Outcomes of Penetrating Keratoplasty Versus Lamellar Endothelial Keratoplasty in Iridocorneal Endothelial Syndrome: A Systematic Review and Meta-Analysis

GÁBOR TÓTH, SZILÁRD VÁNCSA, TAMÁS KÓI, KITTI KORMÁNYOS, PÉTER HEGYI, AND NÓRA SZENTMÁRY

• PURPOSE: To compare surgical outcomes following penetrating keratoplasty (PK), Descemet stripping endothelial keratoplasty (DSEK), and Descemet membrane endothelial keratoplasty (DMEK) in patients with iridocorneal endothelial (ICE) syndrome.

• DESIGN: Systematic review and meta-analysis on individual patient data (IPD).

• METHODS: Pre-registration was performed in the PROSPERO database (registration number: CRD42024539444). Eligible studies from Embase, MEDLINE (via PubMed), and the Cochrane Central Register of Controlled Trials (CENTRAL) were retrieved up to April 24, 2024. Studies were included those reporting clinical outcomes after PK, DSEK, or DMEK- graft survival, best spectacle-corrected visual acuity (BSCVA) and endothelial cell density (ECD) - in people with ICE syndrome. Cochrane Handbook was followed for data extraction/ synthesis, and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) and the Joanna Briggs Institute Critical Appraisal Checklists were used to assess risk of bias. Meta-analyses were conducted using a random-effects model. Heterogeneity between studies was assessed using Q-test and I^2 statistics.

• RESULTS: Nineteen of the 1963 screened studies were included in the meta-analysis. Multivariate pooled Kaplan-Meier curves with 95% confidence intervals, based on IPD from studies with at least 10 cases indicated that graft survival was better after PK compared to DSEK in patients with ICE syndrome. No significant difference ($P = .92$) was found in BSCVA improvement between PK [-0.77 (95% CI, -1.45 to -0.09)], DSEK [-0.87 (95% CI, -1.35 to -0.39)] and DMEK [-0.85 (95% CI, -1.07 to -0.62)]. No significant differences in ECD were observed between DSEK and DMEK 6 ($P = .88$) and 12 months ($P = .33$) postoperatively. IPD analysis revealed no significant difference in graft survival between patients with and without anytime glaucoma (-0.04 ± 0.50 SEM; $P = .940$) or cataract surgery (-0.45 ± 0.40 SEM; $P = .265$).

• CONCLUSIONS: PK demonstrated better graft survival compared to DSEK in patients with ICE, however, further research and additional evidence are needed to draw more definitive conclusions. Improvements in BSCVA were comparable across PK, DSEK and DMEK. Glaucoma surgery, whether performed before or after keratoplasty, appear to have no significant impact on graft survival. (Am J Ophthalmol 2025;276: 218–229. © 2025 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/))

INTRODUCTION

Iridocorneal endothelial (ICE) syndrome, first described by Yanoff in 1979, is a rare ocular disorder with 3 distinct clinical subtypes: progressive iris atrophy, Chandler syndrome, and Cogan-Reese syndrome.[1,2] Although its cause remains unknown, ICE syndrome is characterized by abnormal corneal endothelium, iris atrophy with nodules, and peripheral anterior synechiae. This unilateral, non-hereditary condition predominantly affects Caucasian women.[3]

In ICE syndrome, the endothelium exhibits a distinctive hammered-silver appearance, which can result in irreversible corneal oedema and decompensation. Pathologic endothelial-like cells, known as ICE cells, proliferate and migrate to the trabecular meshwork, potentially causing glaucoma and vision loss.[4] Corneal oedema in individuals with ICE syndrome is thought to arise from both the impaired pump function of the ICE cells and elevated intraocular pressure.[5] As a result, the management of corneal

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From the Dr. Rolf M. Schwiete Center for Limbal Stem Cell and Congenital Aniridia Research (G.T., N.S.), Saarland University, Homburg/Saar, Germany; Centre for Translational Medicine (S.V., T.K., P.H.), Semmelweis University, Budapest, Hungary; Institute of Pancreatic Diseases (S.V., P.H.), Semmelweis University, Budapest, Hungary; Department of Stochastics, Institute of Mathematics (T.K.), Budapest University of Technology and Economics, Budapest, Hungary; Department of Ophthalmology (K.K.), Semmelweis University, Budapest, Hungary

Inquiries to Gábor Tóth, Dr. Rolf M. Schwiete Center for Limbal Stem Cell and Congenital Aniridia Research, Saarland University, Homburg, Germany; e-mail: gabortothgabor@gmail.com

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decompensation in ICE syndrome presents a significant surgical challenge.

Management of ICE syndrome primarily involves addressing corneal oedema and glaucoma.[6] Traditionally, penetrating keratoplasty (PK) was the primary surgical approach for resolving corneal edema and restoring vision. However, PK has shown high rates of graft rejection and failure in ICE syndrome.[7] Endothelial keratoplasty techniques such as Descemet stripping endothelial keratoplasty (DSEK) and Descemet membrane endothelial keratoplasty (DMEK), selectively replace the posterior corneal layers, while preserving the stroma and the epithelium. These approaches offer significant advantages over PK for treating corneal endothelial failure. DSEK and DMEK are considered less invasive than PK, providing better and faster visual recovery.[8-10] DMEK allows for the selective replacement of the endothelium and Descemet membrane without involving additional corneal stroma, yielding even better surgical outcomes compared to DSEK.[11] However, the limited number of studies and small sample sizes make it challenging to determine the long-term outcomes and graft survival rates for these techniques in ICE syndrome.[7]

This study aims to perform a systematic review and meta-analysis to compare graft survival, visual acuity, and endothelial cell density following PK, DSEK, and DMEK in patients with ICE syndrome. The hypothesis is that significant differences in postoperative outcomes among the 3 keratoplasty techniques may exist, providing valuable insights to guide the optimal surgical approach for managing ICE syndrome.

