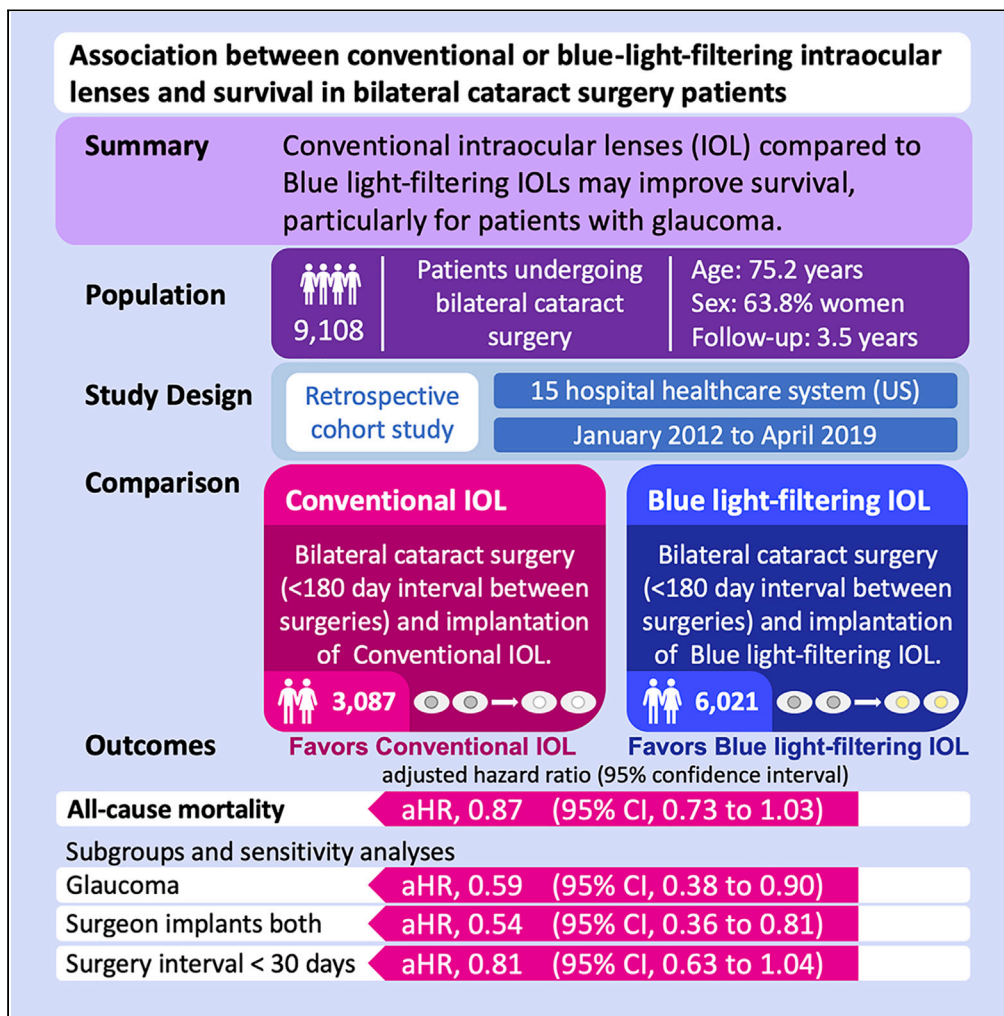


Article

# Association between conventional or blue-light-filtering intraocular lenses and survival in bilateral cataract surgery patients



John E. Griepentrog, Xianghong Zhang, Oscar C. Marroquin, ..., Hamed Esfandiari, Nils A. Loewen, Matthew R. Rosengart

mrr18@pitt.edu

**HIGHLIGHTS**

Risk of all-cause mortality in 9,108 patients after bilateral cataract surgery

Comparison of conventional intraocular lenses to blue-light-filtering intraocular lenses

Conventional lenses that transmit the entire visible spectrum may improve survival

Glaucoma patients particularly may benefit from conventional intraocular lenses

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## Article

## Association between conventional or blue-light-filtering intraocular lenses and survival in bilateral cataract surgery patients

John E. Griepentrog,<sup>1</sup> Xianghong Zhang,<sup>1</sup> Oscar C. Marroquin,<sup>2</sup> Michael B. Garver,<sup>2</sup> AnnaElaine L. Rosengart,<sup>1</sup> Joyce Chung-Chou Chang,<sup>3</sup> Hamed Esfandiari,<sup>4,5</sup> Nils A. Loewen,<sup>5,6</sup> and Matthew R. Rosengart<sup>1,7,\*</sup>

## SUMMARY

**Circadian rhythms regulate adaptive alterations in mammalian physiology and are maximally entrained by the short wavelength blue spectrum; cataracts block the transmission of light, particularly blue light. Cataract surgery is performed with two types of intraocular lenses (IOL): (1) conventional IOL that transmit the entire visible spectrum and (2) blue-light-filtering (BF) IOL that block the short wavelength blue spectrum. We hypothesized that the transmission properties of IOL are associated with long-term survival. This retrospective cohort study of a 15-hospital healthcare system identified 9,108 participants who underwent bilateral cataract surgery; 3,087 were implanted with conventional IOL and 6,021 received BF-IOL. Multivariable Cox proportional hazards models that included several *a priori* determined subgroup and sensitivity analyses yielded estimates supporting that conventional IOL compared with BF-IOL may be associated with significantly reduced risk of long-term death. Confirming these differences and identifying any potential causal mechanisms await the conduct of appropriately controlled prospective translational trials.**

