Graft Failure After Pediatric Penetrating Keratoplasty in the United States

Isdin Oke, MD, MPH,† Lyvia J. Zhang, DO,* Tobias Elze, PhD,* Alice C. Lorch, MD,* Joan W. Miller, MD,* Reza Dana, MD, MPH,* and Thomas H. Dohlman, MD,*† on behalf of the IRIS Registry Analytic Center Consortium*

Purpose: In contrast to adult patients, corneal transplants performed in pediatric patients tend to fare poorly, with relatively higher graft failure rates. The purpose of this study was to analyze the indications and outcomes of pediatric patients undergoing penetrating keratoplasty (PK).

Methods: This retrospective cohort study included children ≤18 years in the IRIS Registry (Intelligent Research in Sight) who underwent PK (January 1, 2013–December 31, 2020). Corneal graft failure was identified using International Classification of Diseases codes. The Kaplan–Meier estimated 5-year cumulative incidence of graft failure after PK. Hazard ratios (HR) derived from multivariable Cox regression models were used to evaluate the association of graft failure with sociodemographic and clinical factors.

Results: Five hundred forty-four children underwent PK (median age 15 years; 43% [234] female). Indications for surgery included nontraumatic acquired (58%, N = 318), congenital (18%, N = 100), other (9.6%, N = 52), and traumatic acquired (8.6%, N = 47). The cumulative incidence of graft failure within 5 years of PK was 50% (95% confidence intervals [CI], 45%—56%). The incidences did not differ between patients in various etiology groups. Graft failure was associated with glaucoma (HR, 1.46; 95% CI, 1.05–2.01; $P = 0.023$), dry eye disease (HR, 1.86; 95% CI, 1.18–2.92; $P = 0.007$), and corneal neovascularization (HR, 1.76; 95% CI, 1.00–3.08; $P = 0.050$).

Conclusions: Approximately half of children undergoing PK in the IRIS Registry experienced graft failure within 5 years of transplantation. The association of graft failure with ocular conditions such as glaucoma and dry eye disease suggests potential avenues to decrease the high incidence of graft failure in this population.

Key Words: cornea, penetrating keratoplasty, graft failure, pediatric ophthalmology

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Corneal opacity is a leading cause of blindness among children and adults, accounting for 5.1% of blindness worldwide.[1] Corneal opacification in childhood may interfere with visual development leading to deprivation amblyopia, a permanent cause of vision loss if left untreated. Early detection and appropriate management of corneal opacities is critical to optimizing the visual and global developmental outcomes of children.

Corneal transplantation, or penetrating keratoplasty (PK), is a mainstay in the surgical management of corneal opacities and one of the most commonly performed forms of solid-organ transplantation.[2] PK performed in adults is generally successful, with a 19.7% probability of graft failure at 5 years in the avascular and uninflamed corneas.[3] In contrast, PK in pediatric patients has a lower likelihood of success with the 2-year probability of graft failure reported to

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From the *Massachusetts Eye and Ear, Harvard Medical School, Boston, MA; and †Boston Children's Hospital, Harvard Medical School, Boston, MA.

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See Appendix 1 for members of the IRIS Registry Analytic Center Consortium.

I. Oke and L. J. Zhang contributed equally to this work.

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Correspondence: Isdin Oke, MD, MPH, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115 (e-mail: Isdin.Oke@childrens.harvard.edu).

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be as high as 67.4%.[4] Multiple factors may contribute to suboptimal outcomes in pediatric versus adult PK, including differences in the underlying etiologies and ocular comorbidities, postoperative complications, and compliance with treatments. Compared to corneal transplantation in adults,[5] pediatric corneal transplantation has been relatively understudied. A greater understanding of the factors associated with graft failure in children undergoing PK may lead to new opportunities to improve surgical outcomes for these patients.[5]

The IRIS Registry (Intelligent Research in Sight) is a nationwide electronic health record (EHR) database established by the American Academy of Ophthalmology that contains the clinical encounters of over 72 million patients from over 15,000 eye care providers.[6] This large, centralized data repository enables investigations into the outcomes of infrequently performed procedures such as corneal transplantation in children. This study leverages the IRIS Registry to describe the primary indications for pediatric PK, the incidence of graft failure after pediatric PK, and the factors associated with graft failure in children.