METHODS

The systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement,[12] and was pre-registered in the PROSPERO database (registration number: CRD42024539444). The study methodology adhered to the recommendations outlined in the Cochrane Handbook.[13]

• **INFORMATION SOURCE AND SEARCH STRATEGY:** The electronic databases of Embase, MEDLINE (via PubMed), and the Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched for relevant studies up to April 24, 2024, without language restrictions. The search strategy included the following keywords: (irido-corneal endothelial syndrome) OR (iridocorneal-endothelial syndrome) OR (iridocorneal endothelial syndrome) OR (essential iris atroph*) OR (Chandler's syndrome) OR (Chandler syndrome) OR (iris nevus syndrome) OR (Cogan-Reese syndrome). No search filters were applied.

• **ELIGIBILITY CRITERIA:** The research question was developed using the Population-Intervention-Comparator-Outcomes (PICO) framework. Eligible studies included patients with ICE syndrome (P) who underwent PK, DSEK/DS(A)EK, or DMEK (I and C). These studies reported outcomes (O) such as graft survival, pre- and postoperative best-corrected visual acuity, endothelial cell density (ECD) and endothelial cell loss (ECL).

Studies were included if they provided data on at least 1 treatment modality for ICE syndrome and reported the specified outcomes. No distinction was made between DSEK and Descemet stripping automated endothelial keratoplasty (DSAEK) in the included studies. Both retrospective and prospective studies, as well as case series, were eligible for inclusion, while duplicates, case reports, and non-human studies were excluded.

• **SELECTION PROCESS:** The articles were managed using EndNote 20 reference manager (Clarivate Analytics, Philadelphia, PA, USA). After the automatic and manual removal of duplicates, the titles, abstracts, and full texts were independently screened by 2 authors working in pairs (GT and KK). Any disagreements were resolved by a third reviewer (NS). The full texts of potentially eligible publications were further evaluated for inclusion. In cases of overlapping study populations, the publication with the larger sample size was selected for inclusion.

• **DATA COLLECTION PROCESS AND ITEMS:** Data from articles meeting the inclusion criteria were extracted into an Excel spreadsheet (Office 2016, Microsoft, Redmond, WA, USA). The extracted data included general information such as author, year, study design, patient demographics (age, gender), number of subjects, and follow-up duration. For each study, baseline (preoperative) and postoperative values were recorded, and outcomes were collected at multiple time points when available.

Extracted data included graft survival, mean best spectacle-corrected visual acuity (BSCVA) converted into logMAR, ECD in cells/mm^2 and ECL in %. Data about simultaneous cataract surgery was also collected.

For outcomes such as graft survival presented in Kaplan-Meier (KM) curves as figures, quantitative data were extracted using the WebPlotDigitizer software (https://automeris.io/WebPlotDigitizer.html, accessed on 9 November 2024) to enable further analysis.

Where available, individual patient data (IPD) were collected as provided by study authors. Any disagreements in data extraction were discussed and resolved through team consensus.

• **QUALITY ASSESSMENT OF INCLUDED STUDIES:** The risk of bias was assessed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool,[14] for non-randomized interventional studies and the Joanna

Briggs Institute Critical Appraisal Checklists,[15] for observational studies, case series, and case reports. Disagreements among review authors regarding bias assessments were resolved through discussion. If consensus could not be achieved, a third reviewer was consulted to make the final decision.

• **STATISTICAL METHODS AND DATA SYNTHESIS:** Statistical analyses were carried out using packages "IPDfromKM," "meta," "metafor," "nlme" and "survival" of the R statistical software (version 4.1.2.). The statistical analyses follow the advice of Harrer et al.[16] For all statistical analyses, a p-value of less than 0.05 was considered significant. All the performed analyses included random effect terms.

We performed individual meta-analyses on IPD. We used linear mixed effect regression for this purpose except for the pooled hazard ratio, for which we used the mixed effects (frailty) Cox Proportional Hazards model. We analyzed the impact of the different covariates by including them in the regressions.

For each outcome, only 1 part of the studies reported IPD. Hence, we also performed study-level meta-analyses, including studies reporting IPD data and studies reporting only summary statistics. Classical inverse variance random-effect meta-analysis was applied using the REML tau estimator and Hartung-Knapp adjustment to pool mean and mean differences. We applied this approach to the log-transformed probabilities to pool the 36-month survival (no graft failure) probabilities within a slightly more complex framework. When a study provides graft survival results in 2 subgroups, even though the underlying patients are different, the random effects are correlated. For this reason, we used a 3-level meta-analysis model.[16]

We visualized the pooled outcomes and their 95% confidence and prediction intervals on forest plots. Besides the prediction interval, heterogeneity was assessed by calculating I^2 measure and its confidence interval and performing the Cochrane Q test. We also performed several study-level subgroup and meta-regression analyses. We visualized meta-regression results on bubble plots. When the meta-regression is based on aggregated variables, then the results must be interpreted with caution due to the possibility of aggregation bias, see section 7.6.2. of Schmid et al.[17] for the details.

We used the WebPlotDigitizer tool to read digitized KM curves. We estimated IPD data from the digitalized KM curves by direct calculation via inverting the construction of the KM curve similarly as described in Guyot et al.[18] We plotted the study-level KM curves on the sample plot. Moreover, we also created pooled survival curves with confidence intervals using the multivariate methodology of Combescure et al.[19]

In the majority of the meta-analyses, only studies with at least 3 observations were included. In case of the study-level meta-analysis of the 36-month survival probability, we only included studies having at least 10 patients. For the individual Cox regression we performed the analyses under both criteria.