## INTRODUCTION

During the process of aging, the lens undergoes progressive changes that perturb the transmission of light (Turner and Mainster, 2008; Kessel et al., 2010). The accumulation of yellow crystalline deposits within the lens inhibits the transmission of light, particularly the short-wavelength (400–500 nanometers, nm) visible blue spectrum (Kessel et al., 2010). The transmission capacity of the human lens decays to less than 25% by 70 years, with the blue spectrum being disproportionately affected (Turner and Mainster, 2008; Kessel et al., 2010). Importantly, it is this short blue wavelength that maximally entrains our circadian rhythms, which orchestrate adaptive alterations in physiology, metabolism, and immunity to prepare us for the impending metabolic demands and septic threats of the active day (Berson et al., 2002). More recent basic investigation supports that heightened exposure to blue light favorably modulates the biological and immunological response to disease, such as sepsis (Lewis et al., 2018; Yuan et al., 2016). Collectively, these data suggest that perhaps an age-related loss of exposure to light, particularly the visible blue spectrum, may underlie the increased risk of circadian rhythm disorders and other mental and physical health complications experienced by the elderly population (Hood and Amir, 2017; Fung et al., 2016).

Pathologic “clouding” of the lens is called cataract disease, and the typical management involves the removal of the cataractous lens and implantation of an artificial intraocular lens (IOL). Some studies have drawn attention to improved all-cause survival after cataract surgery (Tseng et al., 2016; Zhu et al., 2016; Fong et al., 2013). Yet not all IOLs are created equal. There are two predominant types that differ in transmission properties: conventional UV blocking (conventional IOL) and blue-light filtering (BF-IOL) (Brockmann et al., 2008). BF-IOL, in addition to UV, also impede the transmission of the lower visible blue spectrum between 400 and 500 nm (Brockmann et al., 2008). This technological advancement developed from an appreciation that the higher energy of short wavelength light may be phototoxic and damage the retinal pigment epithelium, thereby accelerating the progression of ocular diseases, such as age-related macular degeneration (Downie et al., 2018; Pollack et al., 1996; Wang et al., 2003). This variation in practice and spectral properties of implanted IOLs lends itself to a natural experiment to explore the ramifications

<sup>1</sup>Department of Surgery, University of Pittsburgh, Pittsburgh, PA 15213, USA

<sup>2</sup>Department of Clinical Analytics, University of Pittsburgh Medical Center Health Services Division, Pittsburgh, PA 15213, USA

<sup>3</sup>Department of Medicine, Biostatistics, and Clinical and Translational Science, University of Pittsburgh, Pittsburgh, PA 15213, USA

<sup>4</sup>Department of Ophthalmology, Northwestern University Feinberg School of Medicine, Chicago, IL 60208, USA

<sup>5</sup>Department of Ophthalmology, University of Pittsburgh, Pittsburgh, PA 15213, USA

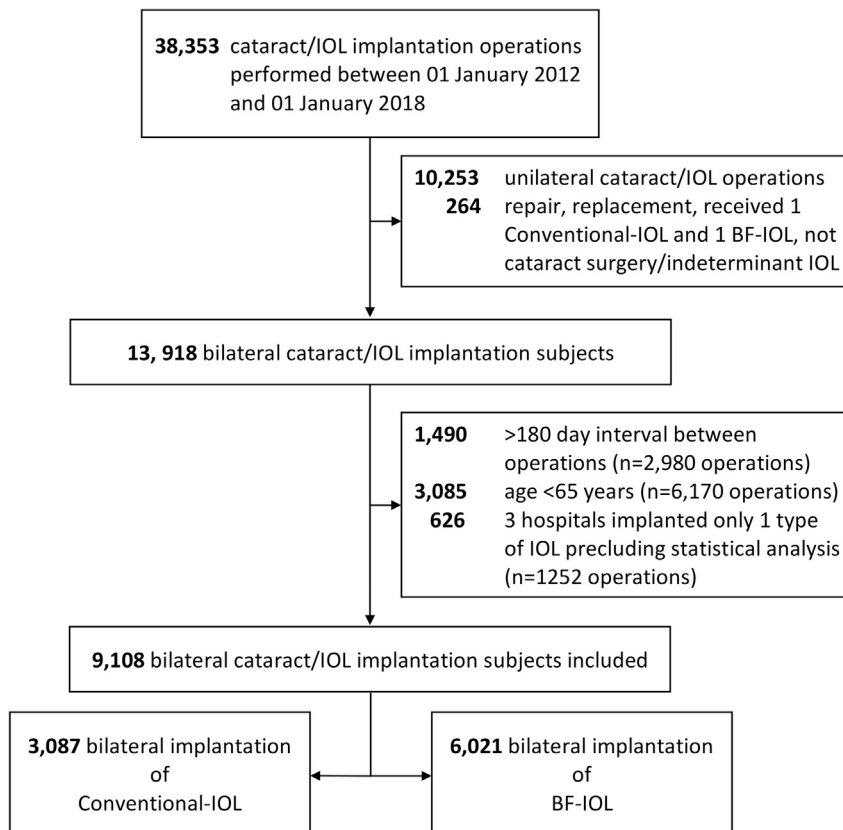
<sup>6</sup>Department of Ophthalmology, University of Würzburg, Würzburg 97070, Germany

<sup>7</sup>Lead contact

\*Correspondence: mrr18@pitt.edu

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**Figure 1. Flow diagram of cohort selection process of eligible patients who underwent bilateral cataract surgery and implantation of intraocular lens (IOL)**

Adults aged 65 years and older who underwent bilateral cataract surgery and implantation of intraocular lenses (IOL) with an interval between surgeries of equal to or less than 180 days. A total of 411 patients undergoing bilateral cataract surgery were excluded on multiple criteria.

of restoring exposure to blue light (i.e., implantation of conventional IOL) or continued loss of blue light (i.e., implantation of BF-IOL) on the long-term health outcomes of patients undergoing bilateral cataract surgery. We hypothesized that conventional IOL will be associated with improved survival relative to BF-IOL.