MATERIALS AND METHODS

This retrospective cohort study was performed using EHR data of patients followed at practices participating in the IRIS Registry. The database version used in this study was frozen on December 24, 2021 and accessed on November 26, 2022. The data collection methodology of the IRIS Registry has been described previously.[7] The investigation was approved by the Massachusetts General Brigham Institutional Review Board with the exemption of informed consent. The research adhered to the Declaration of Helsinki and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Participants

We identified pediatric patients who underwent PK at age ≤18 years and between January 01, 2013 and December 31, 2020 using Current Procedure Terminology codes (see Table 1, Supplemental Digital Content 1, http://links.lww.com/ICO/B819). Patients undergoing endothelial keratoplasty or deep anterior lamellar keratoplasty were excluded because of insufficient data. Patients without a record of the laterality of corneal transplantation were excluded. All individuals undergoing bilateral PK had a single eye selected at random for inclusion.

Methods

Data collected included patient demographics, indications for corneal transplantation, ocular comorbidities, and incidence of graft failure (see Table 1, Supplemental Digital Content 1, http://links.lww.com/ICO/B819). The demographic variables included age, sex, race and ethnicity, geographic location, and type of insurance. Patients were stratified by age group: ≤1, 2 to ≤6, 7 to ≤10, 11 to ≤14, and 15 to ≤18 years. Race and ethnicity were categorized into non-Hispanic White, Black or African American, Hispanic, and other races based on EHR. The other category included Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and all other races. Geographic location was categorized based on the US Census region of residence into the South, Midwest, West, and Northeast regions. Insurance type was categorized into private and nonprivate insurance. The etiology for corneal opacity necessitating PK was identified based on International Classification of Diseases Revision 9 and 10 codes (see Table 2, Supplemental Digital Content 1, http://links.lww.com/ICO/B819) in those identified patients who underwent PK. The indications for corneal transplantation surgery were grouped into traumatic acquired, nontraumatic acquired, congenital, and other etiologies based on current literature and AAO guidelines[8–10] (see Table 2, Supplemental Digital Content 1, http://links.lww.com/ICO/B819). We also determined the incidence of graft failure for specific diagnoses of interest that patients carried (at any point before surgery), including corneal scarring, keratoconus, and congenital hereditary endothelial dystrophy, Peters anomaly, aniridia, corneal stromal dystrophy, sclerocornea, and metabolic disorders (see Tables 3 and 4, Supplemental Digital Content 1, http://links.lww.com/ICO/B819). Finally, we evaluated risk factors for graft failure by determining hazard ratios (HR) for specific ocular comorbidities that were present before corneal transplantation, including secondary glaucoma, dry eye disease, and corneal neovascularization. Graft failure was identified using ICD-9 and 10 codes (see Table 1, Supplemental Digital Content 1, http://links.lww.com/ICO/B819).

The primary outcome of the study was the time between PK and diagnosis of graft failure. The Kaplan–Meier estimator was used to determine the 5-year cumulative incidence of graft failure. Log-rank tests were used to compare the Kaplan–Meier estimated incidence of graft failure across each clinical factor. Multivariable Cox Proportional Hazards regression was used to assess the association of graft failure with each demographic and clinical factor. HR with 95% confidence intervals (CI) are reported from the regression models. We report medians and interquartile ranges (IQR) for continuous variables and frequencies and percentages for categorical variables. All statistical tests were two-sided, and significance was defined as $P < 0.05$. All analyses were performed using R version 4.2.0 (R Core Team, 2023; R Foundation for Statistical Computing).

