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BRIEF REPORT

A Predictive Model for Graft Failure in Femtosecond Laser-Assisted Penetrating Keratoplasty Among Chinese Patients: A 2-Year Study

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ABSTRACT

Introduction: Graft failure is a major challenge in femtosecond laser-assisted penetrating keratoplasty (Fs-PKP). This study focuses on the development and validation of a clinical predictive model aimed at identifying the risk of graft failure in individuals undergoing Fs-PKP in China, offering a tailored approach to improve surgical outcomes.

Methods: This retrospective cohort study at Nanjing First Hospital involved 238 patients and followed the TRIPOD statement. The cohort was divided into a training set ($n=166$) and a validation set ($n=72$) in a 7:3 ratio. It analyzed 23 predictor variables related to recipient, donor, and surgical factors, defining graft failure as "visually significant and irreversible corneal stromal edema, haze, or scarring." A comprehensive nomogram was created using univariate and multivariate Cox regression analyses and assessed by concordance index (C-index), time-dependent receiver operating characteristics (ROC) curve, calibration plots, and decision curve analysis (DCA).

Results: Five critical risk factors were identified: recipients' history of systemic autoimmune disorders, ocular trauma, prior penetrating keratoplasty (PKP) history, donors' diabetes history, and the endothelial cell density of the donor cornea. The nomogram showed a C-index of 0.72 (95% CI 0.65–0.79) in the training group and 0.66 (95% CI 0.55–0.76) in the validation group, indicating robust predictive accuracy. Time-dependent ROC curves, calibration plots, and DCA consistently validated the model's reliability, predictive power, and clinical utility across both training and validation cohorts.

Junxin Ma, Xueqian Cao, and Yang Liu contributed equally to the study and should be regarded as joint first authors.

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Conclusions: Our study developed and validated a model incorporating five key factors, enhancing preoperative prediction and management for Chinese patients with Fs-PKP graft failure.

Keywords: Predictive model; Femtosecond laser-assisted penetrating keratoplasty; Graft failure; Chinese patients

Key Summary Points

Why carry out this study?

Graft failure remains a critical issue in femtosecond laser-assisted penetrating keratoplasty (Fs-PKP).

Current nomograms for predicting failures in conventional penetrating keratoplasty mainly use data from Western populations, overlooking the specific requirements of femtosecond laser technology and anatomical differences between Chinese and Western eyes.

This study aims to develop and validate a clinical predictive model to identify graft failure risks in Chinese patients undergoing Fs-PKP.

What was learned from the study?

We developed and validated a nomogram that achieves high sensitivity and specificity by integrating key factors such as the recipient's systemic autoimmune disorders, history of ocular trauma, previous PKP experiences, the donor's history of diabetes, and the endothelial cell density of donor corneas.

This nomogram allows for the preoperative prediction of graft failure risk in patients undergoing Fs-PKP, facilitating the implementation of targeted management strategies to enhance patient outcomes.

INTRODUCTION

Penetrating keratoplasty (PKP) stands as a cornerstone in the treatment of various corneal diseases and has undergone significant evolution over the years [1]. The integration of femtosecond laser-assisted penetrating keratoplasty (Fs-PKP) marks a pivotal advancement, demonstrating significant enhancements over conventional PKP techniques in terms of surgical precision and outcomes. The precision afforded by femtosecond laser cutting has been instrumental in enhancing the integration between grafts and hosts, a factor of paramount importance for the success and longevity of corneal transplants [2–5]. Comparative studies between traditional methods and Fs-PKP have demonstrated a significant reduction in graft rejection and endothelial cell loss rates among patients undergoing Fs-PKP, underscoring the marked benefits of this advanced technology in improving transplant outcomes [2–5].

Despite these technological advancements, graft failure—characterized by irreversible changes in the corneal stroma such as edema, haze, or scarring that negatively affect visual acuity—remains a major challenge in Fs-PKP. In conventional PKP, graft success hinges on various recipient and donor factors. Issues like active ocular inflammation, corneal neovascularization, and ocular comorbidities (e.g., glaucoma) can elevate graft rejection risks or compromise graft stability due to effects on intraocular pressure. Likewise, donor attributes, notably endothelial cell density and cornea health, critically influence the graft's initial viability and function. Surgical specifics, such as graft size and precise positioning, also play a key role, impacting the graft–host integration. Correct sizing and alignment are essential for smooth graft integration, reducing edge irregularities and potential complications like poor healing. These interconnected factors significantly determine transplant outcomes, emphasizing the need for meticulous risk factor management to enhance PKP success [6–11].

However, these studies have predominantly targeted individual risk factors, frequently omitting an encompassing evaluation. The

emergence of predictive models—integrating varied data types and employing sophisticated statistical and machine learning methods to enhance precision and facilitate individualized risk assessments—has offered new insights. For instance, a study conducted in 2005 aimed at predicting short-term graft survival but was constrained to a 1-year postoperative period and did not incorporate a diverse range of data sources [12]. More recently, a 2021 study in the United States developed a predictive nomogram for conventional PKP, utilizing a larger patient sample and extending the follow-up period up to 5 years [13]. While existing predictive models for PKP boast advancements beyond the scope of traditional epidemiological approaches, their primary design caters to Western populations, focusing predominantly on conventional PKP techniques. Such geographical and technological specificities necessitate a reassessment of these models' applicability in the context of Fs-PKP, particularly in light of the latest technological improvements and the adoption of precise preventative measures for well-documented risks.