## RESULTS

### Patient characteristics

A total of 38,353 individual cataract surgeries were performed on a total of 24,300 patients. A total of 13,918 participants underwent bilateral cataract surgery; for 1,490 participants the operations were not performed in a concomitant ( $\leq 180$  days) manner, and 3,085 subjects were younger than 65 years, yielding a cohort of 9,754 participants (Figure 1). The cataract operations performed within three hospitals and upon 626 subjects were uniformly of one IOL type, precluding a within-hospital comparative analysis and thus yielding a final cohort of 9,108 participants (Figure 1). The mean age was 75.2 (SD 6.5) years, 5,811 (63.8%) were women, 792 (8.7%) had a diagnosis of glaucoma, and 291 (3.2%) age-related macular degeneration. Of these participants, a total of 3,087 (33.9%) underwent bilateral implantation with a conventional IOL and 6,021 (66.1%) with BF-IOL (Table 1). The median interval between cataract surgeries was 28.0 (IQR, 14–48) days, and the median duration of follow-up was 3.5 (IQR, 2.3–5.1) years, during which 1,185 (13.1%) participants died.

### Primary outcome

In a univariable Cox proportional hazards model using a within hospital inverse probability of treatment weighting (iptw) using the propensity score for type of IOL implanted (see Transparent Methods),

**Table 1. Baseline characteristics of patients by type of intraocular lens**

Characteristic	Original cohort		p value
	Blue light filtering (n = 6,021)	Conventional (n = 3,087)	
Age, mean (sem), y	75.2 (0.1)	75.1 (0.1)	0.42
Women, No. (%)	3,822 (63.5)	1,989 (64.4)	0.37
Race, No. (%)			<0.001
White	5,521 (91.7)	2,728 (88.4)	
Black	403 (6.7)	254 (8.2)	
Other	97 (1.6)	105 (3.4)	
Comorbidities, No. (%)			
Myocardial infarction	185 (3.1)	100 (3.2)	0.67
Congestive heart failure	317 (5.3)	160 (5.2)	0.87
COPD	904 (15.0)	458 (14.8)	0.82
Peripheral vascular disease	473 (7.9)	241 (7.8)	0.93
Cerebrovascular disease	506 (8.4)	282 (9.1)	0.24
Diabetes			0.82
Without complications	748 (12.4)	384 (12.4)	
With complications	427 (7.1)	230 (7.5)	
Renal disease	508 (8.4)	246 (8.0)	0.44
Dementia	79 (1.3)	45 (1.5)	0.57
Rheumatic disease	230 (3.8)	128 (4.2)	0.45
Peptic ulcer disease	166 (2.8)	65 (2.1)	0.06
Liver disease			0.56
Mild/Moderate	114 (1.9)	54 (1.8)	
Severe	4 (0.1)	4 (0.1)	
Malignancy			0.82
Without metastases	816 (13.6)	420 (13.6)	
With metastases	65 (1.1)	29 (1.0)	
Hemiplegia	14 (0.2)	7 (0.2)	0.96
Body mass index <sup>a</sup> , No. (%) underweight	89 (1.5)	53 (1.7)	0.50
Normal	1,543 (25.8)	786 (25.7)	
Overweight	2,153 (36.0)	1,135 (37.1)	
Obesity I	1,370 (22.9)	651 (21.3)	
Obesity II	534 (8.9)	274 (9.0)	
Extreme obesity	296 (5.0)	162 (5.3)	
Glaucoma, No. (%)	506 (8.4)	286 (9.3)	0.17
Macular degeneration, No. (%)	178 (3.0)	113 (3.7)	0.07
Mammogram, No. (%)	2,093 (34.8)	1,003 (32.5)	0.03
Colonoscopy <sup>b</sup> , No. (%)	2,540 (44.3)	971 (38.4)	<0.001
Alcohol use <sup>c</sup> , No. (%)	2,425 (42.5)	1,221 (41.7)	0.53
Tobacco smoking status <sup>d</sup> , No. (%)			0.02
Current	530 (8.8)	258 (8.4)	
Prior	2,592 (43.2)	1,244 (40.6)	
Never	2,882 (48.0)	1,565 (51.0)	

(Continued on next page)

**Table 1. Continued**

	Original cohort		
Insurance, No. (%)			<0.001
Commercial	1,918 (31.9)	1,006 (32.6)	
Medicare	4,084 (67.8)	2,045 (66.3)	
Medicaid	19 (0.3)	36 (1.2)	
Year of surgery, No. (%)			<0.001
2012	810 (13.5)	291 (9.4)	
2013	981 (16.3)	414 (13.4)	
2014	1,073 (17.8)	449 (14.5)	
2015	1,047 (17.4)	611 (19.8)	
2016	1,032 (17.1)	713 (23.1)	
2017	1,078 (17.9)	609 (19.7)	
Surgeon cases per year, No. median (IQR)	153 (100–220)	209 (122–305)	<0.001
Interval between surgeries, d median (IQR)	28.0 (14.0–42.0)	28.0 (14.0–49.0)	<0.001
Duration of follow-up, d median (IQR)	3.7 (2.3–5.2)	3.3 (2.2–4.7)	<0.001
All-cause mortality, No. (%)	797 (13.2)	388 (12.6)	0.37

<sup>a</sup>Missing and imputed, n = 62.

