

# Graft survival rate of deep anterior lamellar keratoplasty for keratoconus

## A meta-analysis

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### Abstract

**Background:** Deep anterior lamellar keratoplasty (DALK) is an optional treatment for patients with keratoconus, and the associated graft survival rate varies. Herein, we aimed to explore the graft survival rate of DALK in patients with keratoconus.

**Methods:** PubMed, Web of Science, and ProQuest databases were searched to retrieve the related articles. General data, clinical characters, and graft survival rates were obtained directly from the included studies and analyzed by meta-analysis.

**Results:** A total of 12 articles were included. The merged 1-, 3-, and 5-year graft survival rates were 100% (99.9–100%,  $P < .001$ ), 92.9% (89.8–95.9%,  $P < .001$ ), and 90.4% (86.0–94.8%,  $P < .001$ ), respectively. Lower heterogeneity was shown in each subgroup that was divided neither according to the sample number nor number of surgeons.

**Conclusion:** The survival rate slightly decreases year by year, but the overall trend seems relatively stable. Ensuring that all DALK procedures are performed by a single surgeon might be helpful to improve the graft survival rate after surgery.

**Abbreviations:** CI = confidence interval, DALK = deep anterior lamellar keratoplasty, DLKP = deep lamellar keratoplasty, PKP = penetrating keratoplasty.

**Keywords:** deep anterior lamellar keratoplasty, graft survival rate, keratoconus, meta-analysis

## 1. Introduction

Keratoconus is a progressive eye disease that causes thinning of the cornea and results in mixed vision problems.<sup>[1–4]</sup> Researchers estimate that the prevalence of keratoconus varies worldwide<sup>[5,6]</sup> and affects about 1 in 2000 people.<sup>[7,8]</sup> Keratoconus was first described by the German oculist Burchard Mauchart<sup>[9]</sup> in 1748 and later understood comprehensively on the basis of the exhaustive 270-page treatise by John Nottingham<sup>[10,11]</sup> in 1854. It is characterized by noninflammatory thinning of the corneal stroma, irregular astigmatism, myopia, and protrusion, and decrease in visual acuity.<sup>[3,12,13]</sup> Owing to the complex pathogenesis and early onset, patients with keratoconus who have severe and progressive vision problems or scarring on the cornea have little

choice but accept corneal transplantation. Penetrating keratoplasty (PKP) has been used to treated progressive stage keratoplasty for several decades.<sup>[14–16]</sup> However, in recent years, deep anterior lamellar keratoplasty (DALK)<sup>[17,18]</sup> has been increasingly chosen by patients instead of PKP owing to minimal violation of the intraocular structures and reduced adverse effects of the former. DALK can effectively decrease the failure rates of grafts by retaining patients' corneal endothelium and reducing immunological rejection post-transplantation.<sup>[19]</sup> It was reported that the survival rate of endothelial cells after DALK was higher than that of PKP treatment. However, the studies were limited by small sample sizes and varied 5-year survival rates compared with current research reports about DALK. In this article, we explored the graft survival rate of DALK in patients with keratoconus by single factor of meta-analysis.

Editor: Kaili Wu.

This study was supported by Yunnan Health Science and Technology Project (Grant No. 2017NS064).

The authors have no conflicts of interest to disclose.

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Medicine (2018) 97:28(e11404)

Received: 18 January 2018 / Accepted: 12 June 2018

<http://dx.doi.org/10.1097/MD.0000000000011404>

## 2. Methods

### 2.1. Literature research

Different databases including PubMed, Web of Science, and ProQuest were searched to retrieve randomized controlled trials related to DALK. “Deep anterior lamellar keratoplasty” OR “DALK,” “keratoconus,” and “graft survival” were used as keywords. The literature retrieval was dated from inception to May 15, 2017. All collected articles were scanned and recruited according to preset inclusion and exclusion criteria. Any difference of opinion was resolved by a third researcher. As the data included in our study were extracted from published literatures, no ethical approval and patient consent were required.

