 same-day patients. Visual utility-better eye: 0.92 = 20/20 with < 20/40 in the other eye, 0.87 = 20/25, 0.84 = 20/30.[16] Visual utility-both eyes: 0.96 = better eye 20/20—20/40 and worse eye >20/200, 0.88 = better eye 20/50—20/80 and worse eye >20/200.[17]
Abbreviations: Diff, Differential; FU, follow up time in months; IS-t, independent-samples *t*-test; MD, mean deviation; MW, Mann-Whitney rank-sum test; N, n, number of eyes; non-OP, non-operated eye; OP, operated eye; pre-CS, before cataract surgery; prop, proportion; PSD, pattern specific deviation; pseudo, pseudoexfoliation; VA, visual acuity; w/, with.
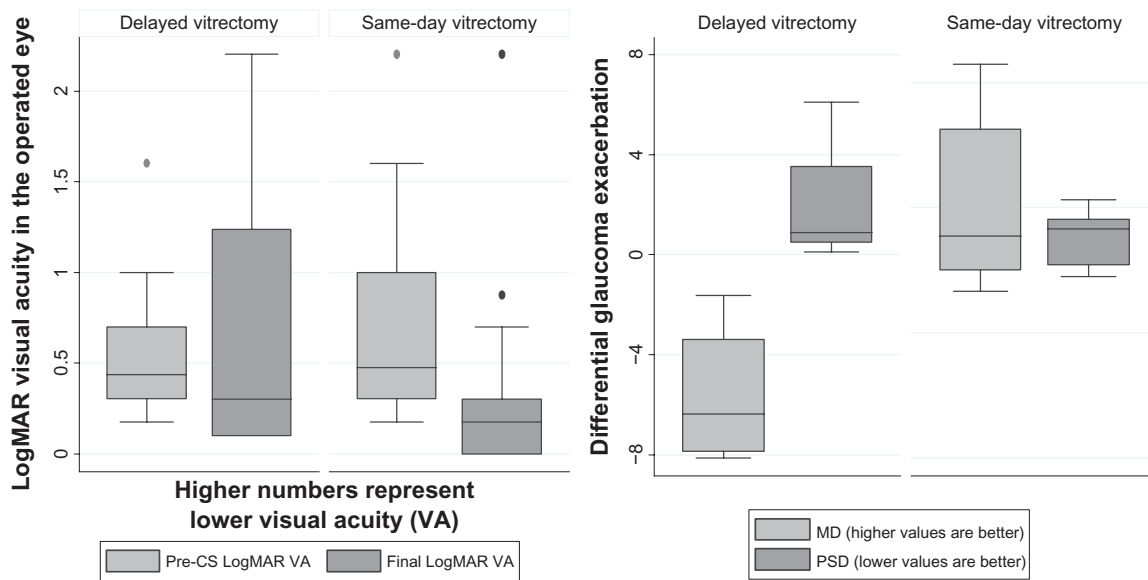
Figure 1 Box-and-whisker plot comparisons of precataract surgery (Pre-CS) logMAR visual acuity (VA) and final logMAR VA in the operated eye and differential glaucoma progression (exacerbation) (mean deviation [MD] and pattern-specific deviation [PSD]) by treatment group.

Data for differential glaucoma progression were available for only four delayed and eight same-day patients. Both the mean MD differential (difference = −5.79, 95% CI = −10.27, −1.32, $t = -2.88$, $P = 0.016$) and the mean PSD differential (difference = 1.66, $Z = 2.55$, $P = 0.011$) were significant (Table 5, models 6 and 7) and indicated greater glaucoma-related loss of sensitivity in delayed vitrectomy eyes. Table 3 shows estimated mean final MD and PSD for the operated eye, based on precataract surgery values and actual changes in the fellow eye (data not shown) if the patients had been in the other group.