<sup>b</sup>Missing and imputed, n = 843.

<sup>c</sup>Missing and imputed, n = 470.

<sup>d</sup>Missing and imputed, n = 37.

conventional IOL was associated with reduced all-cause mortality relative to BF-IOL: hazards ratio (HR), 0.80; 95% CI, 0.66 to 0.96;  $p = 0.02$  (Table 2). In a multivariable model, implantation of conventional IOL by comparison to blue-light-filtering (BF-IOL) was associated with a lower risk of all-cause mortality that did not attain statistical significance: adjusted hazards ratio (aHR), 0.87; 95% CI, 0.73 to 1.03;  $p = 0.11$  (Figure 2 and Table 2).

### Subgroup analyses

Data suggest that glaucoma perturbs circadian rhythms (Gubin et al., 2019; Kashiwagi et al., 2000). We observed that participants with glaucoma who received conventional IOL experienced a reduced risk of death relative to those implanted with BF-IOL: aHR 0.59; 95% CI, 0.38 to 0.90;  $p = 0.02$  ( $p$  value for interaction, 0.15). In contrast, there are little data to support that macular degeneration perturbs circadian rhythms (Maynard et al., 2017; Feigl and Zele, 2014). In subjects with macular degeneration, conventional IOL was associated with a reduced risk of death relative to BF-IOL that was similar in direction and magnitude to the point estimate observed for the overall cohort, although not statistically significant: aHR 0.84; 95% CI, 0.38 to 1.88;  $p = 0.67$  ( $p$  value for interaction, 0.99).

### Sensitivity analyses

A more stringent definition of “concomitant” surgery that restricted the “between surgeries” interval to  $\leq 30$  days yielded similar results: aHR 0.81; 95% CI, 0.63 to 1.04;  $p = 0.10$  ( $p$  value for interaction, 0.14) (Table 2). Restricting the analysis to surgeons implanting both types of IOL and to patients residing within the county and geographically proximal to the healthcare system yielded estimates consistent with the primary hypothesis (Table 2).

## DISCUSSION

Recent studies suggest that cataract surgery may improve all-cause survival, particularly among older adults, though equipoise persists (Tseng et al., 2016; Zhu et al., 2016; Blundell et al., 2009; Fong et al., 2013). A variety of causal mechanisms have been considered, most founded upon an enhancement in visual acuity after surgery (e.g., reduced falls, reduced motor vehicle crashes) (Schlenker et al., 2018; Tseng et al., 2012). Overlooked, however, are the known ramifications of light on mammalian biology and physiology. IOL types differ in the degree to which they transmit the shorter wavelength visible blue spectrum. And light, particularly short wavelength blue light, has profound effects on circadian biology

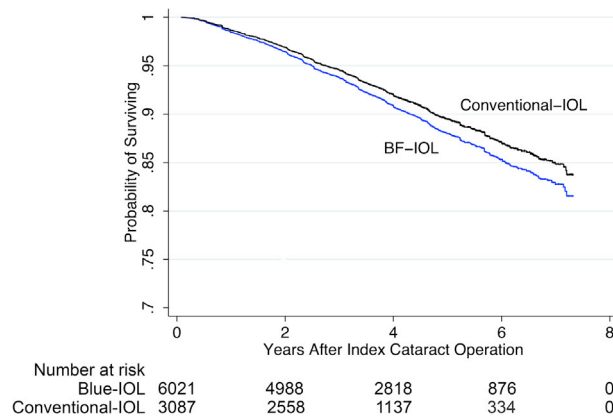
**Table 2. All-cause mortality in total cohort, sensitivity, and subgroup analyses**

	HR	95% CI	p value
<b>Univariable (IPTW) model</b>			
Blue-light-filtering-IOL	Referent		
Conventional-IOL	0.80	0.66–0.96	0.02
<b>Multivariable (IPTW) model</b>			
Blue light filtering-IOL	Referent		
Conventional-IOL	0.87	0.73–1.03	0.11
<b>Subgroup analyses</b>			
Glaucoma	0.59	0.38–0.90	0.02
Macular degeneration	0.84	0.38–1.88	0.67
<b>Sensitivity analyses</b>			
Interval between surgeries $\leq 30$ days	0.81	0.63–1.04	0.10
Surgeon implants both IOL types	0.54	0.36–0.81	0.003
Allegheny County	0.81	0.64–1.04	0.10

and physiology, which serve to promote health (Mohawk et al., 2012; Sancar, 2004). Thus, it is possible that other causal pathways, such as a restoration of circadian biology, are operant and differentially affected by the type of IOL implanted. This analysis of older adults undergoing bilateral cataract surgery found that IOLs that transmit the entire visible spectrum (conventional IOL), including the short wavelength blue spectrum (400–500 nm) are associated with a clinically relevant lower risk of death by comparison to BF-IOL, although this difference did not attain statistical significance. The reduced mortality was significant in sensitivity analyses and in a subgroup of subjects with glaucoma, a pathologic process of ocular structures that has been shown to perturb circadian biology and for which restoring exposure to the entire visible spectrum may offer the greatest health benefit (Gubin et al., 2019; Kashiwagi et al., 2000). Although not definitive, these data contribute to the biologic plausibility of our overarching hypothesis that perhaps the spectrum of light restored with cataract surgery is a critical determinant of health.

