Postoperative Complications in Medicare Beneficiaries Following Endothelial Keratoplasty Surgery

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• PURPOSE: To determine national-level incidence rates of major postoperative complications following endothelial keratoplasty (EK) procedures and to stratify these rates based on EK indications over an 8-year period using Medicare claims data.

• DESIGN: Retrospective, cohort study.

• METHODS: Setting: population-based; study population: Medicare beneficiaries aged ≥65 years who underwent EK procedures; main outcome measurements: 1) occurrence of major postoperative complications (i.e., endophthalmitis, choroidal hemorrhage, infectious keratitis, cystoid macular edema [CME], retinal detachment [RD], or RD surgery) following EK surgery; 2) time-to-event analysis for glaucoma surgery; and 3) occurrence of graft complications.

• RESULTS: A total of 94,829 EK procedures (n = 71,040 unique patients) were included in the analysis. Of the total, 29% of patients had pre-existing glaucoma. The overall 90-day cumulative incidence of postoperative endophthalmitis and choroidal hemorrhage following EK was 0.03% and 0.05%, respectively. The overall 1-year cumulative rates of RD or RD surgery, infectious keratitis, and CME were 1.0%, 0.8%, and 4.1%, respectively. Approximately 7.6%, 12.2%, and 13.8% of all eyes in this study needed glaucoma surgery at 1-, 5-, and 8-years of follow-up, respectively. The probability of glaucoma surgery among patients with pre-existing glaucoma was 29% vs. 8% among those without pre-existing glaucoma at 8 years. The cumulative probabilities of developing any graft complications were 13%, 23.2%, and 27.1% at 1, 5, and 8 years, respectively, of follow-up. On average, patients undergoing EK procedures for a prior failed graft had the highest rate of complications, whereas those with Fuchs' corneal endothelial dystrophy had the lowest.

• CONCLUSIONS: The incidence of major postoperative complications including endophthalmitis, retinal detachment, and choroidal hemorrhage following EK procedures is low. A high proportion of eyes undergoing EK eventually require glaucoma surgery and experience graft-related complications. Postoperative outcomes are typically worse for patients undergoing EK for prior failed grafts than for those undergoing EK for Fuchs' corneal endothelial dystrophy. (Am J Ophthalmol 2020;219:1–11. © 2020 Elsevier Inc. All rights reserved.)

OVER THE PAST DECADE, AS OF THIS WRITING, endothelial keratoplasty (EK), which includes selective endothelial replacement by either Descemet stripping endothelial keratoplasty (DSEK) or Descemet membrane endothelial keratoplasty (DMEK), has largely replaced penetrating keratoplasty (PK) as the standard of care for management of endothelial corneal disorders.[1] Multiple studies, including technology assessments by the American Academy of Ophthalmology, have established EK procedures to be both safe and effective and superior to PK in terms of postoperative visual outcomes, visual recovery, and complication rates.[2,3] Indeed, EK has been the most commonly performed keratoplasty procedure in the United States since 2012, with EK accounting for 62% of all keratoplasty procedures in 2018.

Most published data for postoperative complications following EK procedures are derived from single centers, groups with small sample sizes, or shorter term follow-up.[4–12] As a result, current outcomes may not be reflective of real-world outcomes as wide variations tend to exist between institutes with regard to the patient populations served as well as surgeon experience.[13,14] Furthermore, data for the incidence of rare complications after EK are limited because of the small sample sizes of most published studies.[4,5]

The Medicare administrative claims database contains information for almost 45 million beneficiaries ≥65 years of age and more than 19,000 ophthalmologists. The diverse mixture of patient and surgeon populations within the Medicare database provides a unique opportunity for evaluating real-world outcomes of EK procedures. Therefore,

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the purpose of this study was to estimate incidence rates of major postoperative complications following EK on a national level and to stratify those rates based on EK indications over an 8-year period, using Medicare claims data.

SUBJECTS AND METHODS

• **STUDY POPULATION:** The data used for this study were 2010-2019 100% Medicare fee-for-service carrier claims accessed through a Centers for Medicare and Medicaid Services contractor, Research Data Assistance Center (ResDAC, University of Minnesota).

School of Public Health Policy and Management, Minneapolis, Minnesota [https://www.resdac.org/cms-virtual-research-data-center-vrdchttps]. The study population was all Medicare beneficiaries who underwent endothelial keratoplasty (EK) between January 1, 2011, and March 31, 2019. EK procedures were identified by using Current Procedural Terminology code 65756. Procedures were excluded in which the patients did not have 12 months' continuous enrollment in Medicare parts A and B prior to their EK procedure (n = 3,645); in which procedures were performed in patients younger than 65 years old (n = 3,373); and procedures missing demographic information (n = 34). Also excluded were procedures with a different type of transplantation billed on the same day as the EK (Supplemental Table 1) (n = 852), without complete billing information such as a modifier to indicate laterality of the procedure or diagnosis code for indication (n = 4,610) and that had bilateral EKs billed on the same day (n = 42) (Supplemental Figure 1 shows exclusion criteria), as these were presumed to be coding inaccuracies.

The study was approved by the Institutional Review Board of the Johns Hopkins University School of Medicine.