Table 2 Descriptive statistics and normal distribution tests

Variable and its function	Delayed PPV (n = 12)			Same-day PPV (n = 23)			Skew/kurtosis[b] test		Shapiro–Wilk[b] test	
	Min	**Md**	**Max**	**Min**	**Md**	**Max**	**adj χ^2**	**P-value**	**Z**	**P-value**
Independent or confounding variables										
Age at final visit	58.13	81.99	97.03	62.79	85.65	99.45	8.63	0.013*	2.20	0.014*
VA logMAR OP pre-CS	0.176	0.438	1.602	0.176	0.477	2.204	10.88	0.004**	3.92	0.000***
VA Snellen OP pre-CS	20/800	20/55	20/30	20/3077	20/60	20/30	4.07	0.130	−1.64	0.950
VA logMAR non-OP pre-CS	0.000	0.176	0.544	0.000	0.301	1.000	12.44	0.002**	2.89	0.002**
VA Snellen non-OP pre-CS	20/70	20/30	20/20	20/200	20/40	20/20	0.95	0.623	−1.55	0.939
FU post-PPV (months)	5.93	53.28	113.37	3.07	36.57	123.50	2.83	0.243	1.86	0.031*
Total elapsed time (months)	6.33	56.57	115.30	3.07	36.57	123.50	2.85	0.240	1.89	0.030*
VA logMAR non-OP final	0.000	0.018	0.544	0.000	0.097	1.301	18.35	0.000***	4.19	0.000***
VA Snellen non-OP final	20/70	20/30	20/20	20/400	20/25	20/20	2.77	0.250	0.32	0.374
Dependent variables										
VA logMAR OP final	0.097	0.301	2.204	0.000	0.176	2.204	18.23	0.000***	5.05	0.000***
VA Snellen OP final	20/3200	20/40	20/25	20/3200	20/30	20/20	3.24	0.198	−0.39	0.651
Visual utility − better eye[a]	0.74	0.84	0.97	0.77	0.87	1.00	4.15	0.126	1.00	0.160
Visual utility − both eyes[a]	0.805	0.96	0.96	0.83	0.96	0.96	7.27	0.026*	3.04	0.001**
Diff MD glaucoma prog	−8.12	−6.37	−1.63	−3.35	−1.15	5.72	0.21	0.899	−0.63	0.737
Diff PSD glaucoma prog	0.11	0.895	6.11	−2.76	−0.85	0.31	10.38	0.006**	2.10	0.018*

Notes: *$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.001$; [†]$P \leq 0.15$. [a]Visual utility analyses included 22 same-day patients. Visual utility − better eye: 1.00 = 20/20 bilaterally, permanently; 0.97 = 20/20 with 20/20 to 20/25 in the other eye, 0.92 = 20/20 with ≤20/40 in the other eye, 0.87 = 20/25, 0.84 = 20/30, 0.80 = 20/40, 0.77 = 20/50, 0.74 = 20/70.[16] Visual utility − both eyes: 0.96 = better eye 20/20 to 20/40 and worse eye > 20/200, 0.88 = better eye 20/50 to 20/80 and worse eye > 20/200, 0.83 = better eye 20/20 to 20/40 and worse eye < 20/200, 0.88 = better eye 20/50 to 20/80 and worse eye < 20/200;[17] [b]the null hypothesis for the Skew/kurtosis test and the Shapiro–Wilk test is that the data come from a normal distribution.
Abbreviations: adj χ^2, adjusted chi-square statistic; Diff, differential; FU, follow-up time in months; Max, maximum; Md, median; Min, minimum; n, number of eyes; non-OP, nonoperated eye; OP, operated eye; post-PPV, after pars plana vitrectomy; PPV, pars plana vitrectomy; pre-CS, before cataract surgery; prog, progression; VA, visual acuity; Z, Z statistic.

Table 3 Summary comparison of outcomes and actual vs estimated (based on statistical models) if patients had been in the other treatment group

Variable and model	Treatment group	n	Actual treatment group means		Estimated means if patients had been in the other treatment group		
			Pre-CS	Final	Unadjusted	Adjusted for age	Adjusted for pre-CS VA
Final VA in the operated eye (Table 4, model 1A and B)	Same-day PPV eyes	23	20/98	20/40	20/90	20/106	20/112
	Delayed PPV eyes	12	20/75	20/90	20/40	20/34	20/32
Visual utility – better eye[a] (Table 4, model 2A and B)	Same-day patients	22	N/A	0.89	0.85	0.89	0.89
	Delayed patients	12	N/A	0.85	0.89	0.84	0.85
Mean deviation (Table 5, model 6)	Same-day PPV eyes	8	−11.07	−10.32	−17.33	N/A	N/A
	Delayed PPV eyes	4	−5.53	−8.33	−2.53	N/A	N/A
Pattern-specific deviation (Table 5, model 7)	Same-day PPV eyes	8	6.58	5.95	9.65	N/A	N/A
	Delayed PPV eyes	4	3.93	5.91	2.70	N/A	N/A

Notes: [a]Visual utility analysis included 22 same-day patients. Visual utility – better eye: 0.92 = 20/20 with ≤20/40 in the other eye, 0.87 = 20/25, 0.84 = 20/30.[16]
Abbreviations: age, age at final visit; n, number of eyes; N/A, not applicable to this analysis because the adjustments based on these variables were not significant; PPV, pars plana vitrectomy; pre-CS, before cataract surgery; VA, visual acuity.