Light travels through a nonvisual optic pathway to the suprachiasmatic nucleus (SCN), where it serves as the primary environmental cue, entraining seasonal (circannual) and daily (circadian) oscillations in physiology that enable animals to anticipate and prepare for changes in the external environment. This synchrony allows for the coordination of a temporal program of physiology across many tissues at certain times of the day, such as enhanced immune surveillance and elevated hepatic enzymatic activity prior to the foraging and feeding of the active day when the risk of infection and metabolic demands would be highest (Mohawk et al., 2012). And it is the lower blue spectrum that maximally entrains this clock biology and these circadian rhythms (Sancar, 2004). It is within this circadian framework that an additional causal mechanism for the association between cataract surgery and improved outcome becomes possible: a restoration of exposure to blue light. With aging, the lenticular accumulation of a yellow chromophore leads to increased light scattering and absorption, particularly of the short-wavelength visible blue spectrum (Kessel et al., 2010). Importantly, the spectral absorption of melanopsin, the blue-light sensitive photopigment of the retinal ganglion cells (ipRGC) that signal to the SCN, peaks at approximately 467 nm (Turner and Mainster, 2008; Berson et al., 2002). Additional photopigments are also sensitive to blue light: short wavelength cones and neuropsin (van Gelder and Buhr, 2016; Gooley et al., 2010). Thus, a progressive blockage of blue light may perturb circadian biology, and cataract surgery utilizing conventional IOL may restore these homeostatic mechanisms. Recent data derived from basic research support a paradigm in which high illuminance blue spectrum light is protective in animal models of sepsis and ischemia (Yuan et al., 2016; Lewis et al., 2018; Griepentrog et al., 2019). One study incorporated a small translational pilot trial of subjects with appendicitis, and the results suggested a relevance to human biology (Lewis et al., 2018).

The impetus to develop an IOL that filters blue light came from an appreciation that the higher energy of short wavelength light may be phototoxic and damage the retinal pigment epithelium, thereby



**Figure 2. Cumulative incidence of survival according to blue wavelength transmission properties of implanted intraocular lens**

The graph illustrates the estimated cumulative incidence of survival following bilateral cataract surgery and implantation of conventional intraocular lens (conventional IOL) versus blue-light-filtering intraocular lens (BF-IOL). Also shown is the numbers of patients at risk. The Cox model was adjusted for age, sex, race, individual Charlson comorbidities, history of glaucoma, history of macular degeneration, BMI, smoking status, alcohol use, preventive health services of mammography and colonoscopy, insurance status, calendar year of index cataract surgery, interval between cataract surgeries, surgeon annual volume of cataract surgeries, and hospital. The median follow-up was 3.5 years.

accelerating the progression of ocular diseases, such as age-related macular degeneration (Downie et al., 2018; Pollack et al., 1996; Wang et al., 2003). However, a recent systematic review concluded that the practice of using BF-IOL for retinal protection is not supported by the best available evidence (Downie et al., 2018). A recent survey of Australian ophthalmologists reported that half of surgeons do not recommend BF-IOL, and of those who do, the most frequent reason was as a general safety measure against blue light (Singh et al., 2020). Notably nearly 70% of respondents considered there to be low-quality evidence supporting the benefits of BF-IOL on macular health. Similar perspectives were elucidated in the prescribing of blue-filtering ophthalmic devices by optometrists (Singh et al., 2019). Additional possible reasons influencing surgeon choice of type of IOL include availability of preferred IOL type (Singh et al., 2020), handling characteristics (e.g., speed of opening), ease with which it is visualized (BF-IOL are tinted yellow), and presence of certain comorbidities (e.g., glaucoma, diabetes mellitus) (Narendran et al., 2009; Teichman and Ahmed, 2010; Rodriguez-Galietero et al., 2005).

Clinical studies associating the type of IOL replacement with circadian rhythms, cognitive function, and mood and sleep disorders have arrived at disparate conclusions. Several analyses conclude that cataract surgery itself improves sleep quality, daytime alertness, and cognition and may restore peak nighttime melatonin concentrations; but there is little to no difference between conventional UV-only blocking and BF-IOLs (Erichsen et al., 2015; Zhu et al., 2012; Schmoll et al., 2014; Brondsted et al., 2015). In contrast, more recent studies note that the biological effects of cataract surgery may be dependent upon the transmission properties of IOL. Older patients receiving conventional IOL exhibited improved cognitive function and increased slow-wave sleep (Chellappa et al., 2019) and reduced parameters of depression (Mendoza-Mendieta and Lorenzo-Mejia, 2016) and mood disorders (Zambrowski et al., 2018) compared with those implanted with BF-IOL (Ayaki et al., 2015). In a randomized study comparing the long-term effects of type of IOL, the only durable difference was that blue blocking IOLs increased sleep efficiency (Brondsted et al., 2015, 2017). These prior investigations typically included unilateral cataract surgery, focused predominantly on circadian, ocular, and neurophysiologic outcomes, and were modest in sample size. To these data, we add the results of this larger observational study of bilateral cataract surgery and the outcome of long-term survival.