• **OUTCOMES:** The primary outcome was the occurrence of major postoperative complications following EK, that is, incidence of endophthalmitis or choroidal hemorrhage within 30 and 90 days; the incidence of infectious keratitis or cystoid macular edema within 6 months and 1 year; and retinal detachment (RD) or RD surgery within 1 year of surgery (Supplemental Tables 2 and 3 show diagnostic and procedure codes used to identify the complications). For those outcomes, patients were required to have a follow-up period of at least the length of the time frame in which the outcomes were relevant, in order to fully capture the outcome events. For calculation of the cumulative incidence of these outcomes, 2 estimates were generated, 1 low or conservative and 1 high or sensitive. The conservative estimate was calculated by excluding procedures in which the patient underwent intraocular surgery within 90 days before the EK procedure in the contralateral eye or subsequent intraocular surgery in either eye within the same follow-up period as their complication as this could be due to the other intraocular surgery instead of EK. Sensitivity estimates were calculated by excluding procedures in which the patient underwent a subsequent intraocular surgery in the same eye as within the same follow-up period as their complication (Supplemental Table 3). This provided a range of estimates for the complication rates, and the true incidence was likely within this range as the incidence of those complications following EK was assessed on a per-patient basis because International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) codes could not provide information for the laterality of the condition. Patients who had a history of such conditions within 12 months prior to the EK procedure were also excluded to ensure that the complications captured were not pre-existing conditions. Furthermore, the complication was required to be diagnosed by at least 1 ophthalmologist to maximize the diagnosis accuracy.

Given that the development or worsening of glaucoma is a long-term complication, a time-to-event analysis was performed for glaucoma surgery (Supplemental Table 3) after EK, rather than calculating its cumulative incidence within a relatively short time period as was done for the above-mentioned additional outcomes.

The secondary outcome was determining the occurrence of graft complications (Supplemental Table 4) following EK procedures. Graft complications diagnosed prior to October 1, 2015, were generally referred to as mechanical complications due to corneal graft and could have included any graft-related problem including graft rejection, failure, dislocation, or other. The introduction of ICD-10-CM codes on October 1, 2015, provided more granularity and the ability to differentiate between graft failure and graft rejection for study purposes. For estimates of graft rejection and failure, only procedures performed after October 1, 2015, were included in the analysis. The incidence of graft complications following EK was assessed on a per-patient basis because ICD codes could not provide information on the laterality of the condition.

• **PATIENT CHARACTERISTICS:** We obtained patients' demographic information including age, sex, and race from the Medicare Master Beneficiary Summary File. Other patient characteristics included the clinical indication for EK, the occurrence of concurrent ophthalmologic procedure, and ocular comorbidities (glaucoma or diabetic retinopathy, age-related macular degeneration, macular hole, or epiretinal membranes, or a history of intraocular surgery). The clinical indication for EK was determined based on the primary diagnosis code listed on the EK claim (Supplemental Table 5). The calendar year of EK was derived from the claim date. Concurrent ophthalmologic procedures were defined as the procedures performed on the same day as EK were categorized (Supplemental Table 3). Each patient's inpatient, outpatient, and carrier claims were reviewed within 12 months before the EK

TABLE 1. Characteristics of Patients Undergoing EK

Characteristic		EK procedures (N = 94,829; n = 71,040 unique patients)
Age, y	Median (IQR), Mean (SD)	77.0 (71.6-82.9), 77.6 (7.2)
	65-74	38,615 (40.7%)
	75-84	39,748 (41.9%)
	85-94	15,781 (16.6%)
	≥95	685 (0.7%)
Sex	Males	35,905 (37.9%)
	Females	58,924 (62.1%)
Race	White	84,855 (89.5%)
	Black	5,470 (5.8%)
	Asian	1,221 (1.3%)
	Hispanic	1,188 (1.3%)
	North American Native	260 (0.3%)
	Other or unknown	1,835 (1.9%)
Ocular comorbidity status	Glaucoma	27,457 (29.0%)
	Diabetic retinopathy	2,193 (2.3%)
	Age related macular degeneration	9,189 (9.7%)
	Macular hole/ERM	4,633 (4.9%)
Prior intraocular surgical history	Retinal	2,381 (2.5%)
	Glaucoma	5,882 (6.2%)
	Anterior Segment other than routine cataract/PI	7,465 (7.9%)
	Routine cataract	18,633 (19.6%)
	Routine iridotomy/iridectomy	3,951 (4.2%)
	None of the above	64,381 (67.9%)
Clinical indication for EK	Fuchs' endothelial dystrophy	51,212 (54.0%)
	Bullous keratopathy	14,087 (14.9%)
	Other corneal edema	14,790 (15.6%)
	Prior failed graft	8,487 (9.0%)
	Other	6,253 (6.6%)
Complex EK or not	Complex EK[a]	9,792 (10.3%)
	Noncomplex EK	85,037 (89.7%)

EK = endothelial keratoplasty; ERM = epiretinal membrane; PI = peripheral iridotomy.
[a]Defined as EK performed with concurrent retinal, glaucoma or anterior segment surgery other than routine cataract or PI.

procedure date to determine their ocular comorbidity status (Supplemental Table 6). In a sensitivity analysis, a look-back period of 36 months was used to assess patients' ocular comorbidity status, which would increase the sensitivity of detecting comorbidities such as glaucoma but result in a smaller sample size as patients without 36 months' enrollment prior to their EK procedures were accordingly excluded. The sensitivity analysis yielded similar findings and did not significantly alter the results.

• **STATISTICAL ANALYSIS:** For the secondary outcome, the Kaplan-Meier method was used for the time-to-event analysis of graft complications. Any graft complication was studied as a general outcome for all EKs performed during the study period. For EKs performed on or after October 1, when ICD-10-CM codes were in effect, graft failure and graft rejection could be studied separately.

All statistical analyses were performed using SAS Enterprise version 7.1 software (SAS Institute, Cary, North Carolina). All statistical tests were 2-sided, and the level of significance was set at a P value of ≤.05.