Moreover, the unique demographic and clinical characteristics of Chinese patients, who represent a significant portion of the Fs-PKP recipient base, are not fully captured by models primarily designed for Western populations. Factors such as better overall ocular health, access to more sophisticated surgical techniques, and the economic aspects of accessing state-of-the-art medical care set Chinese Fs-PKP candidates apart from their counterparts considered for traditional PKP. The demographic consistency of the Chinese population, mainly composed of Han Chinese and characterized by a low immigration rate, reduces the relevance of the variability that international models, intended for ethnically and clinically diverse groups, aim to address. This suggests that a predictive model tailored to the specific features of the Chinese population would offer greater accuracy and relevance, thereby improving its utility for this particular group.

This divergence highlights the urgent necessity for developing predictive models that are specifically attuned to the nuances of the Chinese clinical environment, ensuring they are both relevant and applicable to the patient population in China. Therefore, our research aims to fill this critical void by developing and validating a comprehensive nomogram for graft failure in Chinese patients undergoing Fs-PKP. By integrating a broad spectrum of risk factors, we anticipate that our model will more accurately reflect the unique healthcare needs and clinical scenarios of the Chinese demographic, thereby providing a refined instrument for preoperative assessment and informed decision-making in the domain of Fs-PKP.

METHODS

Study Design and Population

This retrospective cohort study, adhering to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement, included 274 patients who underwent Fs-PKP performed by the same ophthalmic surgeon at Nanjing First Hospital from January 2019 to June 2021. This institution is recognized as the premier corneal transplant center in Jiangsu Province, Eastern China, and stands among the leading facilities in China for Fs-PKP. To mitigate the limitations inherent in retrospective studies, stringent inclusion criteria were applied. This approach led to the exclusion of patients under 18 years, those with incomplete medical records, or those unable to adhere to the follow-up schedule. Additionally, we employed robust data verification procedures and adjusted for confounders to enhance the reliability and applicability of our findings. The final cohort of 238 patients was randomized into a training set ($n=166$) and a validation set ($n=72$) in a 7:3 ratio for establishing and verifying the nomogram. The study was approved by the Ethics Committee of Nanjing First Hospital (KY20240318-KS-01) and adhered to the principles of the Declaration of Helsinki. Given the retrospective nature of the study, the Ethics Committee determined that informed consent from participants was not required. Nevertheless, ethical principles were strictly observed throughout the entirety of the research process.

Fs-PKP Procedure and Management

Fs-PKP was conducted utilizing the Femtosecond Laser 200 (Wave Light, Germany), adhering to the protocol delineated in prior research [2]. The procedure employed the laser's capabilities of a 200-kHz repetition rate and a pulse energy within the range of 160–200 nanojoules (nJ) specifically for crafting a meticulous mushroom-shaped incision. Postoperative management was guided by established protocols and tailored to individual patient needs. All patients received a standard postoperative regimen of antibiotics and corticosteroids to prevent infection and control inflammation [13]. For patients with a history of preoperative conditions such as infections (viral, fungal, or bacterial), glaucoma, or systemic immunological disorders, an enhanced pharmacotherapy approach was adopted. This involved both local and systemic treatments, adjusted according to the severity and nature of the pre-existing conditions.

Follow-Up Evaluations

Follow-up evaluations were meticulously conducted at predefined intervals, including a minimum of 1 week before surgery, and subsequently at 1 week, 1 month, 6 months, 1 year, and 2 years postoperatively. In cases where patients exhibit significant postoperative clinical anomalies (including but not limited to persistent epithelial defects, elevated intraocular pressure, or infectious keratitis), the protocol mandates additional follow-up assessments at 3, 9, or 18 months following the surgery.

Candidate Predictor Variables

We meticulously selected 23 variables as potential predictors for our model, grounded in an exhaustive review of existing literature and their established clinical significance in influencing outcomes of corneal grafts [6–11]. These predictors are systematically categorized into three primary groups:

- Recipients' Parameters: gender, age, diabetes history, systemic autoimmune disorders history, glaucoma history, smoking history, operative eye, diagnosis of ocular disease, viral ocular diseases history, ocular trauma history, prior penetrating keratoplasty (PKP) history, presence of corneal neovascularization, presence of hypopyon, and active ocular microbial infection status;
- Donors' characteristics: age, diabetes history, and mortality cause of donor; the endothelial cell density, death-to-preservation time, storage duration, and reservation technique of donor cornea;
- Surgery-related variables: the corneal graft diameter and intraoperative plan.

Study Outcome

The primary outcome of the investigation was "graft failure" as characterized in line with details set by a previous study. Succinctly, we defined it as "visually significant and irreversible corneal stromal edema, haze, or scarring". Additionally, we assert that instances of stromal edema responsive to topical corticosteroid therapy, as well as peripheral edema that does not compromise visual acuity, should not be categorized as graft failure. The date of graft failure in our study was identified as the time of the first postoperative detection of clinical abnormalities that ultimately led to graft failure.

Statistical Analysis

Data Processing

Data processing and analysis were performed using R software (Version 4.1.0) and IBM SPSS Statistics (Version 22.0). Continuous data were expressed as means ± SD or medians with interquartile ranges, and categorical variables were analyzed using chi-square tests. All statistical tests were two-sided, with $P < 0.05$ as the significance threshold.

Establishment of the Nomogram Prediction Model

Using a training dataset, independent graft failure predictors were identified with univariate and multivariate Cox regression ($P < 0.20$ for inclusion). The nomogram, generated using R's "rms" package, was based on significant multivariate factors. Survival rates were estimated with the Kaplan–Meier method, and differences assessed using stratified log-rank tests.

Assessment of the Nomogram Prediction Model

Both training and validation datasets were used for evaluation. Time-dependent ROC analysis for 6, 12, and 24 months was performed using R's "time ROC" package. The model's discriminative power was measured by the C-index, and calibration curves were generated with the "rms" package. Clinical utility was assessed through DCA using the "dca.R" package.