Discussion

The reported incidence of RLF following cataract surgery varied between 0.1% and 1.6%,[2,7,23,24] sometimes higher for inexperienced surgeons.[3,6,25] Our rate of 0.46% (35/7565) represents the 11-year history at MCF, a single academic institution, with all cataract surgeries performed by five experienced, fellowship-trained cataract surgeons. During this time, MCF developed its no-move, no-wait (more than 15 minutes) policy for same-day vitrectomies. If a cataract surgeon experiences an intraoperative complication with posteriorly dislocated lens fragments, he immediately calls the on-site vitreoretinal surgeon for assistance. The immediate surgical goals include complete pars plana removal of the lens fragments with placement of an IOL. All RLF cases during the past 6 years were handled in this manner.

Although some eyes with crystalline RLF are treated medically (at other facilities) with good long-term outcomes, most develop sufficiently severe postoperative complications (elevated IOP, visual obscuration, and inflammation) to warrant removal by vitrectomy. This may be performed during the same surgical episode (depending on the availability, experience, and philosophy of the vitreoretinal surgeon) or delayed. Patient displeasure is common following complicated cataract surgery,[1,4] and tends not to improve if reduced VA persists.[26] One author reported that "… most [RLF] patients, who had expected a rapid visual recovery after cataract surgery, were very dissatisfied with poor vision post-operatively."[4] Same-day vitrectomy, when feasible, could mitigate patient dissatisfaction,[27] prevent the need for a second procedure, and hasten visual recovery.[28]

Some previous studies have suggested that same-day vitrectomy yields better outcomes[5,7,8,29] whereas others have reported poorer same-day outcomes.[3,11,23,25] For good VA (≥20/40), three studies favored same-day vitrectomy by >30%: Chen et al[8] (36.2%), Romero-Aroca et al[7] (35.7%), and Stefaniotou et al[5] (31.9%); while three others favored delayed vitrectomy by >10%: Stilma et al[23] (26.3%), Borne et al[25] (18.75), and Tajunisah and Reddy[3] (12.5%). For bad VA (≤/<20/200), two studies favored same-day vitrectomy by >20%: Stefaniotou et al[5] (27.8%) and Chen et al[8] (22.0%); while two others favored delayed vitrectomy by ≥20%: Tajunisah and Reddy[3] (42.9%) and Watts et al[11] (20.0%). Compared to our delayed group, our same-day group included more patients with good final VA (78.3% [18/23] versus 58.3% [7/12], difference = 20.7%); fewer patients with bad final VA (4.3% [1/23] versus 25.0% [3/12], difference = 20.7%); and better mean (unadjusted) final VA (20/40 versus 20/90), despite having poorer mean initial VA (20/98 versus 20/75), and older mean age (3+ years).

None of these previous studies randomized patients to same-day or delayed vitrectomy, so perhaps these inconsistent same-day versus delayed results have been confounded by different practice patterns and noncomparable treatment groups. Some inconsistency might be due to the fact that many previous studies included same-day vitrectomy patients who were transported between facilities and had much longer (>15 minutes) wait between cataract surgery and vitrectomy. No stratification (by waiting time or location of cataract surgery) was found in any previous analysis of same-day versus delayed vitrectomy outcomes. If waiting

Table 4 Analysis of covariance (ANCOVA) and ordinal logistic regression models comparing final visual acuity in the operated eye and final visual utility (two scales)

Model: dependent variable ANCOVA	Source	df	SS	MS	F	B	t	P-value	Model B: 95% CI	Bootstrapped CI B: 95% BC CI	Robust CI B: 95% CI	Jackknife Δ signif
1A: VA final	Model	2	2.35	1.17	3.93			0.030*		# BSR = 1000		D (1, 9, 12)
Model properties	Group[a]	1	1.37	1.37	4.57	−0.42	−2.14	0.040*	(−0.83, −0.02)	(−0.84, −0.03)*	(−0.87, 0.03)†	
	Age	1	1.38	1.38	4.61	0.02	2.15	0.040*	(0.00, 0.05)	(0.01, 0.04)*	(0.01, 0.04)**	
R-sq = 19.7%												
Adj R-sq = 14.7%	Total	34	11.91	0.35								
1B: VA final	Model	2	6.34	3.17	18.22			0.000***		# BSR = 1000		None
Model properties	Group[a]	1	1.54	1.54	8.86	−0.45	−2.98	0.006**	(−0.75, −0.14)	(−0.83, −0.16)**	(−0.80, −0.92)*	
	VApreCS	1	5.37	5.37	30.87	0.79	5.56	0.000***	(0.50, 1.08)	(0.41, 1.14)***	(0.41, 1.17)***	
R-sq = 53.2%												
Adj R-sq = 50.3%	Total	34	11.91	0.35								
2A: Visual utility 1	Model	2	0.03	0.01	2.67			0.085†		# BSR = 1000		D (1 and 2)
Model properties	Group[a]	1	0.01	0.01	2.62	0.04	1.62	0.116†	(−0.01, 0.10)	(−0.01, 0.09)†	(−0.01, 0.09)†	SD (16)
	Age	1	0.02	0.02	3.56	0.00	−1.89	0.069†	(−0.01, 0.00)	(−0.01, 0.00)†	(−0.01, 0.00)†	
R-sq = 14.9%												
Adj R-sq = 9.2%	Total	33	0.19	0.01								
2B: Visual utility 1	Model	2	0.03	0.01	2.76			0.079†		# BSR = 1000		D (1, 2, 4, 8–11)
Model properties	Group[a]	1	0.01	0.01	2.19	0.04	1.48	0.149†	(−0.01, 0.09)	(−0.01, 0.08)†	(−0.01, 0.09)†	
	VApreCS	1	0.02	0.02	3.75	−0.05	−1.94	0.062†	(−0.10, 0.00)	(−0.11, −0.00)*	(−0.10, 0.00)†	SD (6, 8, 12–16, 19 and 23)
R-sq = 15.1%												
Adj R-sq = 9.7%	Total	33	0.19	0.01								