RESULTS

• **PATIENT CHARACTERISTICS:** A total of 94,829 EK procedures (n = 71,040 unique patients) performed between 2011 and 2019 were included in the analysis. The mean age ± SD of patients undergoing EK was 77.6 ± 7.2 years, and the majority were females (62.1%) and white (89.5%) (Table 1). Approximately 29% had a pre-existing glaucoma diagnoses, and 6.2% had prior glaucoma surgery. The most common indications for EK were Fuchs'

TABLE 2. Complication Rates (conservative and sensitive)[a,b,c] for All EK Procedures

Outcome	Time Frame	Conservative (n/N)[b]	Sensitive (n/N)[c]	Time frame	Conservative (n/N)[b]	Sensitive [(n/N)c]
Endophthalmitis	30 days	3/78,087 (0.01%)	10/81,051 (0.01%)	90 days	7/76,010 (0.01%)	23/78,952 (0.03%)
Choroidal hemorrhage	30 days	0/78,146 (0.0%)	0/81,114 (0.0%)	90 days	17/79,008 (0.05%)	41/79,008 (0.05%)
Infectious keratitis	6 mos	200/61,698 (0.3%)	337/63,565 (0.5%)	1 y	278/56,385 (0.5%)	467/58,085 (0.8%)
Cystoid macular edema	6 mos	1,115/60,408 (1.9%)	1,856/61,852 (3.0%)	1 y	1,384/55,259 (2.5%)	2,291/56,590 (4.1%)
Retinal detachment or retinal detachment surgery				1 y	306/56,677 (0.5%)	552/58,400 (1.0%)

EK = endothelial keratoplasty.

[a]The follow-up period is different for the different complications hence the total counts vary for each complication based on exclusion criteria.

[b]Calculated by excluding patients whose underwent intraocular surgery within 90 days before the EK procedure in the contralateral eye or subsequent intraocular surgery in either eye within the follow-up period.

[c]Calculated by excluding patients who underwent a subsequent intraocular surgery in the same eye as within the follow-up period as their complication.

TABLE 3. Complication Rates (Sensitive Estimates)[a,b] by Clinical Indications for EK

		Indication for EK				
Outcome	Time Frame after EK Procedure	Fuchs' Endothelial Dystrophy (n/N)	Bullous Keratopathy or Other Corneal Edema (n/N)	Prior Failed Graft (n/N)	Other (n/N)	*P* Value
Endophthalmitis	90 days	7/42,990 (0.02%)	11/23,731 (0.05%)	4/7,002 (0.06%)	1/5,229 (0.02%)	.07
Choroidal hemorrhage	90 days	8/43,004 (0.02%)	22/23,756 (0.09%)	6/7,012 (0.09%)	5/5,236 (0.10%)	<.001
Infectious keratitis	1 y	171/32,137 (0.5%)	176/16,992 (1.0%)	70/5,019 (1.4%)	50/3,937 (1.3%)	<.001
Cystoid macular edema	1 y	978/31,824 (3.1%)	921/16,082 (5.7%)	237/4,876 (4.9%)	155/3,808 (4.1%)	<.001
Retinal detachment or retinal detachment surgery	1 y	160/32,210 (0.5%)	278/17,138 (1.6%)	66/5,082 (1.3%)	48/3,970 (1.2%)	<.001

EK = endothelial keratoplasty.

[a]The follow-up period is different for the different complications, hence the total counts vary for each complication.

[b]Calculated by excluding patients who underwent a subsequent intraocular surgery in the same eye as within the follow-up period as their complication.

endothelial dystrophy (54%), bullous keratopathy or other corneal edema (30.5%), and prior failed graft (9%). Most EK procedures (89.7%) performed were noncomplex (i.e., an EK procedure performed without any concurrent procedure other than routine cataract extraction or an iridotomy) (Table 1). In this cohort, 77.9% of the patients had 1 eye included in the analysis, and 22.1% had both eyes undergo the EK procedure at different times during the study period. Approximately 29% of patients had more than 1 EK procedure performed during the study period. The median follow-up time for the 94,829 EK procedures was 34.9 months.

• **PRIMARY OUTCOMES:** *Endophthalmitis*. The overall cumulative incidence of postoperative endophthalmitis after EK was 0.01% for both conservative and sensitivity estimates at 30 days and between 0.01% and 0.03% at 90 days (Table 2). When estimates were stratified by indication, the 90-day sensitivity estimates of incidence of endophthalmitis for procedures performed for Fuchs' was 0.02% (7 of 42,990), whereas for bullous keratopathy or other corneal edema it was 0.05% (11 of 23,731). The 90-day incidence of endophthalmitis for EK procedures performed for prior failed grafts was 0.06% (4 of 7,002). The differences in rates between the indications were not statistically significant ($P = .07$) (Table 3).

Choroidal hemorrhage. No cases of choroidal hemorrhage were identified in the 30-day postoperative window. The overall cumulative incidence of 90-day choroidal hemorrhage following EK was 0.05% (41 of 79,008) (Table 2). The incidence of choroidal hemorrhage stratified by indication was 0.02% (8 of 43,004; Fuchs'), 0.09% (22 of 23,756; bullous keratopathy and/or other corneal edema), and 0.09% (6 of 7,012; previously failed graft). The differences between indications were statistically significant ($P < .001$) (Table 3).