A leave-one-out sensitivity analysis was conducted by systematically excluding 1 study at a time to evaluate the robustness of our findings. For the analysis of mean differences in BSCVA, the univariate nature of the data allowed for the generation of leave-one-out plots using the dmetar R package. For all other outcomes, leave-one-out results were presented in tabular format.

Publication bias analysis was not possible since, in each subgroup, the number of involved studies was less than 10.

• **ASSESSMENT OF THE GRADE OF EVIDENCE:** Given the limited number of comparative studies, it was not possible to determine the level of evidence for the analyzed outcomes.

• **PROTOCOL AMENDMENT:** As there were not enough articles and reported data on rates of rejection and rebubbling, we deviated from the original plan and did not analyse their incidences.

RESULTS

• **SEARCH AND SELECTION:** Our systematic search identified a total of 2813 articles. After removing duplicates, 1963 publications were screened. Ultimately, 19 studies were deemed eligible for inclusion in the qualitative and quantitative synthesis (Figure 1).

• **BASIC CHARACTERISTICS OF INCLUDED STUDIES:** Table 1 shows the baseline data of the included studies. We included 1 prospective and 2 retrospective cohort studies involving 311 patients with ICE, along with 16 case series comprising 208 patients. In total, 519 patients were included in the meta-analysis and systematic review. Additionally, we utilized IPD from 13 studies.

Keratoplasty was performed with concurrent phacoemulsification and intraocular lens implantation if a cataract was observed at the time of surgery. Goniosynechiolysis was performed if significant synechiae were present.

• **GRAFT SURVIVAL:** Although 3 studies reported no cases of primary graft failure among the analyzed subjects [7,28,33], the lack of information in other studies resulted in limited evidence regarding primary graft failure.

Original data on graft survival from all included studies on PK and DSEK in patients with ICE syndrome, derived from deconstructed KM curves and available IPD, are represented in Figure 2A. Multivariate pooled KM curves with 95% confidence intervals, based on IPD from studies with at least 10 cases, are shown in Figure 2B. These data indicate that graft survival was better after PK compared to DSEK in

TABLE 1. Basic characteristics of the included studies ($n = 19$).

First author (year)	Design	Country	Recruitment period	No. (woman %)	Age (years)	GR 1	GR 2	Mean follow up (months)	Outcome
Alvim et al. (2001) [20]	RCS	USA	1985-1999	14 (57.14)	53; NR	PK	-	58.21	GS, BSCVA
Ao et al. (2017) [21]	RCS	China	2008-2015	18 (72.2)	51.1 ± 13.0	DSEK	-	19.0	GS, BSCVA, EDC, ECL
Chang et al. (1993) [6]	RCS	USA	1980-1991	12 (66.7)	52.9 ± 12.9	PK	-	30.3	GS, BSCVA, ECL
Chaurasia et al. (2013) [22]	RCS	India	2009-2011	7 (42.9)	50.4 ± 7.5	DSEK	-	12.5	GS, BSCVA
Chaurasia et al. (2021) [23]	RCS	India	NR	3 (100)	35.3 ± 6.7	DSEK	-	53.3	GS, BSCVA, EDC
Crawford et al. (1989) [24]	RCS	USA	1975-1983	9 (88.9)	54.6; NR	PK	-	42	GS, BSCVA
DeBroff et al. (1994) [25]	RCS	USA	1971-1992	6 (50.0)	64.3 ± 10.7	PK	-	45.5	GS, BSCVA
Fajgenbaum et al. (2015) [7]	RCS	United Kingdom	2006-2014	4 (75.0)	56.8 ± 17.0	DSEK	-	55.3	GS
Joshi et al. (2022) [26]	RCS	India	NR	5 (40.0)	48.2 ± 10.8	DMEK	-	29.6	GS, BSCVA, EDC, ECL
Li et al. (2023) [27]	RCS	China	2018-2021	24 (54.2)	53.9; NR	DSEK	-	12.0	GS, BSCVA, EDC, ECL
Mohamed et al. (2022) [28]	RCS	India	2010-2019	52 (63.5)	48.8 ± 10.8	DSEK	-	28.8	GS, BSCVA, EDC, ECL
Price et al. (2007) [29]	RCS	USA	2005-2006	3 (0)	55.0 ± 10.6	DSEK	-	8.3	GS, BSCVA
Quek et al. (2015) [30]	Observational, retrospective cohort study	Singapore; USA	1991-2011	29 (58.6)	55.3 ± 10.2	PK	DSEK	5.2	GS
Roberts et al. (2023) [31]	Observational, prospective, multicenter, cohort study	Australia	1985-2020	196 (58.7)	56 ± 14	PK	DSEK, DMEK	NR	GS
Rotenberg et al. (2020) [32]	Observational retrospective, multicenter, cohort study	United Kingdom	2000-2017	86 (48.3)	56.2; NR	PK	DSEK	NR	GS
Siddharthan et al. (2020) [33]	RCS	India	NR	4 (75.0)	48.8 ± 7.5	DMEK	-	36.0	GS, BSCVA, EDC, ECL
Wu et al. (2021) [34]	RCS	China	2014-2018	24 (58.3)	48.5 ± 6.4	DMEK	-	24.9	GS, BSCVA, EDC, ECL
Ziaei et al. (2018) [35]	RCS	New Zealand	NR	3 (66.6)	45.7 ± 15.0	DMEK	.	12.0	GS, BSCVA
Zhang et al. (2023) [36]	RCS	China	2015-2022	20 (50.0)	52.5 ± 10.9	DSEK	-	18.8	GS, BSCVA, EDC, ECL

RCS = retrospective case series; GR = Group; PK = penetrating keratoplasty; DSEK = Descemet stripping endothelial keratoplasty; DMEK = Descemet membrane endothelial keratoplasty; NR = not reported; GS = graft survival; BSCVA = best spectacle-corrected visual acuity; ECD = endothelial cell density; ECL = endothelial cell loss.