The inclusion criteria were as follows: Studies related to patients with conical cornea who were treated with deep lamellar keratoplasty (DLKP) were recruited. Different research types like randomized controlled trials, nonrandomized controlled trials, case-control

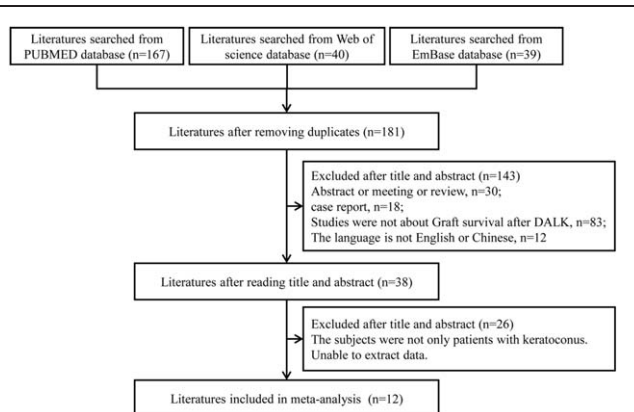


Figure 1. Literature screening process.

studies, cohort studies, and serial case reports were included. Studies that had data of the 5-year transplant success rate. In case of duplicate publications, studies that were of higher quality and had a more complete outcome were included. The language of the included publication was limited to English and Chinese.

The exclusion criteria were as follows: Studies like letters, notes of meetings, and reviews were excluded. Studies with no exact outcome or those wherein data extraction was not possible were excluded.

## 2.2. Quality evaluation and data extraction

Quality evaluation tool of literatures was chosen according to different research types. General data including country and year of publication, study design, and study duration were extracted. Definition of graft failure, number of patients, and follow-up

information were also extracted. Quality evaluation and data extraction of the included studies were performed and discussed with the third researcher.

## 2.3. Statistical analysis

The 5-year transplant success rate after DLKP was used as the final indicator for this meta-analysis. Heterogeneity of the recruited studies was analyzed by Cochran Q test and  $I^2$  test. The  $P$  value of Cochran Q test  $< 0.05$  or  $I^2$  value  $> 50\%$  was indicative of significant heterogeneity, and the random-effect model was used; otherwise, a fixed-effect model was chosen.

## 3. Results

### 3.1. Literature research and data extraction

The literature screening process is shown in Fig. 1. A total of 246 articles (167 from PubMed, 40 from Web of Science, and 39 from Embase) were included after searching by the keywords and preliminary screening by the database literature screening tool. After duplicates were automatically removed with Endnote software or manually, 181 articles remained. Then, the titles and abstracts were scanned, 30 articles with only abstract or report of meeting or reviews, 18 case reports, 83 unrelated studies, and 12 articles which were not written in English or Chinese were eliminated. The full text of the remaining 38 articles were screened and 12 studies<sup>[20–31]</sup> that finally matched the inclusion or exclusion criteria were analyzed in this report.

As shown in Table 1, general information and clinical data were abstracted from the 12 recruited articles. All these studies were retrospective research and focused on people of Mongolian and Caucasian ethnicity. Included samples were mainly collected from