Infectious keratitis. Based on conservative estimates, a total of 0.3% (200 of 61,698) and 0.5% (278 of 56,385)

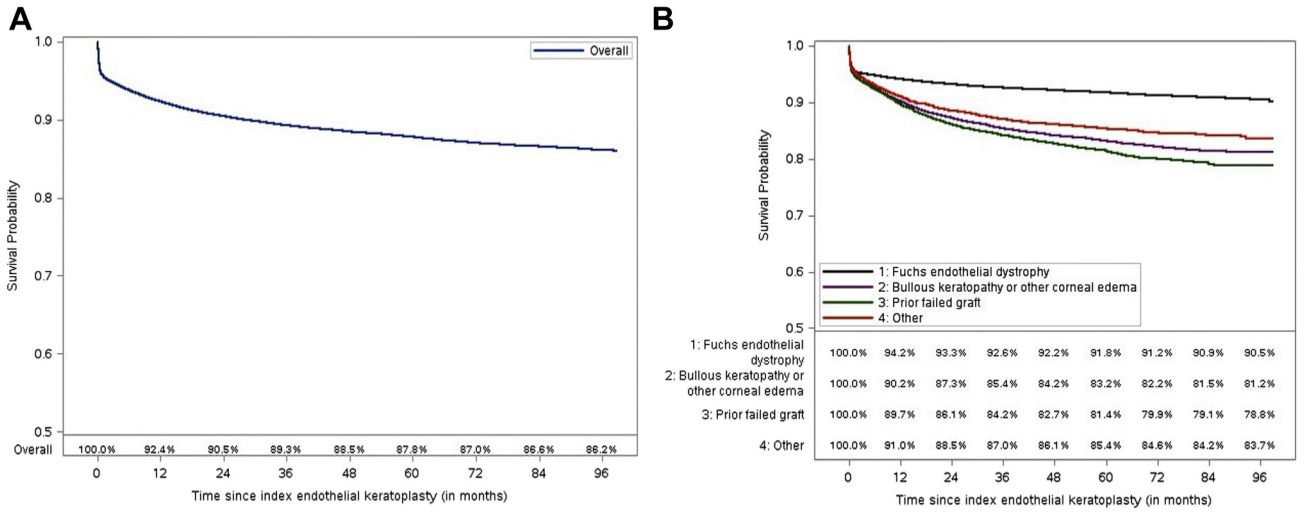

FIGURE 1. (A) Kaplan-Meier curve for requiring glaucoma surgery in the overall study population. (B) Kaplan-Meier curve for requiring glaucoma surgery stratified by indication.

of patients developed infectious keratitis within 6 months and 1 year of their EK procedure, respectively. The sensitivity estimates for infectious keratitis were 0.5% (337 of 63,565) at 6 months and 0.8% (467 of 58,085) at 1 year (Table 2). When 1-year estimates were stratified by indication, the estimates for infectious keratitis were highest among patients undergoing EK for a prior failed graft (1.4%,70 of 5,019), followed by those with bullous keratopathy or other corneal edema (1.0%; 176 of 16,992) and Fuchs' endothelial dystrophy (0.5%, 171 of 32,137). The differences in incidence among the indications were statistically significant ($P < .001$) (Table 3).

Cystoid macular edema. The overall 6-month and 1-year cumulative rates of cystoid macular edema (CME) were 1.9% and 2.5%, respectively, with conservative estimates, and 3.0%-4.1%, respectively, with sensitivity estimates (Table 2). The 1-year sensitivity estimates for CME rates were highest for bullous keratopathy or other corneal edema (5.7%, 921 of 16,082) followed by prior failed graft (4.9% 237 of 4,876) and Fuchs' (3.1% (978 of 31,824)). The difference in incidence between the indications was statistically significant ($P < .001$) (Table 3).

Retinal detachment. The 1-year incidence of postoperative retinal detachment (RD) or retinal detachment surgery was between 0.5% (306 of 56,677) and 1.0% (552 of 58,400) among patients undergoing EK (Table 2). Cumulative incidence of RD stratified by indications were 0.5% (160 of 32,210; Fuchs'), 1.6% (278 of 17,138; bullous keratopathy or other corneal edema), and 1.3% (66 of 5,082; prior failed graft). The difference in incidence between the indications was also statistically significant ($P < .001$) (Table 3).

Glaucoma Surgery. The 1-, 5- and 8-year probabilities of eyes needing glaucoma surgery in the present study population were 7.6%, 12.2%, and 13.8%, respectively (Figure 1, A). Glaucoma surgery rates were highest among eyes undergoing EK for a prior failed graft, followed by those with bullous keratopathy or other corneal edema. Almost 20% of eyes in each group were at risk of requiring glaucoma surgery at the 8-year follow-up (Figure 1, B). Furthermore, the probability of glaucoma surgery was significantly higher for patients with pre-existing glaucoma than for those without pre-existing glaucoma (29% vs. 8.1%, respectively, at 8 years) (Figure 2). The risk of undergoing glaucoma surgery was highest during the first postoperative year and persisted throughout the study period. The respective probabilities of eyes that required glaucoma surgery at 1 and 8 years of follow-up was: 5.8% and 9.5% for Fuchs', 9.8% and 18.8% for bullous keratopathy, and 10.3% and 21.2% for prior failed graft.