RESULTS

Cohort Demographics

A total of 544 children who underwent PK at ≤ 18 years of age were included in the study (Table 1). Just over half (56.3%, N = 306) of patients were between the ages of 15 and 18 years, with the remaining patients in the age groups of 11 to ≤14 (14.2%, N = 78), 7 to ≤10 (9.9%, N = 54), 2 to ≤6 (7.9%, N = 43), and ≤1 (11.6%, N = 63) years. Approximately 57% (N = 306) of patients were male and 43% (N = 234) were female. The underlying etiologies requiring PK were nontraumatic acquired in 318 (58%), congenital in

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TABLE 1. Demographics of Children Undergoing PK Stratified by Indication for Surgery

	Nontraumatic Acquired, N = 318	Traumatic Acquired, N = 47	Congenital, N = 100	Other, N = 52	Unknown, N = 27
Age at transplant (yr), median (IQR)	17.0 (15.0–18.0)	11.0 (7.0–15.0)	4.0 (0.0–14.0)	11.0 (3.0–15.0)	11.0 (7.0–17.0)
Age group (yr), n (%)					
15 to ≤18	241 (76)	15 (32)	21 (21)	18 (35)	11 (41)
11 to ≤14	41 (13)	11 (23)	13 (13)	10 (19)	3 (11)
7 to ≤10	22 (6.9)	11 (23)	9 (9.0)	7 (13)	5 (19)
2 to ≤6	8 (2.5)	9 (19)	17 (17)	8 (15)	1 (3.7)
≤1	6 (1.9)	1 (2.1)	40 (40)	9 (17)	7 (26)
Sex, n (%)					
Male	176 (56)	36 (77)	49 (49)	30 (58)	17 (63)
Female	140 (44)	11 (23)	51 (51)	22 (42)	10 (37)
Unknown	2	0	0	0	0
Race and ethnicity, n (%)					
Black or African American	73 (23)	7 (15)	14 (14)	6 (12)	6 (22)
Hispanic	91 (29)	12 (26)	25 (25)	13 (25)	4 (15)
Non-Hispanic white	96 (30)	22 (47)	42 (42)	21 (40)	8 (30)
Other	14 (4.4)	1 (2.1)	4 (4.0)	2 (3.8)	0 (0)
Unknown	44 (14)	5 (11)	15 (15)	10 (19)	9 (33)
US census region, n (%)					
South	166 (52)	24 (55)	50 (51)	37 (73)	15 (60)
Midwest	41 (13)	3 (6.8)	6 (6.1)	2 (3.9)	1 (4.0)
West	63 (20)	9 (20)	10 (10)	5 (9.8)	4 (16)
Northeast	47 (15)	8 (18)	33 (33)	7 (14)	5 (20)
Unknown	1	3	1	1	2
Type of insurance, n (%)					
Private	187 (59)	28 (60)	63 (63)	29 (56)	14 (52)
Nonprivate	95 (30)	10 (21)	26 (26)	12 (23)	7 (26)
Unknown	36 (11)	9 (19)	11 (11)	11 (21)	6 (22)
Laterality, n (%)					
Left	176 (55)	27 (57)	55 (55)	22 (42)	8 (30)
Right	142 (45)	20 (43)	45 (45)	30 (58)	19 (70)

18% (N = 100), traumatic acquired in 8.6% (N = 47), other in 9.6% (N = 52), and unknown in 5.0% (N = 27) (Table 1). Of note, 76% (N = 241) of patients with nontraumatic acquired etiologies were within the 15 to 18 years age range. Patients with a traumatic acquired etiology were primarily males (77%, N = 36), and the mean age at the time of transplant was 11 years. In the congenital etiology group, there was a nearly equal distribution of males and females, with 40% (N = 40) of these patients being under the age of 1 year.

The Incidence of Graft Failure

The 5-year cumulative incidence of graft failure for the entire cohort was 50% (95% CI, 45%–56%) (Fig. 1A). When stratified by age category, the 5-year incidence of graft failure was 53% (95% CI, 44%–60%) for 15 to ≤18 years, 57% (95% CI, 35%–71%) for ages 11 to ≤14 years, 48% (95% CI, 29%–61%) for ages 7 to ≤10 years, 52% (95% CI, 30%–66%) for ages 2 to ≤6 years, and 35% (95% CI, 20%–48%) for age ≤1 year (Fig. 1B). When stratified by etiology category, the 5-year incidence of graft failure was 53% (95% CI, 45%–60%) for nontraumatic acquired, 50% (95% CI, 30%–64%) for traumatic acquired, 49% (95% CI, 35%–60%) for congenital, and 41% (95% CI, 22%–55%) for other (Fig. 1C). There was no significant difference in graft failure rates based on sex, race and ethnicity, or insurance type. There was some evidence of geographic variation in the incidence of graft failure with a slightly lower incidence in the Northeast region (33%; 95% CI, 20%–43%) compared with the South, Midwest, and West regions (range, 49%–57%) (Table 2).