Ordinal logistic regression	Source	df	LL		χ²	OR[c]	Z	P-value	OR: 95% CI	OR: 95% BC CI	OR: 95% CI	Δ signif
3A: Visual utility 2	Model	2	−23.2		8.21			0.017*		# BSR = 1116		D (9)
Model property	Group[a]					7.38	2.07	0.038*	(1.12, 48.78)	(1.14, 85.50)*	(1.02, 53.16)*	
P R-sq = 15.0%	Age					0.87	−2.04	0.041*	(0.75, 0.99)	(0.76, 0.96)*	(0.79, 0.95)**	
3B: Visual utility 2	Model	2	−21.9		10.84			0.004**		# BSR = 1147		None
Model property	Group[a]					7.26	2.02	0.043*	(1.06, 49.66)	(1.14, 123.9)*	(0.94, 55.98)†	
P R-sq = 19.9%	VApreCS					0.09	−2.63	0.008**	(0.02, 0.54)	(0.01, 0.41)*	(0.02, 0.40)***	

Notes: *$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.001$; †$P \leq 0.15$. [a]For the group variable, the reference category is delayed vitrectomy.

Abbreviations: age, age at final visit; Adj R-sq, adjusted R-squared; B, model coefficient and the adjusted mean difference between the treatment groups; BC, bias-corrected; BSR, bootstrap repetitions; CI, confidence interval; D ( ), delayed vitrectomy patients; df, degrees of freedom; F, F statistic; LL, log likelihood; MS, mean square; OR, odds ratio (OR greater than 1 indicates higher odds of better visual utility for patients with same-day vitrectomy); P R-sq, pseudo R-squared; R-sq, R-squared; SD ( ), same-day vitrectomy patients; SS, partial sum of squares; t, t statistic; VA final, logMAR VA in the operated eye at the final visit; VApreCS, logMAR VA in the operated eye before cataract surgery; Z, Z statistic; χ², chi-square statistic; Δ signif, removal of these patients' data caused a change in the model's significance; VA, visual acuity; visual utility 1, visual utility – better eye; visual utility 2, visual utility – both eyes.

Table 5 Exact Cox proportional-hazards models comparing visual acuity survival times and two-sample tests comparing differential glaucoma progression

Cox proportional-hazards Model and event	Variable	χ^2	HR	Z	P-value	95% CI for HR	Bootstrapped CI 95% BC CI for HR	Robust CI 95% CI for HR	Jackknife Δ signif
4A: Visual acuity	Model	6.46			0.040*		# BSR = 1000		D (1, 9, 12)
< Snellen 20/40	Group[a]		0.34	−1.69	0.092†	(0.01, 1.19)	(0.05, 1.70)	(0.11, 1.07)†	SD (9, 11,
	Age		1.12	2.12	0.034*	(1.01, 1.25)	(1.03, 1.32)	(1.04, 1.20)**	16, 19)
4B: Visual acuity	Model	14.36			0.001***		# BSR = 1000		None
< Snellen 20/40	Group[a]		0.17	−2.13	0.033*	(0.03, 0.87)	(0.01, 1.56)	(0.05, 0.95)*	
	VApreCS		9.17	3.44	0.001***	(2.59, 32.45)	(2.87, 40.92)	(3.60, 17.19)***	
5A: Visual acuity	Model	4.89			0.087†		# BSR = 1001		None
≤ Snellen 20/200	Group[a]		0.16	−1.53	0.126†	(0.02, 1.67)	NMCP	(0.02, 1.61)†	
	Age		1.12	1.54	0.125†	(0.97, 1.29)	(1.02, 6751.6)	(1.04, 1.21)**	
5B: Visual acuity	Model	13.54			0.001**		# BSR = 1027		None
≤ Snellen 20/200	Group[a]		0.07	−1.92	0.055†	(0.00, 1.06)	NMCP	(0.02, 0.29)***	
	VApreCS		42.90	2.45	0.014*	(2.12, 869.3)	NMCP	(4.24, 433.8)***	