• **SECONDARY OUTCOMES:** *Graft complications*. The cumulative probability of developing any graft-related complication at 1, 5, and 8 years of follow-up was 13%, 23.2%, and 27.1%, respectively (Figure 3, A). The probability of developing graft complications was highest among patients undergoing EK for a prior failed graft, with 48% developing graft complications at 8 years. In comparison, graft complications developed in 30% of patients with bullous keratopathy and in 21.5% of patients with Fuchs' at the end of the 8-year follow-up period (Figure 3, B). The risk of graft complications was

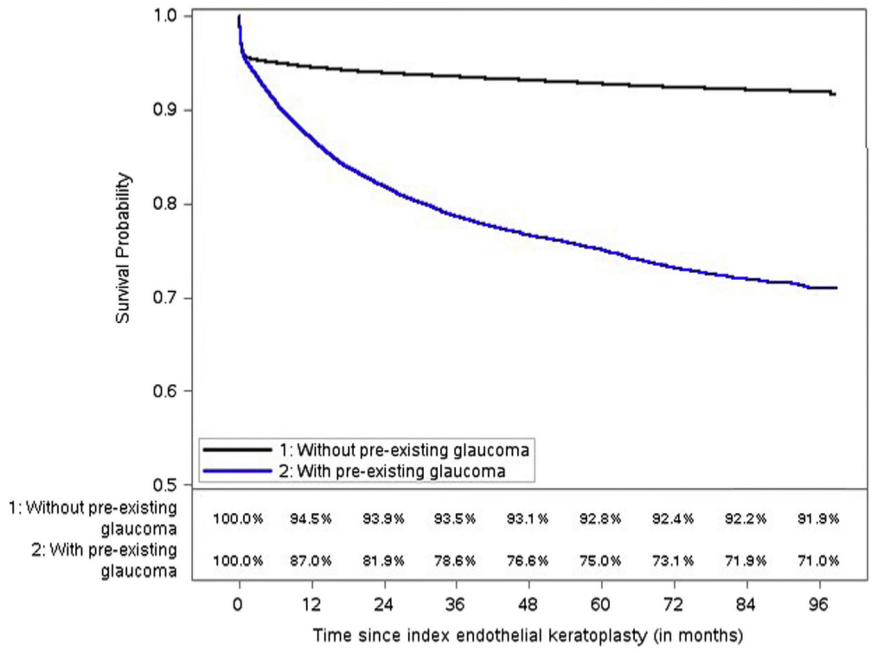

FIGURE 2. Kaplan-Meier curve for requiring glaucoma surgery stratified by presence of pre-existing glaucoma.

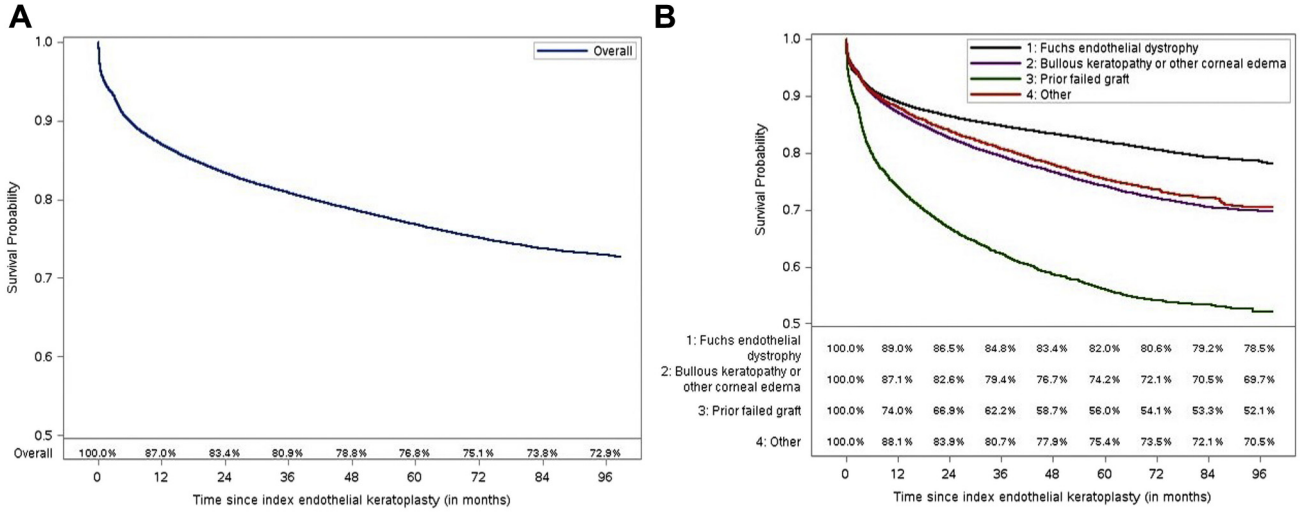

FIGURE 3. (A) Kaplan-Meier curve for developing any graft complication in the overall study population. (B) Kaplan-Meier curve for developing any graft complication stratified by indication.

highest during the first postoperative year: 11% for Fuchs', 12.9% for bullous keratopathy, and 26% for prior failed graft.

Graft failure. For the subset of the procedures performed beginning October 2015, the estimated 1-, 2-, and 3-year probability of developing graft failure episodes in the present study population was 6.3%, 8.6%, and 9.6%, respectively (Figure 4, A). The cumulative 3-year graft failure probability was highest among patients undergoing EK for a prior failed graft (26.5%) followed by bullous keratopathy (11.6%) and Fuchs' endothelial dystrophy (5.8%) (Figure 4, B). The probability of graft failure was highest during the 6-month postoperative period: Fuchs' (3.5%), bullous keratopathy (4.5%), and prior failed graft (12.6%), and the risk of failure persisted throughout the study period.