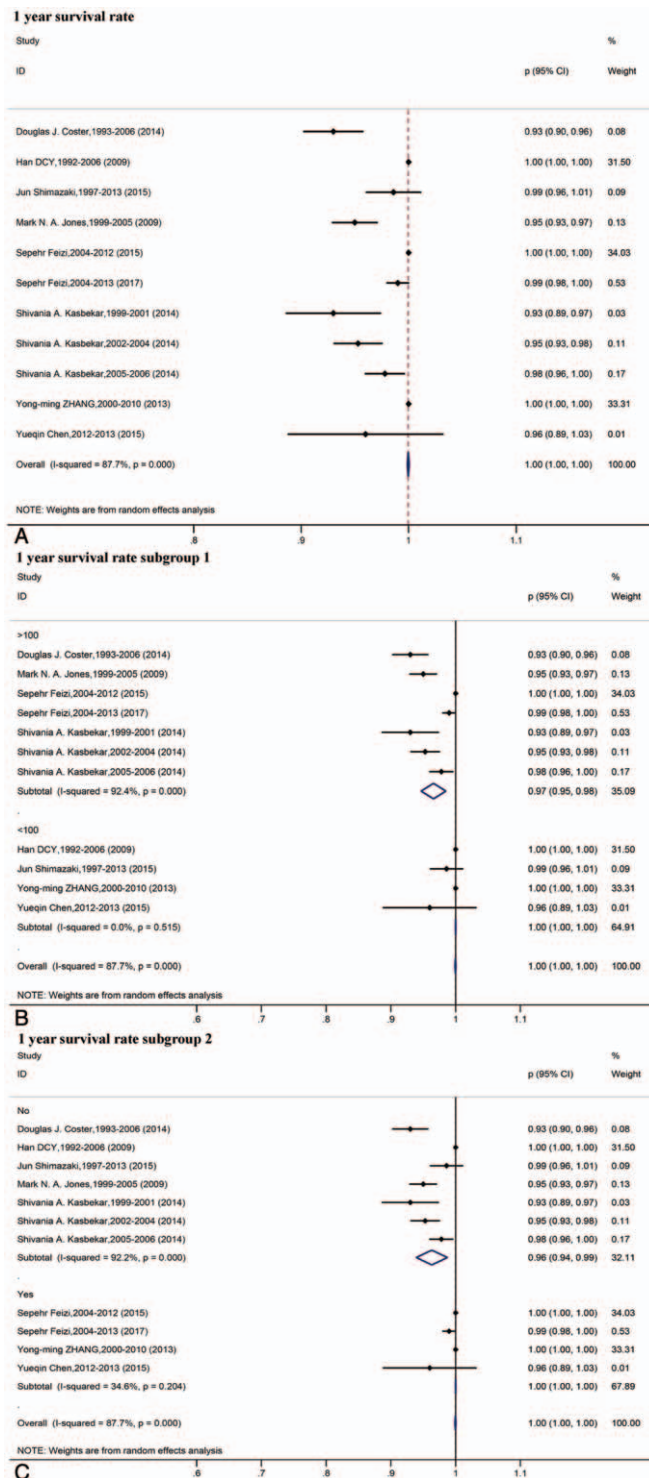
Table 1

General information of the included studies.

Study	Country	Study design	Duration	Single surgeon	Study setting	Defined of graft failure	Patient number	Median or mean recipient age	Follow-up, mo	Follow-up rate, %
Cohen et al <sup>[27]</sup>	USA	Retrospective	2000–2006	Yes	University of Iowa Hospitals and Clinics	Loss of visual acuity that was attributed to central corneal edema or opacities, irrespective of etiology	11	45.5 ± 13.1	22.5 ± 2.5	64
Coster et al <sup>[31]</sup>	Australia	Retrospective	1996–2013	No	Australian Corneal Graft Registry	Loss of corneal clarity or replacement of the graft was considered a failure	317	32 (1–92)	0–180	50
Han et al <sup>[20]</sup>	Singapore	Retrospective	1992–2006	No	Donald T. H. Tan, Singapore National Eye Centre	NR	25	—	16 (mean)	100
Shimazaki et al <sup>[26]</sup>	Japan	Retrospective	1997–2013	No	Electronic and paper records	NR	79	36 ± 12	57 ± 39	100
Jones et al <sup>[28]</sup>	UK	Retrospective	1999–2005	No	NHSBT	Analysis as an indication of the surgeon's experience with the technique	455	—	0–36 mo	91