Independent-samples t-test		mean diff	t	P-value	95% CI for mean diff	Bootstrapped CI for mean diff	Robust CI for mean diff	Jackknife Δ signif
6: Differential mean deviation glaucoma progression		−5.79	−2.88	0.016*	(−10.27, −1.32)	(−9.16, −2.43)***	(−9.96, −1.63)**	D (9)

Mann–Whitney rank-sum test		mean diff	Z	P-value		for the Z statistic		
7: Differential pattern-specific deviation glaucoma progression		1.66	2.55	0.011**	N/A	(2.08, 3.01)***	N/A	None

Notes: *$P \le 0.05$; **$P \le 0.01$; ***$P \le 0.001$; †$P \le 0.15$. [a]For the group variable, the reference category is delayed vitrectomy.

Abbreviations: age, age at final visit; BC, bias-corrected; BSR, bootstrap repetitions; CI, confidence interval; D ( ), delayed vitrectomy patients; Diff, difference; HR, hazard ratio (HR less than 1 indicates lower risk of a decrease in visual acuity for patients with same-day vitrectomy); N/A, not applicable to this statistical test; NMCP, no meaningful calculation possible, possibly due to the low number of events in the sample; SD ( ), same-day vitrectomy patients; t, t statistic; VApreCS, logMAR visual acuity in the operated eye before cataract surgery; Z, Z statistic; χ^2, chi-square statistic; Δ signif, removal of these patients' data caused a change in the model's significance.
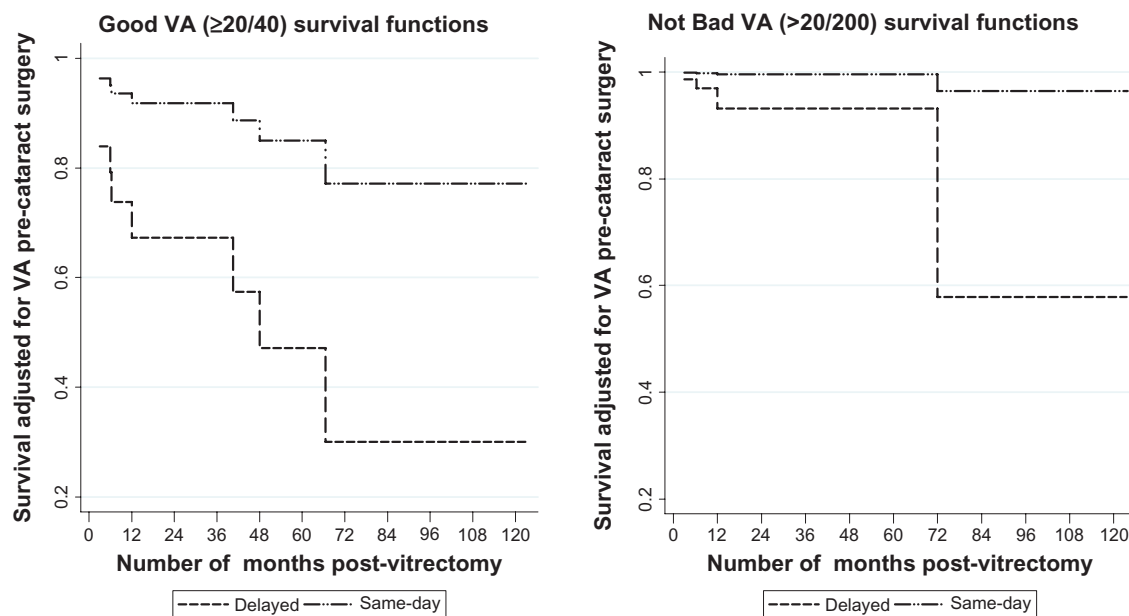
Figure 2 Comparison of Cox proportional-hazards survival functions for good visual acuity (VA ≥ 20/40) and not bad visual acuity (VA > 20/200), in the operated eye, by treatment group, adjusted for precataract surgery VA in the operated eye.

time and/or patient movement between surgeries are important factors in the relative success of same-day vitrectomy, then policy differences among facilities could explain why, in some (but not all) studies, same-day vitrectomy produced better outcomes.