Indications for Corneal Transplantation

We further investigated the incidence of graft failure among specific disease conditions (Table 3). Approximately 45% (N = 247) of the cohort had a diagnosis of corneal scarring at some point before surgery, and the 5-year incidence of failure in these patients was 60% (95% CI, 50%–68%). Keratoconus, a common condition characterized by corneal thinning and steepening, was observed in 35% (N = 190) of patients in our study. The 5-year incidence of graft failure (53%, 95% CI, 43%–62%) for these patients did not differ significantly from the rest of the cohort. Congenital

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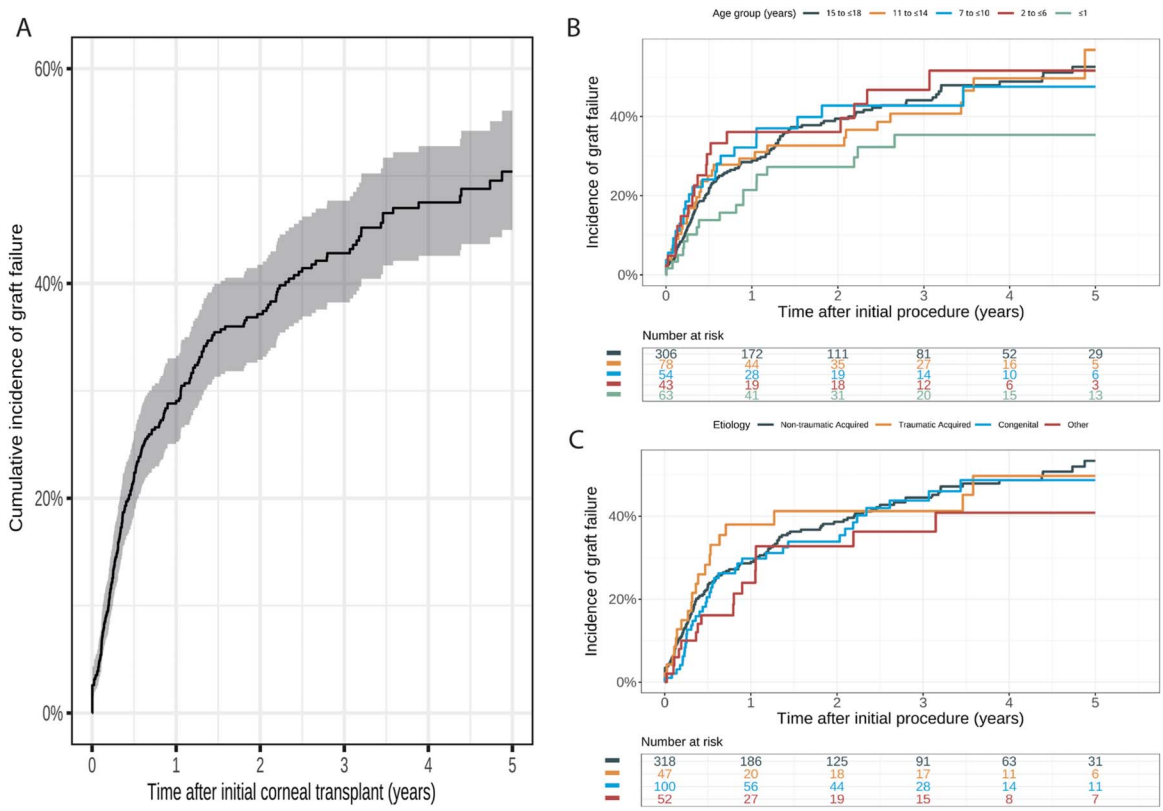