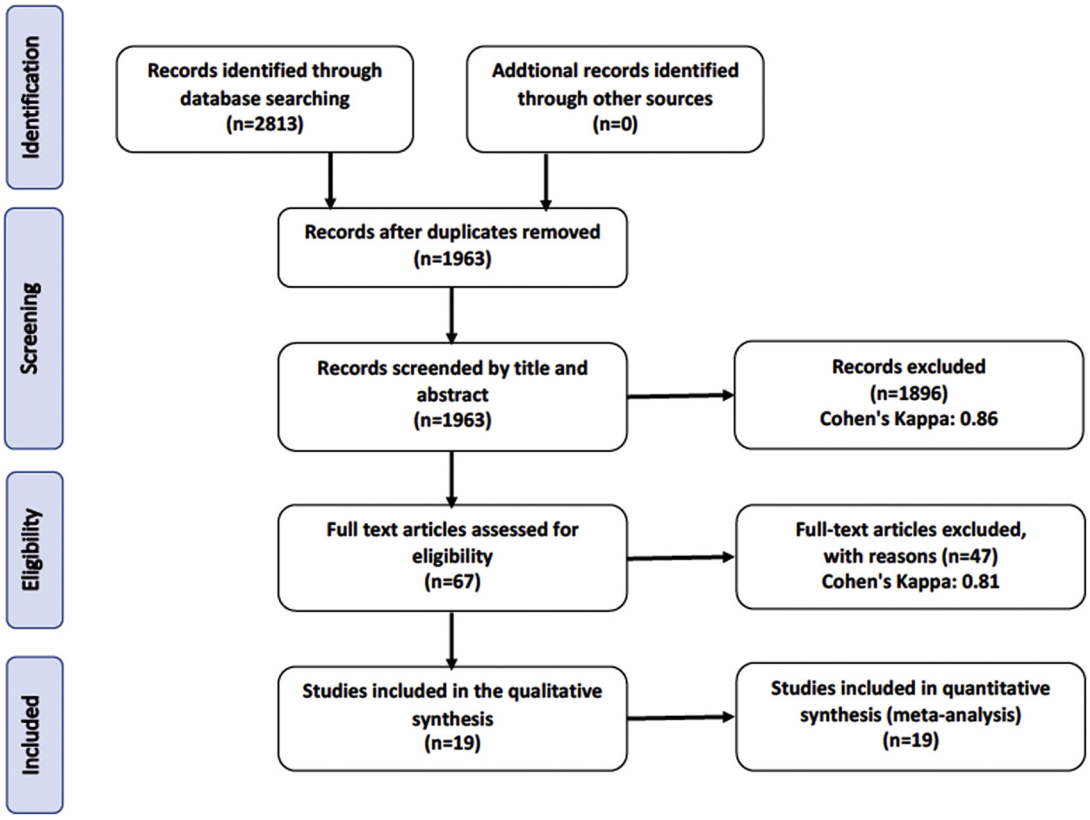

FIGURE 1. Flow chart of study identification.

patients with ICE syndrome. The multivariate pooled graft survival rates for PK were 0.92 (95% CI, 0.86 to 0.99) at 12 months, 0.84 (95% CI, 0.77 to 0.91) at 24 months, 0.73 (95% CI, 0.66 to 0.81) at 36 months, and 0.65 (95% CI, 0.57 to 0.74) at 48 months. For DSEK, the pooled survival rates were 0.85 (95% CI, 0.77 to 0.94) at 12 months, 0.70 (95% CI, 0.59 to 0.82) at 24 months, 0.62 (95% CI, 0.50 to 0.78) at 36 months, and 0.54 (95% CI, 0.42 to 0.70) at 48 months.

Univariate pooled graft survival rate at 36 months did not differ significantly ($P = .619$) between PK [0.73 (95% CI, 0.67 to 0.80)], DSEK [0.71 (95% CI, 0.63 to 0.79)] and DMEK [0.67 (95% CI, 0.44 to 1.00)] (Figure 3). In each leave-one-out sensitivity analysis run, the point estimates remained stable, and the difference between the PK and DSEK groups consistently remained nonsignificant (**Figure S1A**).

Individual COX regression analysis based on studies with at least 3 cases revealed a hazard ratio [0.61 (95% CI, 0.43 to 0.86)] significantly less ($P = .0048$) than 1 for graft survival of PK compared to DSEK, indicating longer survival in the PK group. Similarly, PK demonstrated better graft survival in terms of hazard ratio [0.55 (95% CI, 0.39 to 0.78)], with a statistically significant difference ($P < .001$) in the analysis limited to studies with at least ten cases. When either the PK or DSEK group from the relatively large study by Roberts et al. was omitted, the hazard ratio (HR) for PK vs. DSEK remained below 1, but the results lost statistical significance (HR: 0.76, 95% CI: 0.47-1.23, $P = .26$ and HR: 0.76, 95% CI: 0.48-1.21, $P = .25$, respectively). In all other sensitivity runs, the difference remained statistically significant (**Figure S1B**).

IPD analysis revealed no significant difference in graft survival between patients with and without anytime glaucoma (-0.04 ± 0.50 SEM; $P = .940$) or cataract surgery (-0.45 ± 0.40 SEM; $P = .265$).