RESULTS

Demographic Baseline Characteristics

As shown in Fig. 1, which details the study enrollment process, our cohort consisted of 238 patients. The demographic and baseline characteristics, as presented in Table 1, showed no significant differences between the training group ($n = 166$) and the validation group ($n = 72$).

Univariate and Multivariate Cox Regression Results

In the univariate logistic regression analysis on the training set, nine prognostic factors were identified as significant ($P < 0.20$), subsequent multivariable Cox regression analysis narrowed these down to five independent prognostic factors including recipients' systemic autoimmune disorders history [OR 4.32, 95% CI (1.97–9.47), $P < 0.001$], recipients' ocular trauma history [OR 1.99, 95% CI (1.06–3.74), $P = 0.03$], recipients' prior PKP history [OR 2.18, 95% CI (1.10–4.32), $P = 0.03$], diabetes history of donor [OR 2.24, 95% CI (1.22–4.11), $P = 0.01$], and endothelial cell density of donor cornea [OR 0.50, 95% CI (0.26–0.95), $P = 0.04$] (Table 2).

Overall Survival

Figure 2a illustrated the cumulative overall survival probabilities at various time points based on the training dataset: 12.05% graft failure rate at 6 months (20/166), 28.31% at 12 months (47/166), and 31.93% at 24 months (53/166). Stratified log-rank tests were conducted on independent prognostic factors from Cox regression analysis to evaluate overall survival differences (Fig. 2b–f). Significant variations in overall survival were observed in relation to the recipients' history of systemic autoimmune disorders ($P < 0.001$), previous PKP ($P = 0.02$), donors' diabetes history ($P = 0.01$), and endothelial cell density of the donor cornea ($P = 0.02$). Recipients' ocular trauma history, however, did not significantly impact overall survival ($P = 0.17$).

Construction and Validation of the Nomogram

We developed a graft failure prediction nomogram for Fs-PKP recipients employing the aforementioned five predictive factors (Fig. 3a). The nomogram's C-index was 0.72 (95% CI 0.65–0.79) in the training group and 0.66 (95% CI 0.55–0.76) in the validation group, indicating its effectiveness. Time-dependent ROC analysis for 6, 12, and 24 months showed AUC values ranging from 0.67 to 0.78 in the training set (Fig. 3b) and 0.54–0.69 in the validation set (Fig. 3c). Calibration curves for both groups (Fig. 3d, e) affirmed the nomogram's accuracy in mirroring actual clinical outcomes. Decision curve analysis (DCA) indicated an optimal net benefit at risk thresholds of 20–70% in the training cohort and 20–50% in the validation cohort.