Graft rejection. Similarly, for the subset of procedures performed beginning October 2015, the cumulative probability of graft rejection episodes at 1, 2, and 3 years in this study population was 3.5%, 5.6%, and 6.2%, respectively

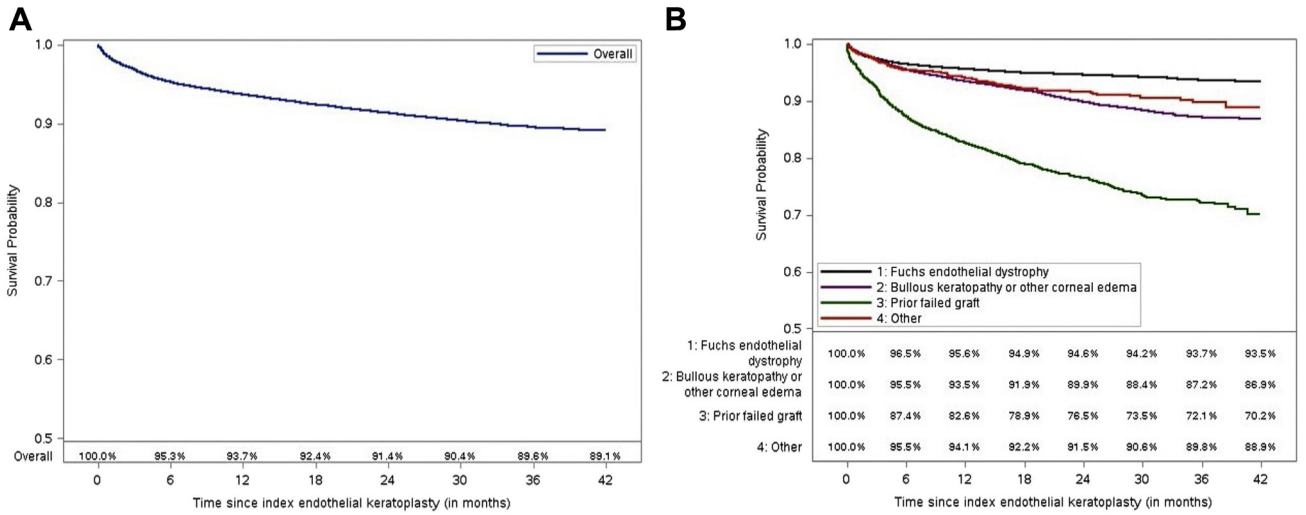

FIGURE 4. (A) Kaplan-Meier curve for developing graft failure in the overall study population. (B) Kaplan-Meier curve for developing graft failure stratified by indication.

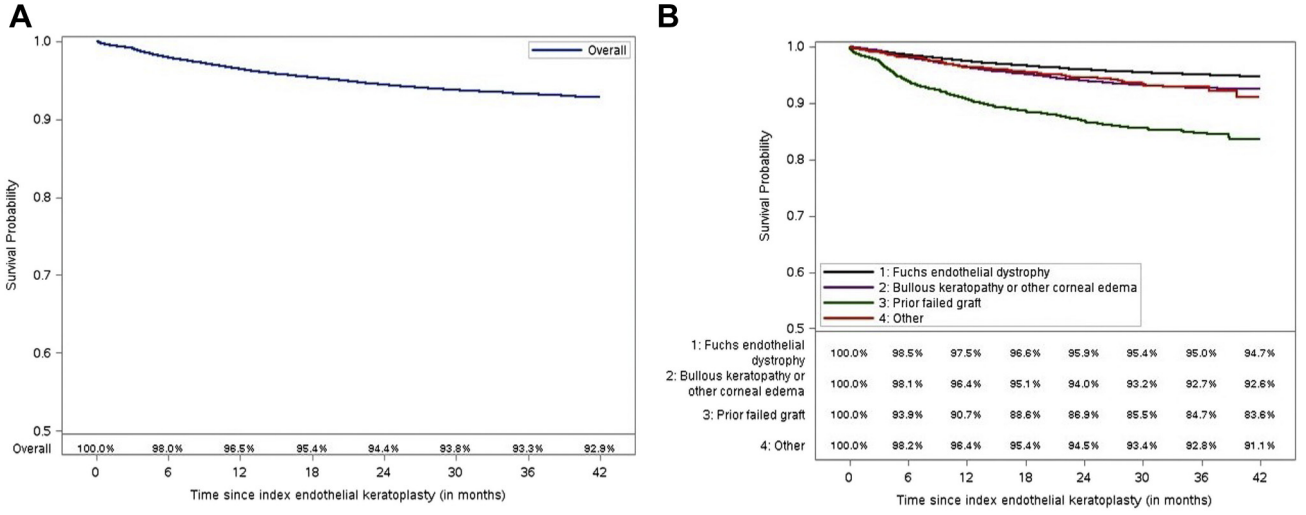

FIGURE 5. (A) Kaplan-Meier curve for developing graft rejection for overall study population. (B) Kaplan-Meier curve for developing graft rejection stratified by indication.

(Figure 5, A). At 3-years, graft rejection was most likely for patients undergoing EK for a prior failed graft (14.5%) followed by bullous keratopathy (6.8%) and Fuchs' endothelial dystrophy (4.6%) (Figure 5, B). The probability of developing graft rejection was highest during the 6-month postoperative period: Fuchs' (1.5%), bullous keratopathy (1.9%), and prior failed graft (6.1%), and the risk of rejection persisted throughout the study period.

DISCUSSION

IN THIS STUDY OF 71,040 MEDICARE BENEFICIARIES WHO UNderwent 94,829 EK procedures between 2011 and 2019, the overall incidence of major postoperative complications was found to be low. Endophthalmitis and choroidal hemorrhage developed in 0.03% and 0.05% of patients undergoing surgery, respectively. CME (4.1%) was more common, followed by RD (1.0%), and infectious keratitis (0.8%) within 1 year. The probability of needing glaucoma surgery was high, increasing from 7.6% at 1 year of follow-up to 13.8% at 8 years of follow-up. Graft complications were seen in 27.1% of patients at the end of the 8-year follow-up period. When patients were stratified by indication, patients who underwent EK for a prior failed graft generally had the highest risk of developing postoperative complications, whereas patients undergoing EK for Fuchs' had the best outcomes in terms of postoperative complications.