Sample sizes for subgroup analysis of ICE syndrome were sufficient to examine graft survival in Chandler's syndrome ($n = 34$), Cogan-Reese syndrome ($n = 6$), and essential iris atrophy ($n = 45$) following PK, DSEK, and DMEK (**Table S1**).

Meta-regression of graft survival data showed no significant difference ($P = .17$) between patients with Chandler's syndrome and those with Cogan-Reese syndrome or essential iris atrophy (**Figure S2**).

Meta-regression of graft survival data at 36 months showed no significant difference between PK and DSEK ($P = .923$) in patients with and without anytime glaucoma surgery (**Figure S3A**). Similarly, meta-regression of the graft survival data at 36 months showed no significant difference between PK and DSEK ($P = .67$) in patients with and without simultaneous cataract surgery (**Figure S3B**).

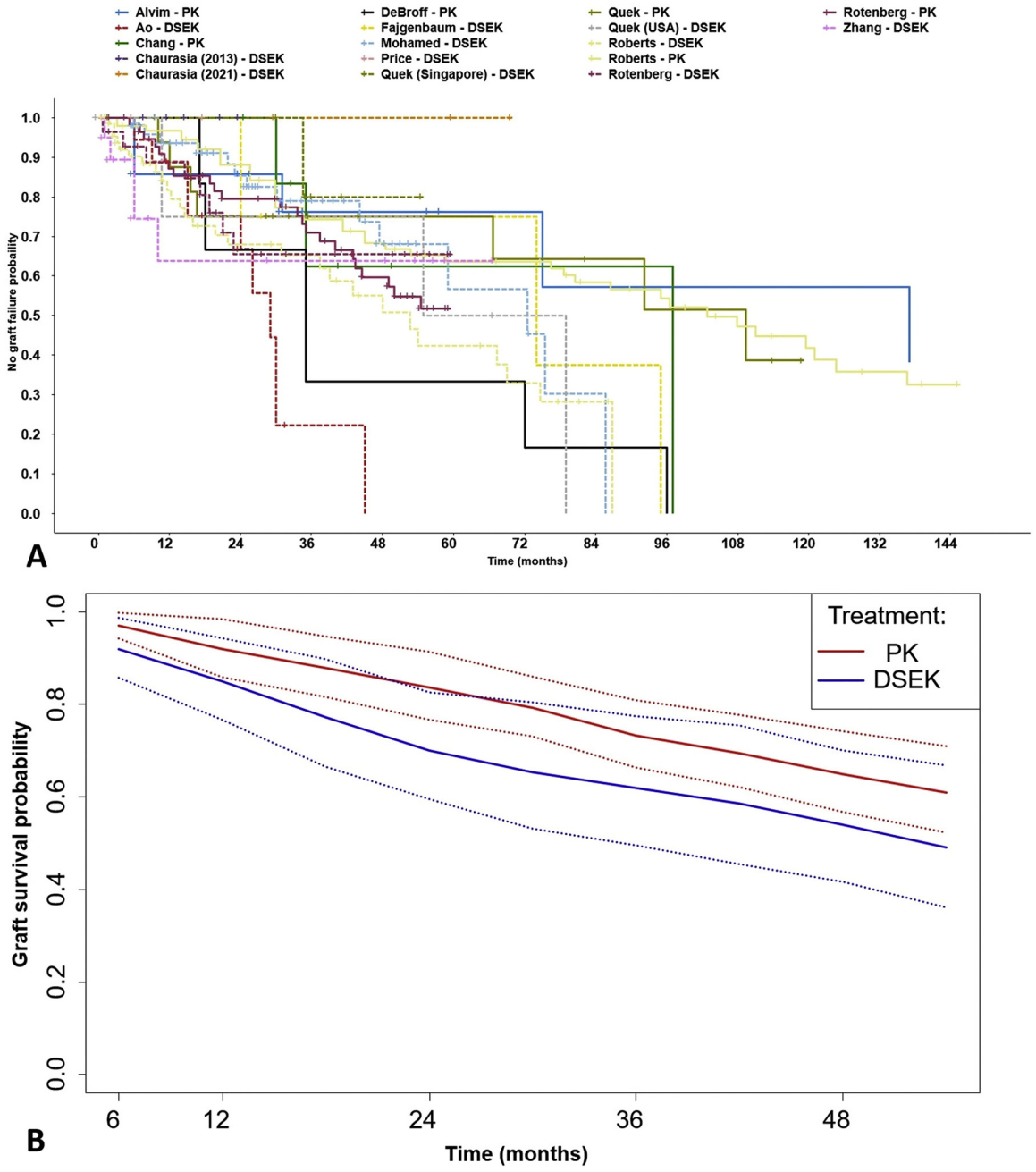

FIGURE 2. Original graft survival data for penetrating keratoplasty (PK) and Descemet stripping endothelial keratoplasty (DSEK) (Figure 2A). Multivariate pooled graft survival rates with 95% confidence intervals, based on individual patient data from studies with at least 10 cases (Figure 2B).

• BEST SPECTACLE-CORRECTED VISUAL ACUITY: Preoperative BSCVA was significantly better ($P = .02$) in DMEK [0.95 (95% CI, 0.47 to 1.43)] compared to PK [1.48 (95% CI, 0.99 to 1.97)] and DSEK [1.41 (95% CI, 0.96 to 1.84)], while no significant difference was observed between PK and DSEK ($P = .71$) (Figure 4A). Heterogeneity among the DSEK studies [91% (95% CI, 84% to 95%)] was higher than that of PK [21% (95% CI, 0% to 92%)] and DMEK [54% (95% CI, 0% to 85%)].