However, it is important to consider the entire visible blue spectrum (400–500nm) in association studies of IOL transmission properties and mammalian biology. Across this range, notable differences do exist between BF-IOL and the crystalline lens of a child, of a middle-aged adult, and of an elderly person (Mainster, 2006; Turner and Mainster, 2008; Brockmann et al., 2008). The BF-IOLs studied herein impede the transmission of 450nm light by more than 50%, with one approximating a 60% reduction; at these shorter

wavelengths the filtration is of considerably greater magnitude than the lens of a child and for some, exceed that of a 50-year-old adult (Mainster, 2006; Turner and Mainster, 2008; Brockmann et al., 2008). We interpret this loss of transmission with BF-IOL across the spectrum of 400–500nm to be substantial and relevant to circadian biology (Turner and Mainster, 2008; Berson et al., 2002; Tahkamo et al., 2019; Tosini et al., 2016). Face validity of biological relevance and the significance of this effect size become more apparent when compared with the properties of conventional IOL, all of which transmit nearly 100% of this wavelength. But beyond light transmittance, the evidence highlights that the ramifications on downstream biology are highly dependent upon type of IOL implanted and age of patient. Indeed, in reports of circadian photoreception gains or losses relative to a 10-year-old, cataract extraction produces significant gains over phakic eyes, particularly with the implantation of conventional IOL; BF-IOL continues to impede circadian photoreception relative to this reference (Turner and Mainster, 2008). Thus, it is of our opinion that blue light does matter and perhaps more so for the population studied herein (median age of 75.2 years) for which the loss of circadian photoreception approximates 80%.

Among patients undergoing cataract surgery, implantation of conventional IOLs that restore transmission of the entire visible spectrum compared with BF-IOLs may reduce the risk of all-cause mortality, particularly in patients with glaucoma. Confirming these differences and identifying any potential causal mechanisms awaits the results of appropriately controlled, prospective translational trials that incorporate biological sampling and disease-specific outcomes, such as that proposed by the CLOCK-IOL color study (Nishi et al., 2015).

### Limitations of the study

Our analysis is one of association rather than causality. However, the temporal nature of our analysis supports a causal mechanism. The improved survival with conventional IOL relative to BF-IOL, although not statistically significant in the multivariable model, was larger and significant in both sensitivity analyses, as well as, in the subgroup of subjects with glaucoma, a disease that has been associated with perturbations in circadian rhythms (Gubin et al., 2019; Kashiwagi et al., 2000); we perceive these results to support the biological validity of our conclusion that it is a difference in the light spectrum transmitted that underlies the difference in survival with type of IOL. We could not directly analyze parameters of circadian biology, such as melatonin, cortisol, or sleep. The reported action spectrum peak for circadian phase-shifting and suppression of melatonin in humans (~460 nm–~480 nm) is incompletely blocked by blue filtering lenses, and some question the degree to which BF-IOL differentially alter circadian biology relative to conventional IOL or even the natural lens (Tahkamo et al., 2019; Tosini et al., 2016; Augustin, 2008). Thus, other pathways besides circadian rhythms, including pupillary light response, and cognitive arousal may contribute to the survival differences observed. We relied upon administrative data to ascertain baseline characteristics, which could be subject to misclassification. However, we imputed missing values, and our analysis did incorporate those covariates used in prior large studies in an effort to facilitate inter-study comparison (Tseng et al., 2016). The prevalence of comorbid disease in our cohort is concordant with census estimates for the entire US population (Virani et al., 2020; Akinbami and Liu, 2011). And both the exposure of interest (i.e., type of IOL) and outcome were definitively ascertained. Many of the baseline covariates (race, insurance status, BMI, use of preventive healthcare services) are perceived to bias our results away from observing reduced mortality with conventional IOL, although perhaps this effect is counterbalanced by a higher prevalence of smoking in the conventional IOL cohort. Nevertheless, the estimates yielded by the adjusted analysis, although retaining clinical relevance, were no longer statistically significant, further underscoring the need for a prospective clinical trial. We were unable to capture data regarding surgeon decision-making in choosing a type of IOL. However, our analytical approach and subgroup and sensitivity analyses address this source of bias. We were unable to quantify visual acuity prior to surgery and thus could not adjust for the baseline degree of visual impairment or of disruption of circadian biology. However, we did extensively adjust for comorbidities, including glaucoma and macular degeneration. We perceive that our inclusion of only those subjects undergoing bilateral cataract surgery within a limited time frame generated a cohort possessing a relatively similar magnitude of visual disturbance in both eyes. The fact that every pair of eyes underwent a complete restoration of light transmission enabled us to focus our exposure of interest on the spectrum of light and minimize the influence of the surgery itself. We could not adjust for any unique spectral or structural properties specific to a particular IOL; and thus, transmission characteristics additional to those affecting the blue spectrum may underlie our results. The exposure of interest, “concomitant” bilateral cataract surgery was modestly graded, as our definition permitted an intervening interval between surgeries of up to 180 days. However, the mean interval between surgeries was narrow, at less than a month, and sensitivity analyses using a more stringent definition of



30 days yielded similar results. Lastly, we were unable to analyze the specific cause of death, which may have enabled more mechanistic insight.