MacIntyre et al <sup>[24]</sup>	Australia	Retrospective	2000–2010	Yes	The single surgeon's surgical database	A clear graft with no history of a repeat graft	31	29.2 ± 7.82	51.8 (14–111)	100
Feizi et al <sup>[29]</sup>	Iran	Retrospective	2004–2012	Yes	NR	The irreversible loss of central graft clarity, significant interface vascularization and haziness, or need for repeat keratoplasty for any reason	290	27.8 ± 8.2	38.6 ± 20.2	100
Feizi et al <sup>[25]</sup>	Iran	Retrospective	2004–2013	Yes	NR	second graft in the same eye performed	382	28.0 ± 8.4	50.8 ± 27.1	100
Kasbekar et al <sup>[21]</sup>	UK	Retrospective	1999.4–2010.3	No	NHSBT	NR	1224	—	1–60	89
Romano et al <sup>[22]</sup>	Italy	Retrospective	2003–2008	Yes	Records from Reggio Emilia Hospital by a single surgeon's surgical database	NR	150	33.6 ± 8.8	76.9 ± 23.2	—
Zhang et al <sup>[30]</sup>	China	Retrospective	2000–2010	Yes	The single surgeon's surgical database	A clear graft with no history of a repeat graft	75	20.6 ± 6.8	46.9 ± 28.0	100
Chen et al <sup>[23]</sup>	China	Retrospective	2012–2013	Yes	The single surgeon's surgical database	NR	28	24.1 ± 6.5	1–12	100