FIGURE 1. A, Cumulative incidence of graft failure within 5 years of pediatric PK. B, Graft failure by age. Cumulative incidence of graft failure stratified by age group (≤1, 2–≤6, 7–≤10, 11–≤14, and 15–≤18 years). C, Graft failure by etiology. Cumulative incidence of graft failure stratified by etiology (nontraumatic acquired, traumatic acquired, congenital, and other).

hereditary endothelial dystrophy had a relatively high incidence of graft failure (69%; 95% CI, 40%–84%); however, the sample size was relatively small (5.5%, N = 30). Similarly, the incidence of graft failure for patients with corneal stromal dystrophy was 56% (95% CI, 0%–83%) within the first year, but the sample size was too small to obtain 5-year estimates (1.1%, N = 6).

Ocular Comorbidities

We next analyzed whether the presence of preexisting ocular comorbidities, specifically conditions that commonly affect pediatric patients, such as allergic conjunctivitis, herpetic keratitis, and blepharoconjunctivitis, might increase the risk of PK graft failure. Among the conditions analyzed, a diagnosis of glaucoma was associated with a 1.46-fold increase in the risk of graft failure (95% CI, 1.05–2.01; P = 0.023). Interestingly, a diagnosis of dry eye disease (HR = 1.86, 95% CI 1.18–2.92, P = 0.007) was associated with an increased risk of graft failure, whereas preexisting giant papillary conjunctivitis, allergies, and/or atopic diseases were not associated with increased risk (HR 1.38, 95% CI 0.88—2.16, P = 0.16). Finally, corneal neovascularization, a strong predictor of graft failure in adults, was associated with an increased risk of graft failure in this cohort (HR 1.76; 95% CI of 1.00–3.08, P = 0.050) (Table 4).

DISCUSSION

The management of corneal opacity in pediatric patients is challenging for patients and physicians alike. In many cases, corneal transplantation must be performed to avoid development of amblyopia. Unfortunately, pediatric PK is often unsuccessful, with a high risk of graft failure because of multiple factors, including limited cooperation, compliance, and unique anatomical findings in children that may complicate the surgery.[11] In addition, the mechanisms underlying graft failure in children are not well understood.

In this study, we used a large nationwide EHR registry to describe the incidence and factors associated with graft failure in children. The most common indications for PK in this cohort were nontraumatic acquired conditions, accounting for approximately half of cases. Congenital corneal conditions requiring penetrating keratopathy accounted for approximately one in 5 cases in this study. Previous studies describing graft failure after PK in children have included a larger percentage of children with congenital corneal conditions (range, 66%–78%), but with smaller cohort sizes.[4,12,13]

We found that the overall cumulative incidence of graft failure was 50% within 5 years of PK. The 5-year incidence of graft failure was similar across the indications for corneal transplantation, including nontraumatic acquired (53%), traumatic acquired (50%), and congenital groups (49%). A

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TABLE 2. Cumulative Incidence of Graft Failure Within 5 years of PK and 5-Year Risk of Graft Failure From Multivariable Cox Regression