### Resource availability

#### Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the Lead Contact, Matthew R. Rosengart ([mrr18@pitt.edu](mailto:mrr18@pitt.edu)).

#### Materials availability

This study did not generate new unique reagents.

#### Data and code availability

Individual participant data that underlie the results reported in this article have been completely de-identified and are available through Mendeley Data. A data dictionary is also available.

The complete original data will be shared with those researchers who provide a methodologically sound proposal and protocol for their re-analysis. Data will be available beginning 12 months and ending 36 months following article publication. Only those data necessary to achieve the aims in the approved proposal will be shared. Proposals should be directed to the corresponding author and will undergo approval by the investigative team. To gain access after proposal approval, data requestors will need to sign a data access agreement. Data will be available for 1 year after proposal approval.

## METHODS

All methods can be found in the accompanying [Transparent methods supplemental file](#).

## SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.isci.2020.102009>.

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## AUTHOR CONTRIBUTIONS

Conceptualization: H.E., N.A.L., M.R.R.

## DECLARATION OF INTERESTS

All authors declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

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**Supplemental Information**

**Association between conventional or blue-light-filtering intraocular lenses and survival in bilateral cataract surgery patients**

**John E. Griepentrog, Xianghong Zhang, Oscar C. Marroquin, Michael B. Garver, AnnaElaine L. Rosengart, Joyce Chung-Chou Chang, Hamed Esfandiari, Nils A. Loewen, and Matthew R. Rosengart**

**Supplemental Data**

**Table S1. Baseline characteristics of patients by type of intraocular lens (IOL) and transmission properties (related to Table 1 and Patient Characteristics)**

<b>Conventional IOL (n=3,087)</b>		<b>Blue light-filtering IOL (n=6,021)</b>	
Type (n)	% light transmission (450nm)	Type (n)	% light transmission (450nm)
MX60 (505)	95%(Bausch & Lomb, 2020b)	SN60WF (5,578)	49%(Alcon Laboratories)
PCB00 (736)	~98%(Abbott Medical Optics)	SNAT (356)	47%(Alcon Laboratories)
MI60L (833)	~97%(Bausch & Lomb, 2020a)	MN60AC (43)	42%(Alcon Laboratories)
Any Z (384)	~93%(Abbott Medical Optics)	Other (44)	
AO60 (178)	~97%(Bausch & Lomb, 2020a)		
SA60WF (43)	88%(Alcon Laboratories)		
Other (408)	~88%(Alcon Laboratories, Alcon Laboratories, Alcon Laboratories)		

**Table S2. STROBE Statement-Checklist of items that should be included in reports of cohort studies (related to Table 1, Summary, Transparent Methods and Results)**

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	3, 4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	Transparent Methods (TM)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	TM
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	TM
		(b) For matched studies, give matching criteria and number of exposed and unexposed	TM
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	TM
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	TM
Bias	9	Describe any efforts to address potential sources of bias	TM
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	TM
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	TM
		(b) Describe any methods used to examine subgroups and interactions	TM
		(c) Explain how missing data were addressed	TM
		(d) If applicable, explain how loss to follow-up was addressed	TM
		(e) Describe any sensitivity analyses	TM
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5 Table 1
		(b) Indicate number of participants with missing data for each variable of interest	TM
		(c) Summarise follow-up time (eg, average and total amount)	5 Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	5, 6 Table 2 Figure 2

## **Transparent Methods (related to Results)**

### **Study Design**

This study was a retrospective cohort analysis of subjects aged 65 years and older, who underwent bilateral cataract surgery.

### **Data Source**

Data were obtained by the UPMC Department of Clinical Analytics (OCM, MBG) from the clinical data warehouse (CDW), which captures 100% of inpatient and outpatient encounters within the healthcare system. The CDW is loaded daily from the core clinical systems electronic health records and all ancillary clinical systems. All informatics standards, such as ICD, SNOMED, Rx Norm, and Loinc codes, are leveraged for data standardization.

### **Study Population**

The study population consisted of all adults ( $\geq 65$  years) who underwent bilateral cataract surgery between January 01, 2012 and January 01, 2018 within the UPMC healthcare system that is comprised of 15 hospitals that serve western Pennsylvania, eastern Ohio, northern West Virginia, Virginia, New York, and New Jersey. The cohort entry date was defined as the date the first cataract surgery was performed. The end of the study was April 30, 2019, 16 months after enrollment of the last new patients. Our group of interest was subjects  $\geq 65$  years of age, in part, because several investigations of the association between cataract surgery and clinical outcomes have focused upon this group.(Tseng et al., 2016, Downie et al., 2018, Zhu et al., 2016) Furthermore, cataract surgery is rare ( $<10\%$ ) in younger populations.(Institute)

**Exposure.** Cataract surgery was identified using International Classification of Diseases, Ninth Revision (ICD-9) and International Statistical Classification of Disease and Related Health Problems, Tenth Revision (ICD-10) procedure codes. We abstracted data regarding the manufacturer, make and model, and serial number of each intraocular lens (IOL) from the implantation record of the electronic medical record (EMR). IOLs were classified as Blue light-filtering (BF-IOL) or conventional full spectrum (Conventional-IOL); both filter UV light (Table S1). To be considered bilateral and concomitant, cataract surgery had to be performed on both the left and the right eye within a 180-day period. We considered this an indication that a threshold magnitude of disease severity was present in the contralateral native lens at the time of the index operation. We excluded patients undergoing unilateral surgery, to minimize

uncertainty regarding the transmission properties of the contralateral native lens; surgery to replace or repair a previously implanted IOL, for a similar rationale; and bilateral implantation with one BF-IOL and one Conventional-IOL, which would generate mixed IOL transmission properties. Collectively, these criteria yielded a cohort possessing a similar threshold severity of cataract disease that underwent a complete restoration of light transmission within a limited timeframe; this enabled us to focus our exposure of interest on the spectrum of light and not cataract surgery. Follow-up started 1 day after the date of the initial cataract surgery when exposure to a different light spectrum commenced; data for participants were censored at the date of death or end of the study (April 30, 2019).