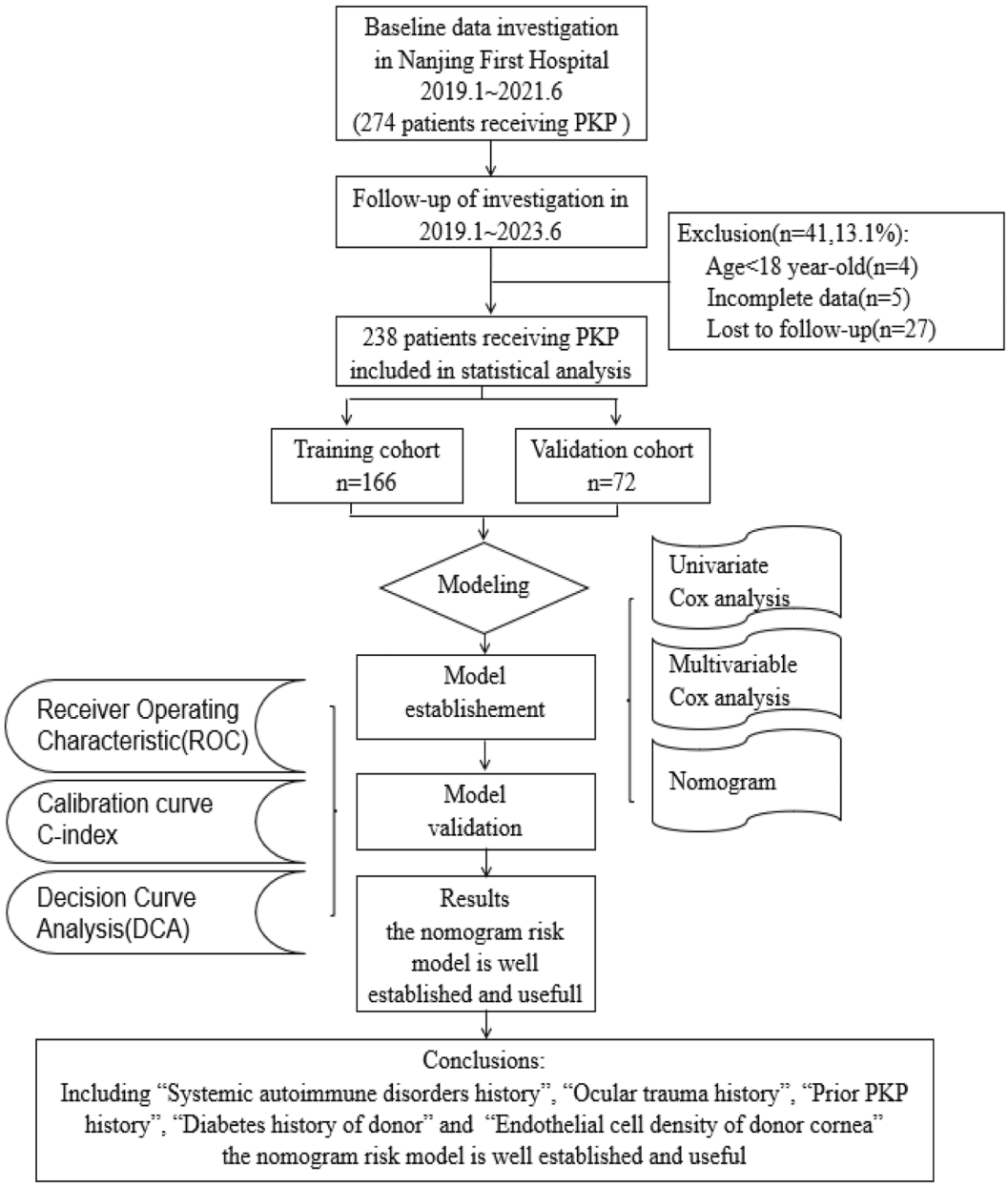


Fig. 1 Enrollment process of this study. *PKP* prior penetrating keratoplasty

DISCUSSION

In this study, we have innovatively developed a nomogram for predicting corneal graft failure in Chinese patients undergoing Fs-PKP. This model, which incorporates factors such as recipients' systemic autoimmune disorders and ocular trauma history, prior PKP, donors' diabetes history, and endothelial cell density of donor corneas, uniquely integrates recipient, donor, and surgical variables. Such a comprehensive approach offers clinicians a valuable tool for assessing and mitigating the risk of graft failure.

The observed 1-year and 2-year survival rates for Fs-PKP (71.69 and 68.07%, respectively) are particularly significant given the limited literature in the Chinese demographic [14–21]. These

Table 1 Baseline data table of the training group and the validation group

Characteristics	Total ($n = 238$)	Training cohort ($n = 166$)	Validation cohort ($n = 72$)	P values[a]
Recipients' parameters				
Gender (male, %)	142 (59.66)	105 (63.25)	36 (50.00)	0.09
Age (years old) (≥ 65 year-old, %)	120 (50.42)	86 (51.81)	34 (47.22)	0.52
Diabetes history (yes, %)	26 (10.92)	19 (11.45)	7 (9.72)	0.70
Systemic autoimmune disorders history (yes, %)	12 (5.04)	9 (5.42)	3 (4.17)	0.68
Glaucoma history (yes, %)	10 (4.20)	7 (4.22)	3 (4.17)	0.99
Smoking history (yes, %)	47 (19.75)	32 (19.28)	15 (20.83)	0.78
Operative eye (left, %)	115 (48.32)	82 (49.40)	37 (51.39)	0.61
Diagnosis of ocular disease				
Corneal leukoplakia	83 (34.87)	54 (32.53)	29 (39.73)	0.20
Corneal ulcer	117 (49.16)	82 (49.40)	35 (48.61)	
Keratoconus	11 (4.62)	10 (6.02)	1 (1.39)	
Bullous keratopathy	15 (6.30)	13 (7.83)	2 (2.78)	
Others	12 (5.04)	7 (4.22)	5 (6.94)	
Viral ocular diseases history (yes, %)	102 (42.86)	74 (44.58)	28 (38.89)	0.42
Ocular trauma history (yes, %)	56 (23.53)	37 (22.29)	19 (26.39)	0.49
Prior PKP history (yes, %)	33 (13.87)	21 (12.65)	12 (16.67)	0.41
Presence of corneal neovascularization (yes, %)	50 (21.01)	39 (23.49)	11 (15.28)	0.15
Presence of hypopyon (yes, %)	57 (23.95)	43 (25.90)	14 (19.44)	0.28
Active ocular microbial infection status (yes, %)	116 (48.74)	81 (48.80)	35 (48.61)	0.98
Donors' characteristics:				
Donor age (≥ 60 years old, %)	156 (65.55)	110 (66.27)	46 (63.89)	0.72
Donor diabetes history (yes, %)	40 (16.81)	29 (17.47)	11 (15.28)	0.68
Mortality cause of donor				
Not cancer	161 (67.65)	109 (65.66)	52 (72.22)	0.32
Cancer	77 (32.35)	57 (34.34)	20 (27.78)	
Donor cornea's endothelial cell density				
< 2500	156 (65.55)	110 (66.27)	46 (63.89)	0.72
≥ 2500	82 (34.45)	56 (33.73)	26 (36.11)	
Death-to-preservation time of donor cornea				
< 4 h	225 (94.54)	155 (93.37)	70 (97.22)	0.23

Table 1 continued

Characteristics	Total ($n = 238$)	Training cohort ($n = 166$)	Validation cohort ($n = 72$)	P values[a]
≥ 4 h	13 (5.46)	11 (6.63)	2 (2.78)	
Storage duration of donor cornea				
< 7 days	168 (70.59)	118 (71.08)	50 (69.44)	0.74
7–14 days	57 (23.95)	38 (22.89)	19 (26.39)	
> 14 days	13 (5.46)	10 (6.02)	3 (4.17)	
Reservation technique of donor cornea				
Liquid nitrogen	12 (5.04)	9 (5.42)	3 (4.17)	0.68
Eusol C	226 (94.96)	157 (94.58)	69 (9.58)	
Surgery-related variables				
Corneal graft diameter (≥ 8 mm)	69 (28.99)	46 (27.71)	23 (31.94)	0.51
Intraoperative plan				0.40
PKP without other surgery	96 (40.34)	64 (38.55)	32 (44.44)	
PKP with other surgery	142 (59.66)	102 (61.45)	40 (55.56)	

[a]By Pearson's chi-square test

PKP prior penetrating keratoplasty

rates are slightly lower than those reported in the Singapore Corneal Transplant Study for conventional PKP and align with the global survival rate range for this procedure [14–21]. This discrepancy might reflect the unique socio-economic and healthcare factors in China, underscoring the importance of considering regional differences in healthcare delivery and patient demographics when evaluating corneal transplantation outcomes.