	Cohort	Graft Failure Within 5 yrs		Five-Year Risk of Graft Failure	
	N (%)	Cumulative Incidence (95% CI)	*P**	HR (95% CI)	*P*
Overall	544	50% (45% to 56%)			
Age at transplant (yr)			0.5		
15–≤18	306 (56)	53% (44%–60%)		—	
11–≤14	78 (14)	57% (35%–71%)		1.00 (0.68–1.48)	>0.99
7–≤10	54 (9.9)	48% (29%–61%)		1.04 (0.66–1.63)	0.88
2–≤6	43 (7.9)	52% (30%–66%)		1.15 (0.70–1.88)	0.59
≤1	63 (12)	35% (20%–48%)		0.66 (0.40–1.08)	0.10
Sex			0.2		
Male	308 (57)	49% (41%–56%)		—	
Female	234 (43)	51% (42%–59%)		1.21 (0.92–1.58)	0.17
Unknown	2				
Race and ethnicity			0.4		
Black or African American	106 (19)	55% (42%–65%)		1.41 (0.98–2.03)	0.068
Hispanic	145 (27)	56% (42%–66%)		1.03 (0.73–1.46)	0.86
Non-Hispanic white	189 (35)	44% (34%–52%)		—	
Other	21 (3.9)	49% (15%–69%)		0.97 (0.47–2.03)	0.94
Unknown	83 (15)	50% (33%–63%)		1.04 (0.67–1.61)	0.88
US census region			0.010		
South	292 (54)	55% (46%–62%)		—	
Midwest	53 (9.9)	49% (31%–63%)		0.86 (0.54–1.36)	0.52
West	91 (17)	57% (40%–69%)		0.83 (0.57–1.19)	0.31
Northeast	100 (19)	33% (20%–43%)		0.49 (0.32–0.75)	<0.001
Unknown	8				
Type of insurance			0.10		
Private	321 (59)	47% (40%–54%)		—	
Nonprivate	150 (28)	62% (49%–71%)		1.34 (0.99–1.81)	0.058
Unknown	73 (13)	41% (25%–54%)		0.90 (0.58–1.40)	0.65
Laterality			0.2		
Left	288 (53)	54% (46%–61%)		—	
Right	256 (47)	46% (37%–53%)		0.85 (0.64–1.11)	0.23
Diagnosis			0.7		
Nontraumatic acquired	318 (58)	53% (45%–60%)		—	
Traumatic acquired	47 (8.6)	50% (30%–64%)		1.06 (0.66–1.70)	0.80
Congenital	100 (18)	49% (35%–60%)		0.92 (0.64–1.32)	0.65
Other	52 (9.6)	41% (22%–55%)		0.75 (0.45–1.26)	0.28
Unknown	27 (5.0)	33% (8.0%–51%)		0.71 (0.33–1.52)	0.38

*Log-rank test.

TABLE 3. Cumulative Incidence of Graft Failure by Etiology

	n (%)	1 yr	3 yrs	5 yrs
Etiology				
Corneal scarring	247 (45)	35% (29%–41%)	50% (42%–57%)	60% (50%–68%)
Keratoconus	190 (35)	25% (18%–31%)	43% (34%–50%)	53% (43%–62%)
Congenital hereditary endothelial dystrophy	30 (5.5)	46% (24%–62%)	69% (40%–84%)	69% (40%–84%)
Peters anomaly	24 (4.4)	22% (2.9%–38%)	35% (8.7%–54%)	—*
Aniridia	10 (1.8)	22% (0%–45%)	33% (0%–58%)	60% (6.2%–83%)
Corneal stromal dystrophy	6 (1.1)	56% (0%–83%)	—*	—*
Sclerocornea	6 (1.1)	20% (0%–48%)	20% (0%–48%)	20% (0%–48%)
Metabolic disorders	3 (0.6)	0% (0%–0%)	0% (0%–0%)	—*

*Unable to estimate cumulative incidence given sample size.

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TABLE 4. Clinical Factors Associated With Risk of Graft Failure After PK in Children

	n (%)	HR (95% CI)	*P*
Preexisting ocular comorbidity			
Noncongenital glaucoma	94 (17.3)	1.46 (1.05–2.01)	**0.023**
Congenital glaucoma	54 (9.9)	1.03 (0.66–1.60)	0.90
Synechiae	44 (8.1)	1.18 (0.73–1.92)	0.49
Giant papillary conjunctivitis or atopic disease	41 (7.5)	1.38 (0.88–2.16)	0.16
Dry eye disease	36 (6.6)	1.86 (1.18–2.92)	**0.007**
Herpetic keratitis	36 (6.6)	1.23 (0.75–2.02)	0.41
Corneal neovascularization	26 (4.8)	1.76 (1.00–3.08)	**0.050**
Blepharoconjunctivitis	2 (0.4)	3.66 (0.51–26.2)	0.20
Prior procedure			
Previous glaucoma surgery	41 (7.5)	1.52 (0.97–2.38)	0.070

Bold entries are satistically significant $P < 0.05$.

previous report in the literature showed graft failure rates of 72% in nontraumatic acquired cases, 59% in traumatic acquired cases, and 67% in congenital cases.[13] Differences in the categorization of etiologies, criteria for graft failure, and length of follow-up may account for differences in the incidence of failure compared with previous studies.[4,12–15]