Perhaps immediate vitrectomy (within 15 minutes) prevents time-dependent inflammation and the accompanying choroidal congestion that occurs with same-day patient transfer between different surgical facilities. Immediate vitrectomy for RLF closely resembles a planned pars plana lensectomy, something frequently performed without complications by vitreoretinal surgeons. Compared to waiting several hours between surgeries, immediate vitrectomy may take advantage of a clear cornea and minimally inflamed eye to enable better removal of RLF with fewer complications.

RLF have been linked to new cases of glaucoma,[28,30] and although we did not observe a significant difference in new glaucoma cases, we discovered that vitrectomy timing may affect the progression of preexisting glaucoma. Our same-day eyes with preexisting glaucoma experienced less differential visual field loss (glaucoma progression, measured by both MD and PSD, using fellow eyes as controls). Although possible reasons that same-day vitrectomy might have a stabilizing effect on glaucoma are not known, perhaps same-day vitrectomy prevents time-dependent damage to the trabecular meshwork.[30] Eyes with RLF begin to develop macrophage-mediated inflammation after 3 days,[29,31] and these large cells may exacerbate preexisting glaucoma by

further affecting the already-compromised aqueous outflow.[29] No other analyses of the effect of vitrectomy timing on the progression of preexisting glaucoma were found in the literature, nor were other analyses found of visual utility and RLF removal timing.

Study limitations

The primary study limitation was the small, nonrandomized sample. A description of our attempts to minimize its effect may be found in the appendix. Our patients were not randomized to vitrectomy timing, because our preferred practice pattern evolved from mostly delayed vitrectomies in the early study period to exclusively same-day vitrectomies in the latter study years. However, there were no significant between-group differences in any precataract surgery variables. We used several statistical techniques, including robust CIs, bootstrapping, and jackknifing to increase confidence in our small sample's results. In general, robust CIs and bootstrapping validated the primary models' results (Tables 4 and 5).

Future research

Future researchers, who may have more data, can attempt to verify these findings. We suggest future analyses comparing outcomes for same-day versus delayed vitrectomy stratified by cataract surgery location and adjusting for potential confounding variables (eg, age and precataract surgery VA). Statistical adjustment can mitigate the selection bias

inherent in nonrandomized studies, and stratification should yield more homogeneous treatment groups and help determine if vitrectomy delay and/or patient transport between facilities had an effect on the relative success of same-day vitrectomy. Outcomes should be compared for same-day and delayed patients, all of whom had cataract surgery at the same facility as the vitrectomy, possibly with subanalyses limiting the same-day group to only those patients who were not moved to another operating room and who did not wait more than 15 minutes (or another specified time) between cataract surgery and vitrectomy. Separately, outcomes should be compared for same-day and delayed patients, none of whom had cataract surgery at the same facility as the vitrectomy.

Conclusion

These results suggest that same-day vitrectomy for RLF at MCF (performed based on our no-move, no-wait policy) is associated with superior long-term outcomes. Readers should not generalize these results to RLF patients whose same-day vitrectomy was done under different policies for patient waiting and transport. Furthermore, eyes with preexisting glaucoma may benefit from same-day vitrectomy, a result not previously found in the literature. Though our practice's ability to immediately summon a vitreoretinal surgeon to the operating room is not unique, this is not reproducible for many cataract surgeons. Because the previously published data on same-day vitrectomy are mixed, surgeons should carefully examine their own results to determine if this strategy is appropriate for their practices.

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Disclosure

The authors report no conflicts of interest in this work.

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Appendix: how we enhanced the analysis of our small, nonrandomized sample

Statistical techniques and interpretation

Bootstrapping and robust confidence intervals

The robustness of our models' results was assessed by bootstrapping and estimating robust CIs (Tables 4 and 5). Bootstrapping involves repeated sampling (with replacement) of patients from the same treatment group in the original data set. In the bootstrapped samples (at least 1000 samples for each analysis), each treatment group (same-day and delayed) had the same number of eyes as in the original data set. The same model was built with the bootstrapped samples as had been built with the original sample, and CIs were estimated based on the middle 95% of these models' results.[19] In general, the bootstrapped and robust CIs supported the same conclusions as did the primary models. Unstable bootstrapping results for the Cox proportional-hazards regressions (no meaningful calculations were possible) are possibly due to the small number of events in the sample, because the robust CI results did agree with the primary models.

Jackknifing

Jackknifing assessed our models' sensitivity to the exclusion of each eye's data, by rebuilding the models, deleting one observation at a time.[19] Sensitivity to a single observation is common with small data sets, and should not be interpreted as invalidating the original analysis, but rather emphasizes that the results need to be confirmed with larger data sets.