While conventional PKP's graft failure risk factors are well documented, data on Fs-PKP remain notably scarce [6–11]. Our research focused solely on the use of the mushroom-shaped incision technique, a method refined by the precision of femtosecond laser technology. This technique provides consistently uniform and regular incisions, crucial for achieving optimal wound alignment. It offers several benefits to standard trephine: it replaces a significant amount of the anterior stromal tissue, reducing corneal astigmatism by enlarging the anterior stromal segment and lowering the risk of graft rejection with a smaller posterior segment [2]. However, the requirement for suction on transparent corneal areas during laser application limits Fs-PKP's applicability in cases with corneal perforation or severe opacification, where traditional corneal transplantation remains necessary. This limitation highlights the need to reevaluate the risk factors for Fs-PKP, as they might differ from those associated with conventional PKP methods [2–5, 16–18, 22, 23]. Our study identified specific risk factors relevant to Chinese patients undergoing Fs-PKP, including systemic autoimmune disorders, history of ocular trauma, prior PKP, diabetes history in donors, and the endothelial cell density of donor corneas. These findings are in line with recognized risk factors from previous studies on PKP [6–11], thus reinforcing the credibility of our results.

We conscientiously addressed known high-risk factors for graft failure in conventional PKP, such as preoperative infections, elevated intraocular pressure, and systemic autoimmune disorders, driven by ethical imperatives. Despite these

Table 2 Univariate and multivariate Cox regression results for predicting factors of graft failure

Characteristics	Univariate				Multivariate			
	ExpB	Lower	Upper	Sig	ExpB	Lower	Upper	Sig
Recipients' parameters								
Gender								
Female								
Male	1.26	0.71	2.24	0.43				
Age (years old)								
< 65								
≥ 65	1.33	0.77	2.30	0.30				
Diabetes history								
No								
Yes	1.09	0.47	2.55	0.85				
Systemic autoimmune disorders history								
No								
Yes	3.99	1.88	8.51	< 0.001	4.32	1.97	9.47	< 0.001
Glaucoma history								
No								
Yes	1.67	0.52	5.35	0.39				
Smoking history								
No								
Yes	0.96	0.48	1.90	0.90				
Operative eye								
Right								
Left	0.92	0.54	1.58	0.76				
Diagnosis of ocular disease								
Corneal leukoplakia								
Corneal ulcer	0.39	0.11	1.39	0.15				
Keratoconus	0.78	0.24	2.56	0.69				
Bullous keratopathy	0.36	0.06	2.15	0.26				
Others	1.05	0.26	4.19	0.95				
Viral ocular diseases history								
No								
Yes	0.93	0.54	1.60	0.80				

Table 2 continued

Characteristics	Univariate				Multivariate			
	ExpB	Lower	Upper	Sig	ExpB	Lower	Upper	Sig
Ocular trauma history								
No								
Yes	1.49	0.82	2.71	0.19	1.99	1.06	3.74	0.03
Prior PKP history								
No								
Yes	2.13	1.10	4.14	0.03	2.18	1.10	4.32	0.03
Presence of corneal neovascularization								
No								
Yes	1.95	1.11	3.42	0.02				
Presence of hypopyon								
No								
Yes	1.77	1.01	3.10	0.05				
Active ocular microbial infection status								
No								
Yes	1.56	0.90	2.69	0.11				
Donors' characteristics								
Donor age								
< 65								
≥ 65	1.49	0.81	2.74	0.20				
Donor diabetes history								
No								
Yes	2.12	1.17	3.86	0.01	2.24	1.22	4.11	0.01
Mortality cause of donor								
Not cancer								
Cancer	0.75	0.41	1.36	0.34				
Donor cornea's endothelial cell density								
< 2500								
≥ 2500	0.50	0.26	0.95	0.03	0.50	0.26	0.95	0.04
Death-to-preservation time of donor cornea								
< 4 h								
≥ 4 h	1.25	0.45	3.45	0.67				

Table 2 continued

Characteristics	Univariate				Multivariate			
	ExpB	Lower	Upper	Sig	ExpB	Lower	Upper	Sig
Storage duration of donor cornea								
< 7 days								
7–14 days	0.62	0.24	1.57	0.31				
> 14 days	0.37	0.12	1.13	0.08				
Reservation technique of donor cornea								
Liquid nitrogen								
Eusol C	0.61	0.22	1.70	0.35				
Surgery-related variables								
Corneal graft diameter								
< 8 mm								
≥ 8 mm	1.21	0.67	2.17	0.53				
Intraoperative plan								
Fs-PKP without other surgery								
Fs-PKP with other surgery	1.43	0.80	2.55	0.22				

fs-PKP femtosecond laser-assisted penetrating keratoplasty

targeted efforts, our multivariate Cox regression analysis highlighted that systemic autoimmune disorders remain a significant risk factor for graft failure in Fs-PKP. This highlights the intricate and impactful nature of systemic autoimmune diseases in the context of corneal transplantation. The findings imply that while our strategies effectively managed certain risk factors, systemic autoimmune disorders necessitate more focused and perhaps specialized postoperative care for Fs-PKP patients, underscoring the need for tailored medical attention in these cases.

Interestingly, while anterior chamber hypopyon and corneal neovascularization initially showed significance as risk factors in univariate Cox regression analysis (P values < 0.05), their significance diminished in the multivariate Cox analysis. This suggests that these factors may not independently contribute to graft failure when considered alongside other variables, highlighting the complexity of their influence in corneal transplantation outcomes. This observation may be attributed to the unique nature of Fs-PKP surgery, where patients typically present with less severe forms of these clinical signs [2].