We conducted age-stratified analyses with our cohort using age categories similar to prior studies.[4,16] We did not find significant differences in the graft failure rates with overlapping CI across the different age groups. Younger age at the time of PK has been considered a risk factor for graft failure; however, this study was likely underpowered given the small sample size of children undergoing PK at age ≤1 year as evidenced by the wide CI. Typically, the robust immune response in a young transplant recipient increases the risk of graft rejection and failure. However, infants aged less than 6 months possess an immature immune system that is primarily composed of T suppressor cells and less efficient B cells.[17] The compromised ability to mount a robust response to a donor graft, coupled with the immune privileged status of the cornea, may be advantageous for infants undergoing PK. Hence, it may be advisable to opt for early surgical intervention to improve graft outcomes, and some studies have, in fact, shown a benefit of performing PK as early as children can tolerate general anesthesia.[18] It is also possible that given awareness of the overall poor PK outcomes in young children, these younger children may have benefited from closer follow-up and emphasis on compliance. The lack of consensus in the literature regarding how early to proceed with PK suggests a need for further investigation.

Atopic diseases are common in the pediatric population and are characterized by acute and chronic inflammation, which can predispose to corneal transplant rejection and/or failure. In our analysis of risk factors for graft failure, we hypothesized that patients with preexisting allergic and atopic disease would have a higher risk of graft failure. However, we found that giant papillary conjunctivitis, allergic conjunctivitis, and atopic diseases were not associated with an increased risk of graft failure. However, a diagnosis of dry eye disease, a condition characterized by ocular surface inflammation, was associated with an approximately twofold increased risk of graft failure. This is consistent with a multicenter retrospective study demonstrating that 17.8% of primary PK failures were attributable to ocular surface disease in patients at all ages.[19] These findings and the fact that dry eye disease is likely underappreciated in the pediatric population suggest a need for increased attention for this disease entity. We also evaluated corneal neovascularization as a risk factor for graft failure as corneal neovascularization is a poor prognostic factor in adult PK.[4,20] We found a similar trend in our study. Children with preexisting corneal neovascularization who underwent PK had a 1.76 times the risk of graft failure compared with children without corneal neovascularization.

This study has several limitations. First, it relies on diagnostic codes to identify the underlying indication for PK and surgical outcomes. These administrative billing codes were designed for clinical and reimbursement purposes rather than research, and variability in coding practices across providers and institutions may introduce misclassification errors. In addition, relying on a diagnosis codes for graft rejection may underestimate rejection rates, as some cases may have been considered graft failure or scheduled for repeat PKP without an explicit diagnosis. Second, although the IRIS Registry includes data from a broad range of practices across the United States, it does not include all institutions, particularly academic medical centers that specialize in complex pediatric corneal conditions. These centers are more likely to care for infants and young children with severe congenital anterior segment anomalies. This underrepresentation of high-risk cases may also have influenced the observed graft failure rates and limit the generalizability of our findings to all pediatric PK recipients. Finally, although the IRIS Registry is large and offers an opportunity to study rare conditions and uncommon procedures, the overall sample size for children undergoing PK is small and there may be factors associated with graft failure that were not identified given the limited power of the study.

In conclusion, this nationwide registry-based study found that approximately half of children undergoing PK experienced graft failure within 5 years of transplantation. The association of graft failure with ocular conditions such as glaucoma and dry eye disease suggests potential avenues to decrease the incidence of graft failure in children. Pediatric corneal transplantation is a high-risk grafting situation and an area of unmet need in understanding of the mechanisms underlying graft failure and identifying opportunities to improve clinical outcomes.

Appendix 1

Members of the IRIS Registry Analytic Center Consortium: Suzann Pershing, MD, Stanford University, Palo Alto, CA; Leslie Hyman, PhD, Wills Eye Hospital, Philadelphia, PA; Julia A. Haller, MD, Wills Eye Hospital, Philadelphia, PA; Aaron Y. Lee, MD, MSCI, Department of Ophthalmology and eScience Institute, University of Washington, Seattle, WA; Cecilia S. Lee, MD, MS; Department of Ophthalmology, University of Washington, Seattle, WA; Flora Lum, MD, American Academy of Ophthalmology, San Francisco, CA; Joan W. Miller, MD, Department of

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Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School, Boston, MA; and Alice C. Lorch, MD, MPH, Department of Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School, Boston, MA.