The jackknifing analyses indicated that, while six models were not sensitive to the exclusion of any eye's data, six models were sensitive, although often a model's results remained marginally significant when one eye's data were removed. Patients whose data removal changed the significance of two or more models included four delayed vitrectomy patients and two same-day vitrectomy patients. One of these delayed vitrectomy patients had the longest cataract surgery to vitrectomy delay. If delayed vitrectomy does yield inferior results,[32] it is possible that the patient with the longest delay would show a greater effect. The other three delayed vitrectomy patients were the oldest and had the worst precataract surgery and final VA. Perhaps the effects of a delayed vitrectomy are more acute for older patients and/or those with worse precataract surgery VA. On the other hand, the two same-day vitrectomy patients whose data changed the significance of two or more models were among the youngest, with the best precataract surgery and final VA, so perhaps any benefits of a same-day vitrectomy are greater for younger patients and/ or those with better precataract surgery VA.

Statistical test interpretation

In the literature, many analyses that do not achieve statistical significance are reported as indicating no effect: a common, but not entirely accurate interpretation of the results. Any study with a difference between groups indicates an effect. There is nothing magical about alpha, the significance level of a statistical test. At the "stroke" of 0.05, the treatment effect does not turn into a pumpkin. The effect goes from significant to nonsignificant, but it does not vanish, like Cinderella's coach. Interpretation of statistical test results involves assessing whether or not this difference is clinically significant and sufficiently likely to be generalizable to the population from which the sample was drawn. This is why it is appropriate to note marginally significant results, especially when analyzing small samples, which tend to have low power to detect significant differences.[14]

Appropriate sample selection

In any treatment comparison, confidence in the results depends on the size, representativeness, and homogeneity of the sample and the balance of patient characteristics between treatment groups. Sample size and treatment group balance receive a great deal of attention, but representativeness and homogeneity of the sample receive little. However, homogeneity of the sample affects the estimated standard deviation used in power and sample size calculations,[14] and representativeness of the sample is the foundation of external validity (below).[33]

Homogeneity of the sample refers to how similar the study's patients are, collectively – not across treatment groups. It is better, when comparing treatments, to have a smaller but relatively more homogeneous sample rather than a slightly larger but significantly more heterogeneous sample. When considering the appropriateness of a study with a nonrandomized comparison group, the " … crucial question to ask is whether the two treatment groups truly come from the same population."[34] Of particular importance in this (and any nonrandomized) study is that if you have a relatively homogeneous sample, you are more likely to have balanced treatment groups. Creating balanced treatment groups is, of course, the objective of random assignment (to treatment groups) in clinical trials.

When doing a retrospective study, researchers often have to make a trade-off between sample size and sample

homogeneity. This study's delayed vitrectomy group included only patients who received cataract surgery at MCF, and who, therefore, would have been eligible for a same-day vitrectomy under the MCF no-move, no-wait policy. This inclusion criterion increased our sample's homogeneity and yielded the best nonrandomized delayed vitrectomy comparison group possible.[34] During the period of this study, seven additional patients who did not receive their initial cataract surgery at MCF received a delayed vitrectomy for RLF at MCF, but were not included in this study. Had they been included, they would have confounded the analyses by significantly increasing the heterogeneity of the sample, because these patients were from a different population than that of the patients who received their initial cataract surgery at MCF.

In general, patients who are treated at different facilities are different in clinically significant ways,[20] so nonrandomized studies that combine patients who where treated at different facilities will have a greater risk of unbalanced treatment groups, significant selection bias, and sample heterogeneity. This is especially true if, as in this case, the facility (where the patient received cataract surgery) is correlated with the treatment (no non-MCF cataract surgery patients received a same-day vitrectomy). For example, perhaps the patients who had cataract surgery at MCF were more likely to have been referred by other MCF doctors, and so could have been older and sicker than the typical cataract surgery patient. In fact, these seven additional (non-MCF cataract surgery) patients were significantly younger than the MCF cataract surgery patients, and their inclusion would have resulted in many significant baseline differences between the treatment groups. To summarize, in the absence of randomization, the best way to increase treatment group balance (through increased sample homogeneity) may be limiting the sample to patients of a single facility.[35] By only including patients who had cataract surgery at MCF, we limited the sample to a single population to minimize treatment group imbalances.[34]

Assessing treatment group balance at baseline

It is important to note that properly executed random assignment of patients to treatment groups, contrary to common belief, is unable to guarantee treatment group balance, especially for small samples.[36] Instead, randomization only ensures that any imbalances are due simply to chance.[14] In a randomized study, after randomization, one should use statistical tests to assess whether or not the treatment groups

are in fact balanced on important variables.[34] If no significant differences are found, in general, researchers would conclude that the randomization procedure created balanced treatment groups.