Our study presents a novel nomogram developed and validated for predicting graft failure in patients undergoing Fs-PKP. This nomogram, incorporating five aforementioned risk factors, has demonstrated effective predictive capability, as evidenced by its concordance index (C-index) of 0.72 in the training group and 0.66 in the validation group. Its reliability across various time intervals and clinical scenarios, affirmed by time-dependent ROC curves and calibration plots, reflects its accuracy in mirroring real-world clinical outcomes. The clinical utility of the nomogram, underscored by DCA, confirms its substantial net benefit in diverse clinical settings, reinforcing its role in effectively guiding the management of Fs-PKP patients. This innovation marks a significant contribution to the field of ophthalmic surgery in China, offering precise prognostic insights in an area where the application of predictive models has been limited [11, 24, 25]. While a renowned predictive

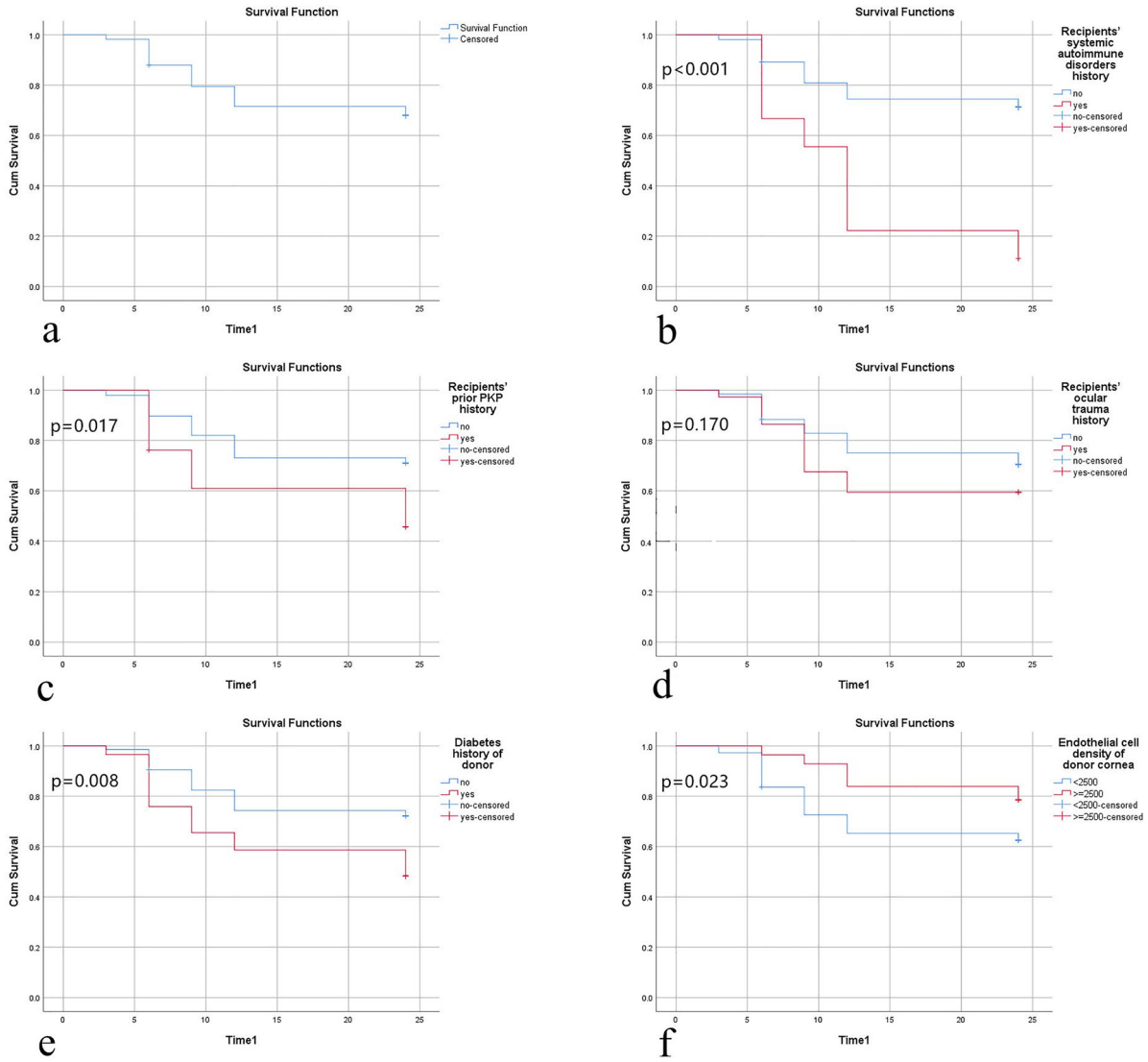


Fig. 2 Overall survival rate and its correlation with independent prognostic factors. **a** Overall graft failure-free survival. Stratified graft failure-free survival by recipients' systemic autoimmune disorders history (**b**), recipients' prior PKP history (**c**), and recipients' ocular trauma history (**d**), diabetes history of donor (**e**), endothelial cell density of donor cornea (**f**). *P* value was calculated by log-rank test. *PKP* prior penetrating keratoplasty