REFERENCES

1. Flaxman SR, Bourne RRA, Resnikoff S, et al. Global causes of blindness and distance vision impairment 1990–2020: a systematic review and meta-analysis. *Lancet Glob Health*. 2017;5:e1221–e1234.
2. Black CK, Termanini KM, Aguirre O, et al. Solid organ transplantation in the 21st century. *Ann Transl Med.* 2018;6:409.
3. Wagoner MD, Gonnah ES, Al-Towerki AE, et al. Outcome of primary adult optical penetrating keratoplasty with imported donor corneas. *Int Ophthalmol*. 2010;30:127–136. Accessed November 2023.
4. Dana MR, Moyes AL, Gomes JAP, et al. The indications for and outcome in pediatric keratoplasty. A multicenter study. *Ophthalmology*. 1995;102:1129–1138.
5. Akanda ZZ, Naeem A, Russell E, et al. Graft rejection rate and graft failure rate of penetrating keratoplasty (PKP) vs lamellar procedures: a systematic review. *PLoS One*. 2015;10:e0119934.
6. *IRIS Registry Data Analysis*. Available at: https://www.aao.org/iris-registry/data-analysis/requirements
7. Chiang MF, Sommer A, Rich WL, et al. The 2016 American Academy of Ophthalmology IRIS® registry (intelligent research in sight) database: characteristics and methods. *Ophthalmology*. 2018;125:1143–1148.
8. Katzman Lee RB. Pediatric Corneal Opacities. American Academy of Ophthalmology; Knight Templar Eye Foundation Pediatric Ophtahlmolog Education Center; www.aao.org/education/disease-review/pediatric-corneal-opacitiesAAO.
9. Wang E, Kong X, Wolle M, et al. Global trends in blindness and vision impairment resulting from corneal opacity 1984-2020: a meta-analysis. *Ophthalmology*. 2023;130:863–871.
10. Kim YJ, Jeoung JW, Kim MK, et al. Clinical features and outcome of corneal opacity associated with congenital glaucoma. *BMC Ophthalmol.* 2018;18:190.
11. Hwang DG, Hwang PH. Pediatric penetrating keratoplasty. *Semin Ophthalmol.* 1991;6:212–218.
12. Xavier dos Santos Araújo ME, Santos NC, Souza LBde, et al. Primary pediatric keratoplasty: etiology, graft survival, and visual outcome. *Am J Ophthalmol.* 2020;212:162–168.
13. Al-Ghamdi A, Al-Rajhi A, Wagoner MD. Primary pediatric keratoplasty: indications, graft survival, and visual outcome. *J AAPOS*. 2007;11:41–47.
14. Cowden JW. Penetrating keratoplasty in infants and children. *Ophthalmology*. 1990;97:324–329.
15. Limaiem R, Chebil A, Baba A, et al. Pediatric penetrating keratoplasty: indications and outcomes. *Transpl Proc*. 2011;43:649–651.
16. Trief D, Marquezan MC, Rapuano CJ, et al. Pediatric corneal transplants. *Curr Opin Ophthalmol.* 2017;28:477–484.
17. Di Zazzo A, Kheirkhah A, Abud TB, et al. Management of high-risk corneal transplantation. *Surv Ophthalmol.* 2017;62:816–827.
18. Sharma A, Sharma R. Pediatric corneal transplant surgery: challenges for successful outcome. *Nepal J Ophthalmol.* 2019;11:197–210.
19. Gómez-Benlloch A, Montesel A, Pareja-Aricò L, et al. Causes of corneal transplant failure: a multicentric study. *Acta Ophthalmol.* 2021;99:e922–e928.
20. Bachmann B, Taylor RS, Cursiefen C. Corneal neovascularization as a risk factor for graft failure and rejection after keratoplasty. *Ophthalmology*. 2010;117:1300–1305.e7.

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