\* Postoperative follow-up time  $< 4$  years was excluded before study.

NHSBT = UK Transplant Registry of National Health Service Blood and Transplant, NR = no reference.



**Figure 2.** Forest graph of 1-year graft survival rate. (A) The 1-year graft survival rate of keratoconus patients after treatment with deep anterior lamellar keratoplasty in 9 studies. (B) Subgroup analysis of 1-year graft survival rate when studies were divided into 2 groups according to the sample number. (C) Subgroup analysis of 1-year graft survival rate when studies were divided into 2 groups according to the number of surgeons.

institutions like hospitals, surgical databases, and National Health Service Blood and Transplant. The duration of these studies were all over 5 years, and the follow-up rates of each study were over 50%.

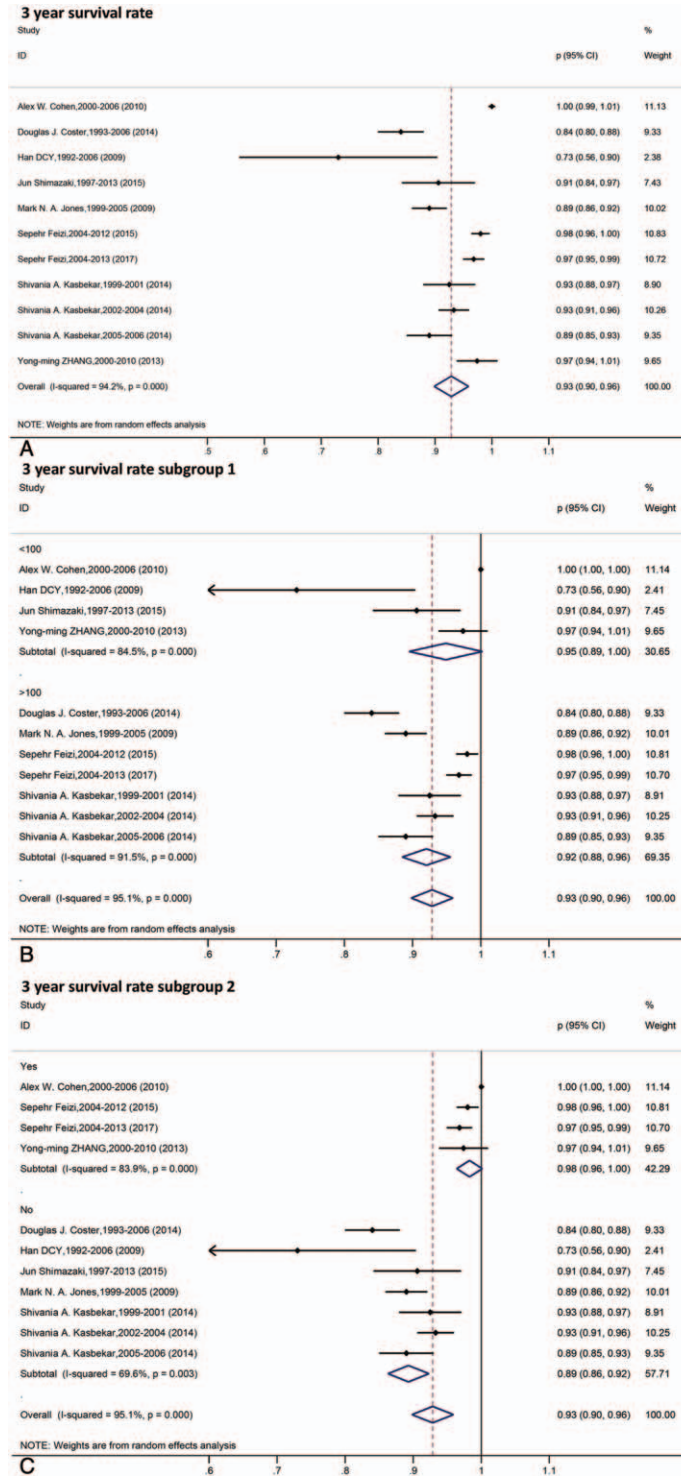
**3.2. Meta-analysis**

**3.2.1. One-year graft survival rate.** Eleven survival rates of 2241 patients from 9 studies<sup>[20,21,23,25,26,28-31]</sup> were analyzed in

this 1-year graft survival rate analysis. The 1-year graft survival rate of the analyzed articles ranged from 93% to 100%. The merged 1-year graft survival rate of keratoconus patients after treatment with DALK was (95% confidence interval [CI]): 100% [99.9-100%],  $P < .001$  (Fig. 2A). However, the  $I^2$  value was 87.7%, which suggested a significant heterogeneity. To confirm the source of heterogeneity, subgroup meta-analysis was further

analyzed. No heterogeneity was shown in each subgroup, divided either according to the sample number or number of surgeons (Fig. 2B and C) which indicated that these might be the 2 main reasons of heterogeneity. In subgroup analysis, the merged 1-year graft survival rate of bigger sample number group (>100), 97% (95–98%)  $P < .001$  was lower than the smaller sample number group (<100) (Fig. 2B).

**3.2.2. Three-year graft survival rate.** A total of 2224 patients' 11 graft survival rates from 9 studies<sup>[20,21,23,25,26,28–31]</sup> were analyzed. Three years after treatment with DALK, the merged graft survival rate was (95% CI): 92.9% (89.8–95.9%),  $P < .001$  (Fig. 3A). Similar to the 1-year survival rate analysis, significant heterogeneity was observed ( $I^2 = 94.2%$ ;  $P < .001$ ). Sample number and number of surgeons in the entire procedure were