Most published studies of postoperative outcomes after EK have been limited to either single-center studies or studies with small sample sizes, which may limit generalizability.[4–10] There is often a tendency for outcomes derived from such series to be viewed as representing EK outcomes more generally.[14] Additionally, although eye banks are required to track and report adverse events following corneal transplants to the Eye Bank Association of America, adverse event reporting is voluntary and self-reported by surgeons and the Eye Bank Association of America only track the adverse reactions that were deemed to be tissue-related.[15] In contrast, the present study includes data for a large and diverse sample mixture of patients and surgeons and captures EK procedures performed across a range of facilities between 2011 and 2019. The authors believe that the findings reported in this study are therefore more representative of real-world outcomes. Moreover, this study design excluded patients who had concurrent procedures and assessed postoperative complications (except for glaucoma surgery) at short-term follow-ups. Therefore, the adverse events reported in this study are most likely attributable to EK procedures.

The incidence of postoperative CME observed in this study population is comparable to that in existing medical literature. Previous studies have reported that CME rates vary between 2% and 4.2% for DSEK[5,6] and between 0.7% and 15.6% for DMEK.[7–11,16] Although the present study did not evaluate risk factors associated with the development of CME post-EK, recent studies by Satoru and associates[17] and Kacobo and associates[10] suggest DMEK itself is a risk factor for postoperative CME. Although the exact reason for this increased risk remains unclear, iris damage during the procedure and air in the anterior chamber have been hypothesized as potential aggravating factors.[17] However, it is also noteworthy that DMEK is associated with significantly lower rates of rejection than DSEK.[18] Consequently, differences among postoperative steroid regimens, with ophthalmologists potentially prescribing weaker steroids for DMEK, may also contribute to differences in CME rates between the 2 procedures. The present study could not differentiate between results or DMEK or DSEK procedures because the procedural codes are the same.

To date, the largest study evaluating endophthalmitis rates after EK was carried out by Borkar and associates.[12] In their study, which included 2,292 EK procedures, the postoperative endophthalmitis rate was 0.2%. Endophthalmitis rates reported by various eye bank adverse reaction registries vary between 0.04% and 1%.[19,20] However, as previously mentioned, these data contain self-reported adverse events potentially attributable to the donor tissue and are not inclusive of all cases.[15] Furthermore, although a few groups have evaluated the incidence of endophthalmitis by using health care claims data, those studies did not distinguish between PK and EK: rates ranged from 0.11% to 1.18% in those studies.[21,22] The remaining studies reporting endophthalmitis rates after EK have either been smaller case series[4] or case reports.

Long-term data for rare complications of EK including RD and suprachoroidal hemorrhage (SCH) are lacking. Suh and associates[5] reported 1 case of SCH (1 of 118, 0.8%), and no SCH cases were observed after 1,007 DSEK cases in the CPTS (Cornea Preservation Time Study). Data for RD outcomes similarly are available from only 3 studies.[4,5,23] The reported incidence of RD in those studies was 0.5% (2 of 424 patients),[4] 0.6% (1 of 173),[23] and 4.2% (5 of 118 eyes).[5] Shtein and associates[22] evaluated SCH (0.71%) and RD (2.08%) rates using health care claims in 2,187 keratoplasties for eyes with corneal endothelial disease performed between 2001 and 2009. However, their study did not stratify outcomes by the type of keratoplasty (PK or EK) performed and limited the diagnostic indications for the keratoplasty to just corneal endothelial disease. Thus, by assessing SCH (0.05%) and RD (0.6%) rates for over 90,000 EK procedures performed between 2010 and 2019 over a wide range of indications, the present authors believe this study greatly adds to the existing medical literature data for EK outcomes. In addition, this study demonstrated, not surprisingly, that the rates of these complications were higher in eyes with prior failed grafts and bullous keratopathy, which is likely related to their more complex ocular anatomy and ocular history.

Iatrogenic glaucoma is a well-described complication of EK surgery. It has been reported to occur in 0%-24% of patients after DMEK surgery[2] and between 0% and 15% of patients after DSEK surgery.[3] Topical corticosteroid use or pupillary block induced from the air bubble are commonly implicated mechanisms for causing intraocular pressure elevation after EK surgery.[2,3] The present study found that the probability patients will need glaucoma surgery within 1, 5, and 8 years after their EK surgery was 7.6%, 12.2%, and 13.8%, respectively. Glaucoma surgery rates were highest for EK performed for bullous keratopathy or prior failed graft and lowest for Fuchs' endothelial dystrophy. This difference is likely attributable to differences in complexity of the eyes and possible angle damage from the prior intraocular surgery in eyes with bullous keratopathy and prior failed grafts. In addition, eyes with bullous keratopathy or prior failed grafts might have been receiving treatment either with stronger doses of steroid or for extended durations. Increased exposure to corticosteroids might have subsequently increased the risk of developing steroid-induced glaucoma among these eyes as well. Nearly one-third of the eyes in the present cohort had pre-existing glaucoma, and 6.2% had glaucoma surgery previously. Rates of subsequent glaucoma surgery were significantly higher for patients with pre-existing glaucoma than for those without, a finding consistent with existing studies of EK as a risk factor for glaucoma exacerbation.[2,3]