**Characteristics.** We abstracted the following data for each patient: age ( $\geq 65$  to  $< 70$ ,  $\geq 70$  to  $< 75$ ,  $\geq 75$  to  $< 80$ ,  $\geq 80$  to  $< 85$ , and  $\geq 85$  years), sex, race (black, white, other), zip code and state of residence, and health insurance status (Commercial, Medicare, Medicaid) at the index cataract surgery. Systemic comorbidities prior to the index surgery were individually classified using each component of the Charlson Comorbidity Index: myocardial infarction, congestive heart failure, chronic obstructive pulmonary disease (COPD), peripheral vascular disease, cerebrovascular disease, dementia, peptic ulcer disease, liver disease (mild, moderate to severe), diabetes mellitus (uncomplicated, complicated with end-organ damage), hemiplegia, moderate to severe chronic kidney disease, malignancy (regional, with metastasis), and Acquired Immune Deficiency Syndrome (AIDS). (Stavem et al., 2017, Charlson et al., 1987) Ocular comorbidities included age-related macular degeneration and glaucoma. Additional covariates included smoking status (never, prior, current), alcohol use (no, yes), body mass index (BMI,  $< 18.5$  underweight; 18.5-24.9 normal; 25.0-29.9 overweight; 30.0-34.9 obesity I; 35.0-39.9 obesity II;  $> 40.0$  extreme obesity) (Control, 2019), calendar year of cohort entry, and preventive health services (mammography within 365 days of index operation, colonoscopy within 10 years of index operation). We included the time interval in days between surgeries and the surgical volume of the physician ( $< 50$ , 50-103, 104-169, 170-249,  $\geq 250$  cataract surgeries per year). Missing data was present in 4 of 44 variables: smoking status,  $n=37$  (0.4%); alcohol use,  $n=470$  (5.2%), colonoscopy,  $n=843$  (9.3%); and BMI,  $n=62$  (0.7%), and addressed with multiple imputation using chained equations. (Rubin, 1987, White et al., 2011) All of these confounders were incorporated into risk-adjustment to ensure compliance with the methodology of contemporary scientific investigations of cataract disease. (Tseng et al., 2016, Zhu et al., 2016)

## **Outcomes**



The primary outcome was all-cause mortality. Mortality was identified based on the Social Security Death Master File and discharge status.(Administration) Follow-up started from the day after the initial surgery until the end of the study period or death, whichever occurred first. Time to death was calculated as the number of days from the first cataract surgery to death. Participants who did not have a recorded death were censored on April 30, 2019.

### **Statistics**

To address potential bias and confounders for the primary prespecified analysis, we used a within hospital inverse probability of treatment weighting (iptw) using the propensity score for type of IOL implanted.(Austin, 2011, Lunceford and Davidian, 2004) Propensity scores were estimated with logistic regression models to predict assignment of either BF-IOL or Conventional-IOL with the use of all prespecified variables.(Narendran et al., 2009, Teichman and Ahmed, 2010, Downes, 2016, Logothetis and Feder, 2019) Standardized mean differences were compared before and after propensity-score weighting to evaluate how well the pseudo-population generated via weighting balanced the potential confounders. The c-statistics for the final hospital specific propensity models ranged from 0.81 to 0.99. Adjusted hazard ratios (aHR) and 95% confidence intervals (CI) were estimated with weighted multivariable Cox proportional-hazards models, to compare patients receiving Conventional-IOLs with Blue-IOLs for risk-adjusted mortality. The proportional hazards assumption was tested using Schoenfeld residuals. Goodness of fit was assessed using Cox-Snell residual plots. A  $p < 0.05$  was considered statistically significant. All tests were 2-sided. All analyses (MRR, JCC) were conducted using Stata version 16 (StataCorp). The study was reported in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) recommendations (Table S2).

**Subgroup and sensitivity analyses.** We assessed the association between type of IOL implanted and mortality for two prespecified patient subpopulations: 1) glaucoma and 2) macular degeneration. We hypothesized *a priori* that these populations may differ in receipt of IOL, and glaucoma has been shown to perturb circadian rhythms.(Gubin et al., 2019, Kashiwagi et al., 2000) We assessed the sensitivity of our findings by repeating the primary analysis 1) using a more stringent definition of 'concomitant' surgery ( $\leq 30$  days interval between surgeries); 2) restricting the analysis to surgeons implanting both IOL types to account for unmeasured bias introduced at the surgeon-level by surgeons implanting only one type of

IOL; and 3) restricting the analysis to hospitals and subjects both residing within Allegheny County, in an effort to minimize missingness in the documentation of subject-level characteristics.

**Study and ethics approval**

The University of Pittsburgh Institutional Review Board approved this study (PRO#18060034) and determined that a waiver to obtain informed consent was appropriate for this retrospective study. This study was registered under ClinicalTrials.gov: NCT04187157.

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