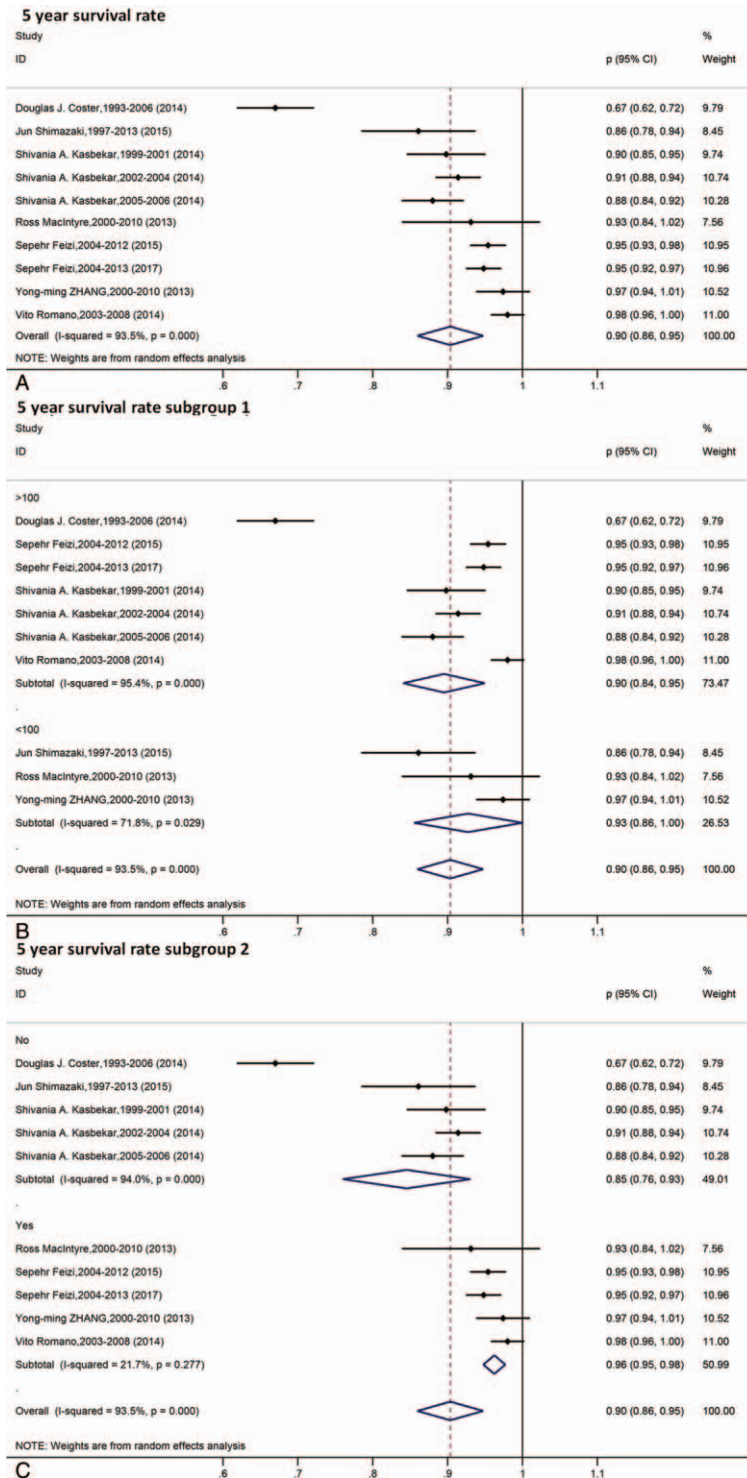


**Figure 3.** Forest graph of 3-year graft survival rate. (A) The 3-year graft survival rate of keratoconus patients after treatment with deep anterior lamellar keratoplasty in 9 studies. (B) Subgroup analysis of 3-year graft survival rate when studies were divided into 2 groups according to the sample number. (C) Subgroup analysis of 3-year graft survival rate when studies were divided into 2 groups according to the number of surgeons.



the main reasons of heterogeneity. After subgroup analysis, the  $I^2$  values of heterogeneity decreased no matter whether the division was by sample number or number of surgeons involved in the whole procedure (Fig. 3B and C). Moreover, the 3-year graft survival rate of patients who received DALK by a single surgeon was 93.8% (96.4%, 100%;  $P < .001$ ), higher than those who received surgery by multiple surgeons (89.3% [86.3%, 92.3%],  $P < .001$ ).

**3.2.3. Five-year graft survival rate.** Ten survival rates of 1970 patients from 8 studies<sup>[21,22,24-26,29-31]</sup> were analyzed in this 5-year graft survival rate analysis. The merged graft survival rate was (95% CI): 90.4% (86.0-94.8%),  $P < .001$  with a significant heterogeneity ( $I^2$  value: 93.5%) (Fig. 4A). According to the former analysis, subgroup analyses were performed to seek the source of heterogeneity (Fig. 4B). Low heterogeneity of the 5-year



**Figure 4.** Forest graph of 5-year graft survival rate. (A) The 5-year graft survival rate of keratoconus patients after treatment with deep anterior lamellar keratoplasty in 9 studies. (B) Subgroup analysis of 5-year graft survival rate when studies were divided into 2 groups according to the sample number. (C) Subgroup analysis of 5-year graft survival rate when studies were divided into 2 groups according to the number of surgeons.