No significant difference ($P = .92$) was found regarding BSCVA improvement between PK [−0.77 (95% CI, −1.45 to −0.09)], DSEK [−0.87 (95% CI, −1.35 to −0.39)] and DMEK [−0.85 (95% CI, −1.07 to −0.62)] (Figure 4B).

Regarding PK, all studies demonstrated consistent and concordant findings. The leave-one-out sensitivity analysis showed that excluding any single study did not substantially alter the point estimates. However, the exclusion of the

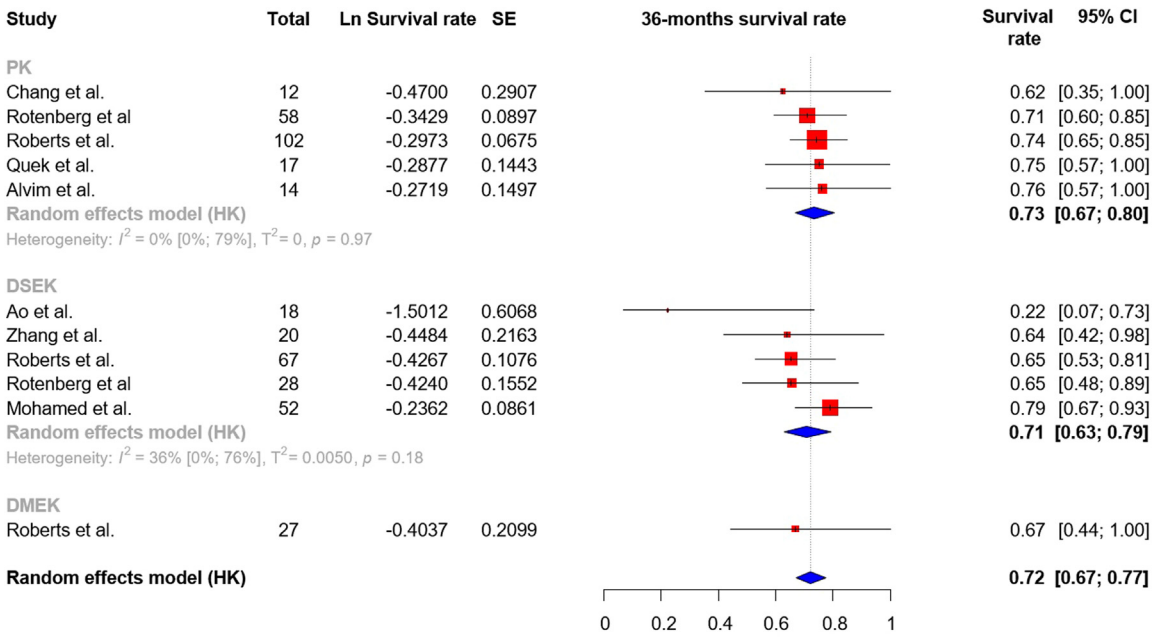

FIGURE 3. Univariate pooled graft survival rates at 36 months for penetrating keratoplasty (PK), Descemet stripping endothelial keratoplasty (DSEK) and Descemet membrane endothelial keratoplasty (DMEK).

Mohamed study from the DSEK group and the Siddharthan study from the DMEK group notably reduced heterogeneity and narrowed the confidence intervals within the respective groups (**Figure S4**).

Postoperative BSCVA was 0.74 (95% CI, 0.23 to 1.26) for PK, 0.44 (95% CI, 0.18 to 0.70) for DSEK and 0.39 (95% CI, 0.22 to 0.55) for DMEK (**Figure S5**). Subgroup analysis revealed a significant difference between the groups ($P < .01$).

IPD analysis revealed no significant difference ($P = .231$) in BSCVA improvement between patients with and without anytime glaucoma surgery (-0.19 ± 0.16 SEM). However, individuals who underwent combined keratoplasty and cataract surgery (-0.33 ± 0.16 SEM) demonstrated significantly better BSCVA improvement compared to those without cataract surgery ($P = .045$).

Meta-regression analysis of BSCVA improvement data comparing patients with and without anytime glaucoma surgery showed no significant difference ($P = .812$) between PK and DSEK (**Figure S6A**). Similarly, meta-regression analysis of BSCVA improvement data comparing patients with and without simultaneous cataract surgery also showed no significant difference ($P = .308$) between PK and DSEK (**Figure S6B**).

• **ENDOTHELIAL CELL DENSITY AND LOSS:** No significant differences in ECD were observed between DSEK and DMEK 6 and 12 months postoperatively (**Figure S7**). For DSEK, the mean ECD was 1593.42 cells/mm^2 (95% CI = 960.62 to 2226.21) at 6 months and 1618.95 cells/mm^2 (95% CI = 1356.03 to 1881.87) at 12 months. For DMEK, the mean ECD was 1632.59 cells/mm^2 (95% CI = 849.59-2415.60) at 6 months and 1364.33 cells/mm^2 (95% CI = 265.92-2462.75) at 12 months. The difference between DSEK and DMEK was not significant at 6 months ($P = .88$) or 12 months ($P = .33$). EDL was significantly higher at 1 month (42.24%) compared to 6 months (47.62%) and 12 months (47.76%) following DSEK ($P < .01$) (**Figure S8**).

• **RISK OF BIAS:** The risk of bias varied slightly among the studies, as assessed using the JBI Critical Appraisal Tool and ROBINS-I (**Tables S2 and S3**).

DISCUSSION

In this meta-analysis, we compared graft survival, visual acuity, ECD, ECL, and the effect of glaucoma surgery on graft survival after corneal transplantation among PK, DSEK, and DMEK.