The probability of experiencing a graft rejection episode following EK in the present study population ranged from

3.5% at 1 year of follow-up to 7.1% at 3.5 years. In published studies, the mean rejection rate reported for DMEK is 1.9% (range: 0%-5.9%) for follow-up periods ranging from 6 months to 8 years.[2] Rejection episodes after DSEK, in comparison, are relatively higher, with an average reported rate of 10% (range: 0%-45.5%) between 3 months and 5 years of follow-up.[3] The present study only assessed the time to first episode of rejection and could not accurately assess recurring episodes of rejection; this might also account for differences between this study and others. The 3-year cumulative probability of rejection in the CPTS study was 3.6%.[24] Finally, it was found that EK procedures with failed grafts had the highest rejection probability: 14.5% at 3 years. Indeed, prior rejection has been shown to be a risk factor for additional rejection episodes.[25] Similar rates were also reported by Pederson and associates,[26] who found 13% of DSEKs performed for prior failed grafts experienced rejection at 4 years.[26] In comparison, the incidence of rejection for Fuchs' or bullous keratopathy were similar, with only 5%-8% of transplants in the present study population experiencing rejection.

Data for graft failure rates after EK are highly variable. Failure rates reported for DMEK have varied between 0% and 7% at 6 months to 8 years of follow-up.[2] For DSEK, failure rates of 0%-45% have been reported for up to 5 years of follow-up,[3,27–29] an average failure rate of 7% at 1 year.[3] Furthermore, rates vary by indication for surgery, and the present finding of eyes with Fuchs' endothelial dystrophy having lower failure rates is consistent with existing medical literature.[30] Repeat grafts, in comparison, often have the worst outcomes. The graft failure probability for repeat grafts was 26.5% at the end of the 3-year follow-up period in the present study. This is comparable to studies by Pasari and associates[31] and Anshu and associates[32] which reported 4-year failure rates of 24% (DMEK) and 26% (DSEK) for eyes with prior failed PKs. The Australian Corneal Registry Study, however, found worse graft survival for PK or EK than with PK and PK.[33] Data for outcomes of repeat EK after initially failed EK surgery is more limited. Baydoun and associates[34] found 12.5% of repeat DMEKs (for initial DMEK) failed at 1 year in their study, whereas Kim and associates[35] noted no graft failures for repeat DSEK (for initial DSEK) after an average follow-up of 27 months. Sorkin and associates[36] reported a graft failure rate of 19.2% between 2 and 20 months for DMEK in eyes with previous DSEK. The present study could not differentiate if the original graft was a failed PK or EK for the prior failed graft group due to limitation of the billing records.

There are several important limitations to our study that derive from the characteristics and limits of the data set used. First, the present study population was limited to Medicare beneficiaries ≥65 years of age, and caution must be used when generalizing findings to other patient populations, including those with private insurance or patients younger than 65 years of age. Second, because EK procedures were identified using CPT codes, this study was unable to differentiate between DSEK and DMEK. However, it is noteworthy that, based on data provided by the Eye Bank Association of America, DSEK accounted for 81.6% of all EK procedures performed in the United States between 2012 and 2018. Thus, while DMEK rates in the United State have increased, we believe that the postoperative complication rates provided in the present study are still most likely reflective of DSEK. Furthermore, data for clinical indications for surgery as well as postoperative complications were extracted from billing records, and it is possible that some patients might have been misclassified because of misdiagnosis or miscoding. Finally, because of insufficient detail as to eye laterality in the database, barring glaucoma surgery, per-person estimates might have been performed for postoperative complications instead of per-eye estimates. Thus, it is possible that the results reported in the study might have been an overestimation of the true incidence of complications. However, it is reassuring that the rates of graft complications including rejection and failure in this analysis are in line with existing studies as discussed above. Moreover, to increase the sensitivity of detecting potential complications following EK procedures, a longer duration of follow-up was used. Longer windows for detection of complications have also been used by previous claims-based studies.[21,22,37] However, it is important to note that, despite the longer follow-up window, the overall incidence of complications in the present population was low, which is reassuring. Additionally, the authors attempted to eliminate the concern of misattribution by excluding scenarios where patients' eye conditions might have been caused by factors other than the EK procedure, such as patients with subsequent surgical procedures in the same or the contralateral eye. Moreover, to better address the lack of information on laterality and increase the robustness of this study, 2 sets of estimates are provided (conservative and sensitive). It is reassuring to see that both the conservative and the sensitivity estimates were similar and, the authors believe, the true incidence of complications is likely within this relatively narrow range for this large nationally based sample.

Strengths of this study include a large national sample size of persons that underwent EK and a mean follow-up duration of 3 years. In addition, the Medicare database contains a diverse mixture of different patients and surgeons and a broad range of indications for the EK, making the present findings potentially more generalizable than data from high-volume single-center studies or studies with small sample sizes. Previous studies have shown center and surgeon effects on EK survival.[14] Thus, the results this analysis can be very helpful perioperative patient counselling and informed consent as surgeons can report personal rates and national rates of complications over a wide range of indications.

In conclusion, we found that over an 8-year follow-up period, major postoperative complications following EK

surgery were low overall. Graft failure and glaucoma escalation were the most common postoperative complications. The 8-year cumulative probability of glaucoma surgery after EK was high (13.8%), and the 3-year cumulative probabilities of graft rejection and graft failure were 6.2% and 9.6%, respectively. EK procedures performed for prior failed grafts had the worst postoperative outcomes, whereas procedures performed for Fuchs' had the best outcomes.

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