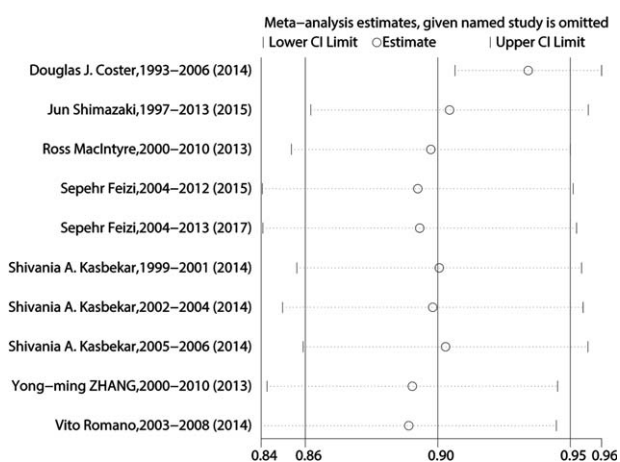


Figure 5. Sensitivity analysis of 5-year graft survival rate.

graft survival rate was shown in those who received DALK by single surgeon ( $I^2$  value: 21.7%,  $P = .277$ ) (Fig. 4C).

However, the 5-year graft survival rate (67%) extracted from Coster et al's study<sup>[31]</sup> was lower than others, which might have been influenced by the large sample size (317), number of surgeons (single or multiple), and long follow-up period (leading to a high rate of follow-up loss). To explore the sensitivity of the results, 5-year graft survival rate was remerged by excluding studies one by one (Fig. 5). When Coster et al's study was excluded, the merged 5-year graft survival rate of the remaining studies was 93.4% (90.9%, 95.7%), which indicates a significant improvement.

#### 4. Discussion

Although the symptoms can be improved by wearing contact lenses or receiving IntraCorneal Ring Segments (INTACS) implants, 15% to 20% of patients<sup>[32]</sup> with keratoconus ultimately require corneal transplant surgery.<sup>[33]</sup> Despite several comparative studies between PKP and DALK,<sup>[34–37]</sup> no general agreement has yet been reached on the optimal method.

Graft survival rate is the most important indicator to evaluate the treatment effect of transplantation. Compared with PKP, various rates can be found on the graft survival rate of DALK for keratoconus patients owing to a short application period. In this meta-analysis, we collected and system integrated the graft survival rates to evaluate DALK treatment effects. As shown in our results, the graft survival rate gradually decreased from over time (1 year > 3 years > 5 years). The lowest graft survival rate seen at 5 years could likely be attributed to the long-time accumulation of immunization and the side effects of transplantation. Interestingly, the result of subgroup analysis indicated that the number of surgeons in 1 complete procedure might influence the graft survival rate. We assumed that this might be related to the skill level of the surgeon,<sup>[28]</sup> or different operational methods. More comprehensive studies should be done to verify this hypothesis.

There are some limitations in this meta-analysis. First, though we focused on the effect of surgical method on graft survival rate, the recruited studies focused on 2 different populations (Mongolian and Caucasian); hence, difference of sample source might have partly contributed to the heterogeneity. Second, it is difficult to carry out a long-term follow-up with a big sample size;

some patients were lost to follow-up which resulted in some studies not being analyzed in the subgroup analysis. Third, the included studies were limited by language, as non-English or non-Chinese publications might have been missed. However, the stable results showed by the sensitivity analysis and lower heterogeneity in the subgroup analysis indicate a high quality of this meta-analysis.

This meta-analysis discusses the graft survival rate of DALK on keratoconus patients. Although the survival rate slightly decreases year by year, the entire trend appears relatively stable. Further, all DALK procedures performed by a single surgeon might be helpful to improve the graft survival rate after surgery.

#### Author contributions

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**Project administration:** Ling Yuan.

**Resources:** Meng Guan, Weijia Zhao, Yang Zhang, Yu Geng, Zonghan Chen, Liuyan Feng.

**Software:** Meng Guan, Weijia Zhao, Yu Geng, Zonghan Chen, Liuyan Feng.

**Supervision:** Ling Yuan.

**Validation:** Yang Zhang, Zonghan Chen, Dongli Li.

**Visualization:** Yang Zhang, Yu Geng, Liuyan Feng, Dongli Li.

**Writing – original draft:** Meng Guan, Weijia Zhao.

**Writing – review and editing:** Ling Yuan.

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