PK has historically been the treatment of choice for patients with corneal decompensation. However, with the introduction of DSEK and later DMEK, these techniques have largely replaced PK and are now considered the gold standard for treating corneal endothelial diseases such as pseudophakic bullous keratopathy (PBK) and Fuchs' endothelial dystrophy (FED). [9]

Comparing clinical outcomes after corneal transplantation in ICE syndrome remains challenging due to the small sample sizes and the heterogeneous clinical presentation of ICE syndrome.

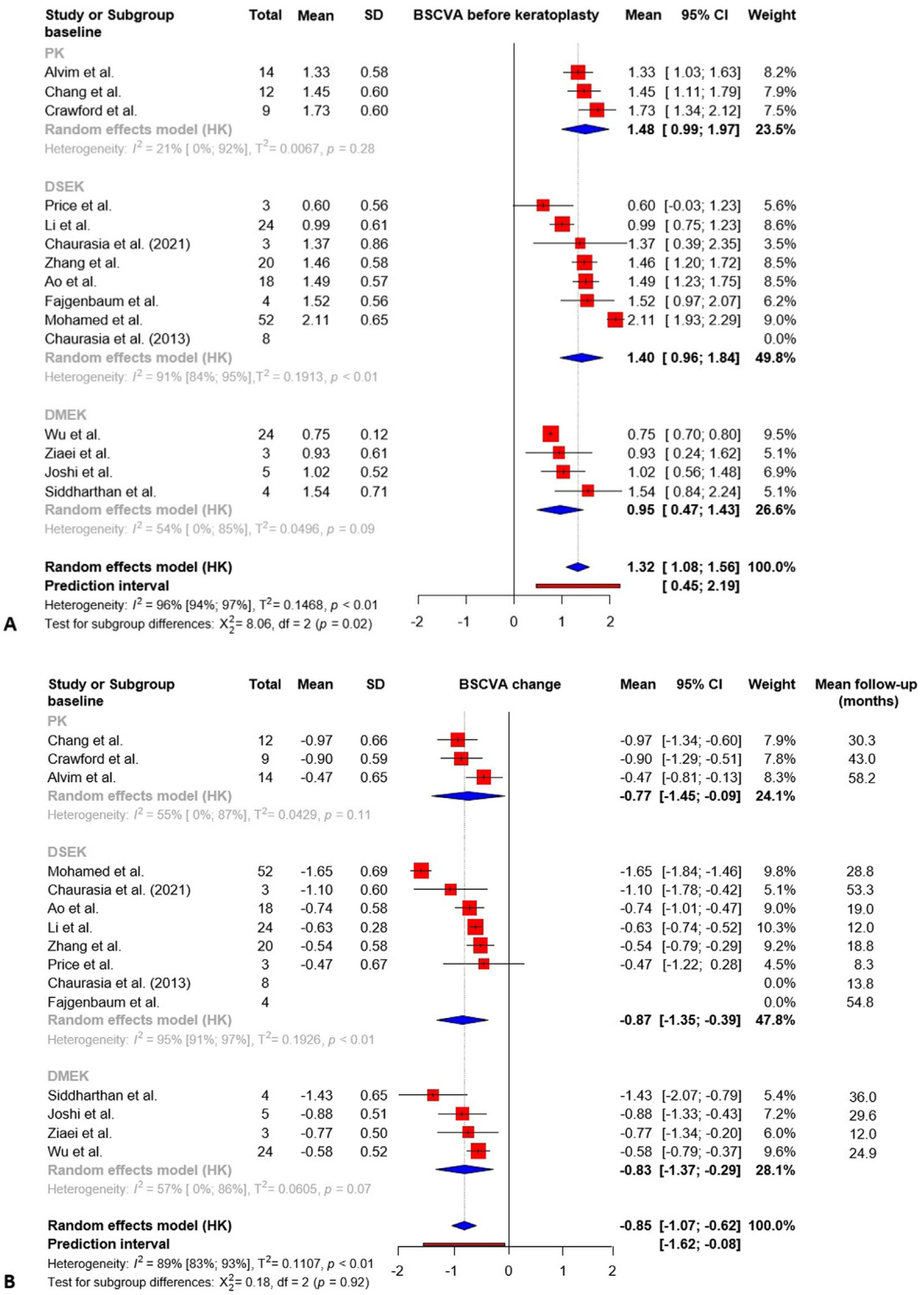

FIGURE 4. Preoperative best spectacle-corrected visual acuity (BSCVA) (Figure 4A) and BSCVA improvement (Figure 4B) following penetrating keratoplasty (PK), Descemet stripping endothelial keratoplasty (DSEK) and Descemet membrane endothelial keratoplasty (DMEK).

Regarding graft survival after DSEK and PK in meta-analyses with PBK and FED, Yang et al.[37] did not find a significant difference, while Akanda et al.[38] reported that PK is associated with a marginally higher risk of graft failure compared to posterior lamellar keratoplasties, primarily in patients with PBK and FED. In contrast to these findings, our results demonstrated that PK is associated with higher graft survival compared to DSEK in people with ICE syndrome, though this difference was not statistically significant. This discrepancy may be attributed to the unique challenges of performing DSEK and DMEK in ICE syndrome. Factors such as small corneal incisions, peripheral anterior synechiae (PAS) and shallow anterior chambers make the placement and positioning of donor tissue more difficult in ICE syndrome compared to the relatively normal anterior chambers in PBK and FED.[29] Managing PAS in ICE syndrome is crucial to prevent disease progression, including chronic angle-closure glaucoma and further synechial spread. Regular IOP monitoring, inflammation control, and early surgical intervention are essential. Avoiding miotics and opting for glaucoma drainage devices over trabeculectomy may improve outcomes.[39] Among the 3 available comparative studies on graft survival for PK and posterior lamellar keratoplasties, Quek et al.[30] and Rotenberg et al.[32] did not observe significant differences, whereas Robert et al.[31] reported higher graft survival rates with PK compared to DSEK and DMEK. However, these comparative studies and other case series must be interpreted with caution due to their small sample sizes.