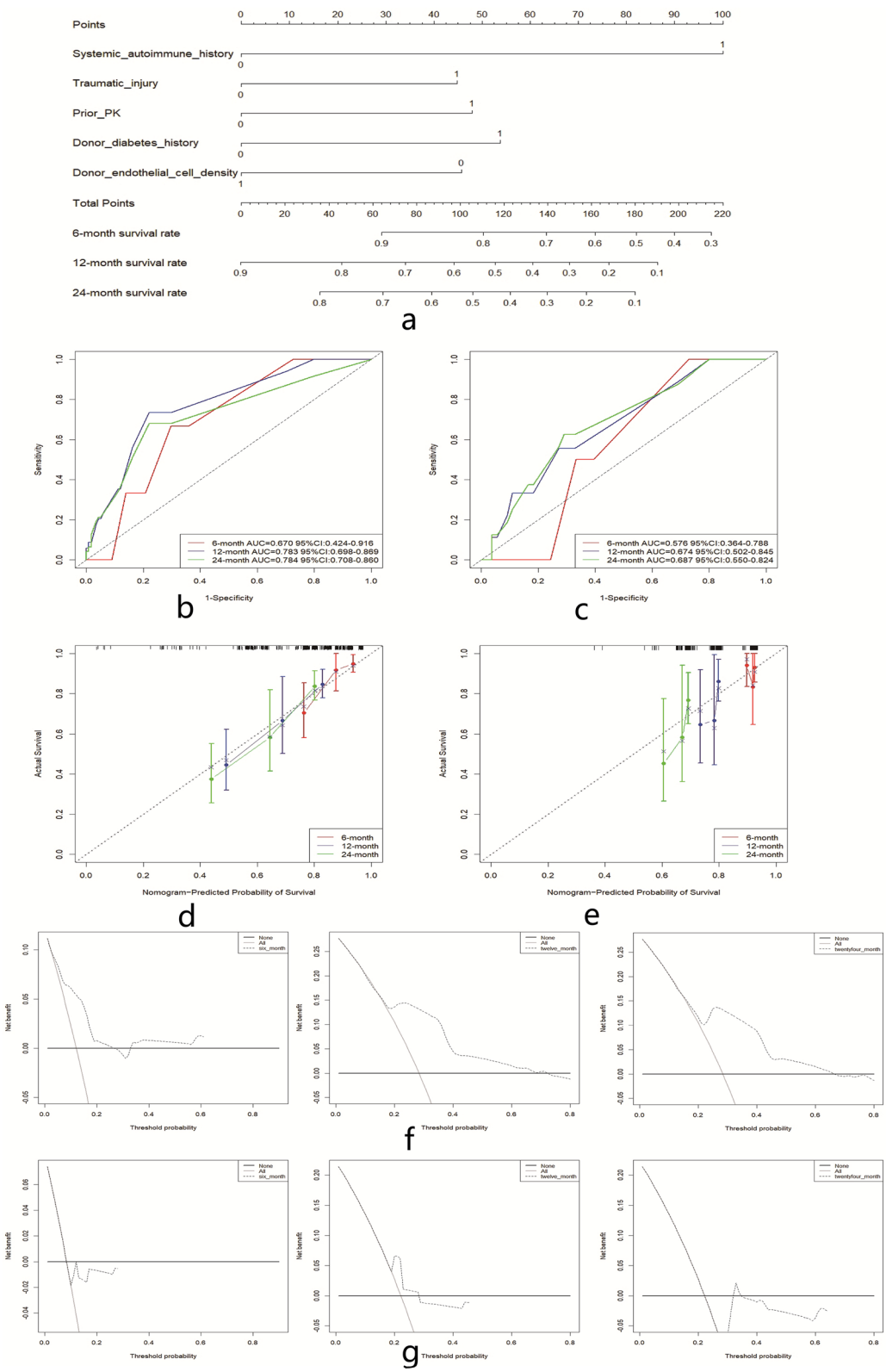
model from the United States for conventional PKP, identified eleven variables significantly associated with graft failure. These variables encompass a range of conditions, from active microbial infection at the time of PK to the presence of intraocular silicone oil and extensive corneal neovascularization. However, our findings reveal that the severe conditions highlighted in previous studies, such as intraocular silicone oil and widespread corneal neovascularization, are notably absent in our Fs-PKP patient cohort. This discrepancy could be attributed to the relatively milder ocular conditions of patients selected for Fs-PKP. Additionally, guided by ethical considerations, our approach included preemptive interventions for specific, well-defined risk factors (e.g., active microbial infection at the time of PK, glaucoma) prior to surgery. Given these observations, we posit that the nomogram developed for traditional PK may not

be directly applicable to predicting outcomes in Fs-PKP patients. This assertion is supported by our model's distinct focus and its adaptation to the unique clinical profiles observed in the Chinese Fs-PKP patient demographic. Consequently, our study not only fills a critical gap in the existing literature but also highlights the need for specialized predictive models that cater to the specific requirements of different surgical techniques and patient populations. This nuanced approach is essential for optimizing patient outcomes in the realm of corneal transplantation surgery.

A key strength of our study is its distinction as the most extensive research focused on developing a clinical predictive model for corneal transplant failure specifically in Chinese patients undergoing Fs-PKP. We conducted an in-depth analysis of risk factors contributing to graft failure, covering a broad spectrum that encompasses recipient characteristics, donor attributes, and surgical variables. Moreover, our study extends beyond the mere development of the model, emphasizing rigorous validation of its multidimensional effectiveness. This thorough methodology enhances the model's clinical applicability and reliability, making a significant contribution to the domain of ophthalmic transplantation within the Chinese healthcare context.

Our study represents one of the most comprehensive investigations into Fs-PKP within the Chinese demographic, despite its limitations arising from a modest cohort size. This limitation largely stems from the nascent stage of Fs-PKP technology adoption in China, which restricts the pool of suitable candidates and the length of the feasible follow-up period. Recognizing the importance of early dissemination, we consider it crucial to publish our data now, even though our follow-up period is limited to 2 years. Our study's initial findings, prompted by its innovative contributions and potential clinical relevance, merit prompt sharing. However, as a single-center study, the specificity of our clinical practices and patient demographics might limit the broader applicability of our results across different geographical and clinical settings. In acknowledging these limitations, we emphasize the preliminary yet significant value of our work, laying the groundwork for future research in this area.