"To the extent that subjects from both experimental and control groups can be demonstrated to be similar in all important characteristics except for the intervention, the validity of the findings will be enhanced."[36] In this study, all univariate statistical tests for between-group differences at baseline (precataract surgery) were nonsignificant (none were even marginally significant; Table 1), including mean logMAR VA in the operated eyes (same-day = 0.69, delayed = 0.57; $Z = -0.33$, $P = 0.739$) and nonoperated eyes (same-day = 0.30, delayed = 0.26; $Z = 0.21$, $P = 0.832$). Therefore, if this had been a randomized study, and if the assessment of that randomization had produced the results in Table 1, these researchers would have concluded that the randomization procedure had created balanced treatment groups. This does not, in any way, imply that this study's treatment groups meet the criteria of randomization (that any imbalances are due only to chance) which is impossible to establish in a nonrandomized study. However, Table 1 indicates that there was no baseline between-group differences on any variable tested. This is the best possible statistical indication of balanced groups in a nonrandomized study, and is often not achieved, even in a randomized study.

Assessing treatment group balance during the study

Table 1 does indicate that the same-day and delayed vitrectomy groups were significantly different after cataract surgery on the variable for the volume of RLF. For patients with this data, those in the same-day group always had a large amount of lens fragments retained, which would tend to make the situation and prognosis worse, compared to patients with a lesser amount of RLF. For example, retinal detachment has been associated with a greater percentage of lens retained.[24] Therefore, the fact that some delayed vitrectomy patients had only a small or moderate amount of lens fragments retained would tend to yield better outcomes in the delayed vitrectomy group. Since the delayed vitrectomy group did not have better outcomes, the treatment-group imbalance for the volume of RLF should not cause concern with the study's results. That is because this imbalance would tend to operate in the opposite direction, ie, causing the delayed group to have better outcomes, when in fact our study indicated that better outcomes were associated with same-day vitrectomy.

Also, when studying the effects of RLF, ophthalmologists often have the luxury of using the nonoperated (fellow) eye (without the RLF) as a control. Table 1 indicates that there was no significant between-group difference in final logMAR VA in the fellow eye (same-day = 0.28, delayed = 0.21; $Z = -0.04$, $P = 0.972$). This does not prove, but lends credibility to, an assumption that no systemic issues (during the study period) adversely affected VA in one treatment group more than the other, and that therefore, the statistically significant group differences in adjusted final VA in the operated eye may be due to the continued presence of RLF in the delayed vitrectomy eyes.

Other internal and external validity considerations

Internal validity

When there is a small sample but many potential dependent variables, if a lot of analyses are performed, and the results collectively indicate that the same group (treatment) is better (as was the case in our study), each result lends support to the others. This does not obviate the issues of using a small, nonrandomized sample, but it can increase confidence in the results, albeit at a risk of increasing the probability of a type I error.[14]

Nonrandomized treatment comparisons can be valuable because " … such studies' outcomes were not defined or assessed for research purposes, but were conditions with objective, standard assessments, recorded *before the study* in a patient's record, as part of contemporary ophthalmologic practice. This reduces information and observer biases and patient misclassification, which sometimes occur during research studies."[32,36] Also, although data collection could not be masked, "… all risk factors were recorded before the outcomes occurred in patients' medical records, which lack research biases."[32,36]

"For a natural or quasi experiment to be able to reveal genuine causal effects – for it to have good internal validity – two basic conditions are needed. First, the treatment or independent variable of interest must be *exogenous*. In other words, variation in the independent variable can't be driven by anything related to the outcome."[33] The MCF practice pattern evolved over time from mostly delayed vitrectomies to exclusively same-day vitrectomies. No clinical or demographic variable, in any way, influenced treatment group assignment. Therefore, in this study, treatment timing was indeed exogenous; that is, it was not based on anything that was related to any of the outcomes.

"Second, the treatment and comparison groups must be truly *comparable* – or homogeneous – the same in all relevant ways. For *measured* characteristics, the researcher can simply look at the available data to see how equivalent the treatment and comparison groups appear to be."[33] As stated above, in this study, all univariate statistical tests for between-group differences at baseline (precataract surgery) were nonsignificant (Table 1). "For *unmeasured* characteristics, we cannot tell so easily and so must try to reason or guess if important unseen differences might lie beneath the surface."[33] As stated above, we increased the sample's homogeneity by including only patients who received cataract surgery at MCF. We are confident that this yielded the best comparison groups possible by minimizing unmeasured group differences.[34]

External validity

"The generalizability – or *external validity* – of quasi experiments and natural experiments often turns out to be better than in randomized field experiments."[33] We avoided volunteer bias, which is present in prospective studies, because this sample was a consecutive series that included every RLF case from cataract surgery at MCF during the study years (1999–2010).[36] Therefore, the results are generalizable, certainly to future patients at MCF.[36] Additional studies are needed to determine if same-day vitrectomies, performed under a no-move, no-wait policy, might be associated with similar, superior long-term outcomes at other facilities.