In most cases, recalcitrant glaucoma either precedes or follows corneal decompensation in ICE syndrome.[40] PAS exposes the corneal endothelium to blood vessels, potentially increasing endothelial cell loss.[41] Glaucoma surgery, both prior to and following keratoplasty is considered a significant risk factor for graft failure.[21] This is attributed to mechanical damage and the disruption of the blood-aqueous barrier caused by procedures such as tube shunt surgery and trabeculectomy, which may promote graft failure.[42,43] However, our results did not demonstrate any significant difference in graft survival rates between patients who underwent glaucoma surgery either before or after keratoplasty. Thus, trabeculectomy and tube shunt surgery appear to have no significant effect on graft survival following keratoplasty in people with ICE.

Better and faster visual recovery after DMEK and DSEK has led to a paradigm shift in corneal transplantation. In the past, corneal surgeons often delayed performing PK for as long as possible.[29] In contrast, DSEK and DMEK, are now typically performed at earlier stages of severity and in patients with better preoperative visual acuity compared to PK.[9] Our results also demonstrated that keratoplasty was performed in milder cases with DSEK and DMEK compared to PK, resulting in better preoperative BSCVA in patients undergoing these procedures. DMEK has been shown to offer superior postoperative visual acuity and faster visual rehabilitation compared to DSEK, with results that surpass those of PK.[10,44,45] Additionally, DMEK achieves near-perfect anatomical restoration of the corneal structure.[33]

However, some conflicting reports exist. van Rooij et al.[46], Fuest et al.[47] and Ishiyama et al.[48] found no significant difference in visual improvement between PK and DSEK. Similar to our findings, these studies also reported that both preoperative and postoperative BSCVA were significantly better in DSEK compared to PK. Furthermore, our meta-analysis did not reveal any significant differences in BSCVA improvement among PK, DSEK and DMEK.

One of the most critical risk factors for graft failure after keratoplasty is ECL.[7] Pooled estimates for postoperative ECD showed no significant differences between DSEK and DMEK at 6 months and 12 months, aligning with previous reports on DSEK and DMEK outcomes in people with PBK and FED.[49] Our results demonstrated a substantial ECL at 1 month after DSEK and DMEK. However, ECL and ECD remained stable beyond 3 months after endothelial keratoplasty, suggesting that significant ECD loss may be attributed to intraoperative mechanical damages or early postoperative processes. It is hypothetized that the challenging insertion of lamellar grafts due to anterior segment alterations in ICE syndrome could contribute to increased intraoperative and/or early postoperative ECD loss.[7,21] These findings are consistent with earlier studies in patients with PBK and FED.[50-52]

• **STRENGTHS AND LIMITATIONS:** Strength: (1) This is the first meta-analysis to directly compare the surgical outcomes of PK, DSEK, and DMEK in patients with ICE syndrome. (2) The use of IPD for data synthesis enhances the accuracy and reliability of the findings.

Limitations: (1) A major limitation is the relatively small number of patients included in the analysis (2) The absence of prospective, interventional studies for inclusion limits the strength of the evidence. (3) The lack of a universally accepted guideline for managing corneal oedema in patients with ICE syndrome introduces potential bias. (4) The limited available data on glaucoma surgery performed before and after corneal transplantation. (5) The lack of data on primary graft failure. (6) The lack of the data on rejection reactions. (7) Heterogeneity in study design, patient selection, baseline characteristics, and inconsistently reported data may have influenced the results.

• **IMPLICATION FOR PRACTICE, RESEARCH, AND POLICY-MAKERS:** This meta-analysis highlights the need for tailored approaches to corneal transplantation in ICE syndrome, considering patient-specific factors. While less invasive techniques like DSEK and DMEK offer quicker recovery, PK may ensure better graft survival in some cases. Clinicians should carefully evaluate the risks and benefits of each technique and emphasize effective postoperative care. Future research should focus on larger, prospective studies to compare long-term outcomes of different surgical approaches for ICE syndrome. Standardized protocols

and deeper exploration of its pathophysiology could lead to better treatments and preventive measures, improving patient care. Policymakers can support rare disease research by funding initiatives and developing uniform management guidelines.

CONCLUSIONS

PK demonstrated better graft survival compared to DSEK in patients with ICE, however, further research and additional evidence are needed to draw more definitive conclusions. Postoperative visual improvement does not seem to differ among the 3 procedures. Trabeculectomy and tube shunt surgery, whether performed before or after keratoplasty, appear to have no significant impact on graft survival.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

GÁBOR TÓTH: Writing – original draft, Methodology, Formal analysis, Conceptualization. **SZILÁRD VÁNCSA:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **TAMÁS KÓI:** Writing – review & editing, Visualization, Methodology, Formal analysis. **KITTI KORMÁNYOS:** Writing – review & editing, Methodology, Formal analysis, Data curation. **PÉTER HEGYI:** Writing – review & editing, Conceptualization. **NÓRA SZENTMÁRY:** Writing – review & editing, Supervision, Project administration, Methodology, Formal analysis, Conceptualization.

Ethical Approval: No ethical approval was required for this systematic review with meta-analysis, as all data were already published in peer-reviewed journals. No patients were involved in the design, conduct or interpretation of our study. The datasets used in this study can be found in the full-text articles included in the systematic review and meta-analysis.
Information on Access Data: Dr Tóth and Dr Szentmáry had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Data available: No.
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