To optimize the application of Fs-PKP within clinical settings, it is imperative that future investigations aim to surmount the existing methodological limitations. A pivotal step in this direction involves the augmentation of study cohorts and the elongation of observational periods. Such measures would permit a more exhaustive appraisal of Fs-PKP's long-term therapeutic efficacy and safety profile. Extending follow-up durations is crucial for the accurate delineation of the sustained impacts of Fs-PKP and the vigilant surveillance for any late-onset adverse effects. Moreover, the intersection of deep learning and artificial intelligence methodologies with clinical datasets, inclusive of imaging modalities and diverse multi-modal data, represents a promising frontier for enhancing prognostic models associated with Fs-PKP. The application of these sophisticated analytical tools can significantly improve the precision and dependability of outcome predictions for Fs-PKP by facilitating the nuanced identification of patient-specific attributes and response patterns. This approach heralds the advent of tailored therapeutic strategies, offering nuanced decision-making support for the administration of Fs-PKP. Further, building on the foundational work of nomograms, there exists an opportunity to construct and empirically validate network-based scoring frameworks aimed at the pre-treatment appraisal of risk and therapeutic outcome probabilities. The development of such scoring systems promises to enrich clinicians' insights into patient-specific prognoses and underpin informed clinical decision-making. The establishment of empirically validated frameworks would not only fortify the decision-making process but also contribute to the refinement of Fs-PKP treatment paradigms. Importantly, these scoring systems would enable the robust validation and reproducibility of research findings, thereby reinforcing the evidence base and facilitating the broader adoption of Fs-PKP in clinical practice.


Points
Systemic_autoimmune_history
Traumatic_injury
Prior_PK
Donor_diabetes_history
Donor_endothelial_cell_density
Total Points
6-month survival rate
12-month survival rate
24-month survival rate
a
Sensitivity
1-Specificity
6-month AUC=0.670 95%CI:0.424-0.916
12-month AUC=0.783 95%CI:0.698-0.869
24-month AUC=0.784 95%CI:0.708-0.860
b
6-month AUC=0.576 95%CI:0.364-0.788
12-month AUC=0.674 95%CI:0.502-0.845
24-month AUC=0.687 95%CI:0.550-0.824
c
Actual Survival
Nomogram−Predicted Probability of Survival
6-month
12-month
24-month
d
e
Net benefit
Threshold probability
None
All
six_month
twelve_month
twentyfour_month
f
g

◂**Fig. 3** Construction and validation of nomogram for graft failure in Fs-PKP recipients. **a** Nomogram for predicting 6-, 12-, and 24-month graft failure-free survival for patients in the training cohort; **b** the time-dependent ROC curves for the training cohort; **c** the time-dependent ROC curves for the validation cohort; **d** the calibration curve for the training cohort; **e** the calibration curve for the validation cohort; **f** the decision curve analysis for the training cohort; **g** the decision curve analysis for the validation cohort. *fs-PKP* femtosecond laser-assisted penetrating keratoplasty, *ROC* receiver operating characteristics

CONCLUSIONS

Our study has successfully developed and validated a predictive model specifically designed for Chinese patients undergoing Fs-PKP. By incorporating critical factors, including the recipient's autoimmune history, history of ocular trauma, prior PKP, the donor's history of diabetes, and the endothelial cell density of the donor corneas, our model represents a significant advancement in the field of corneal transplantation. This development markedly enhances the preoperative prediction and management strategies for Chinese patients at risk of Fs-PKP graft failure, offering a tailored approach to mitigate potential complications and improve surgical outcomes.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. The authors, Junxin Ma, Xueqian Cao, Yang Liu, Jin Huang, Xinyu Pan, Yuting Gong, Zhongguo Li, and Linnong Wang, declare that they have no conflict of interest in relation to this article. All authors have reviewed the manuscript and have agreed to the submission without any reservations.

Ethical Approval. The study was approved by the ethics committee of Nanjing First Hospital (KY20240318-KS-01) and adhered to the tenets of the Declaration of Helsinki of 1964. The requirement for informed consent was waived due to the retrospective nature of the study.

REFERENCES

1. Gain P, Jullienne R, He Z, et al. Global survey of corneal transplantation and eye banking. JAMA Ophthalmol. 2016;134(2):167–73.

2. Deshmukh R, Stevenson LJ, Vajpayee RB. Laser-assisted corneal transplantation surgery. Surv Ophthalmol. 2021;66(5):826–37.

3. Daniel MC, Böhringer D, Maier P, et al. Comparison of long-term outcomes of femtosecond laser-assisted keratoplasty with conventional keratoplasty. Cornea. 2016;35(3):293–8.

4. Levinger E, Trivizki O, Levinger S, et al. Outcome of "Mushroom" pattern femtosecond laser-assisted keratoplasty versus conventional penetrating keratoplasty in patients with keratoconus. Cornea. 2014;33(5):481–5.

5. Fung SSM, Aiello F, Maurino V. Outcomes of femtosecond laser-assisted mushroom-configuration keratoplasty in advanced keratoconus. Eye. 2016;30(4):553–61.

6. Williams KA, Lowe M, Bartlett C, et al. Risk factors for human corneal graft failure within the Australian corneal graft registry. Transplantation. 2008;86(12):1720–4.

7. Borderie VM, Boëlle PY, Touzeau O, et al. Predicted long-term outcome of corneal transplantation. Ophthalmology. 2009;116(12):2354–60.

8. Tan DTH, Janardhanan P, Zhou H, et al. Penetrating keratoplasty in Asian eyes: the Singapore corneal transplant study. Ophthalmology. 2008;115(6):975-982.e1.

9. Patel SV, Hodge DO, Bourne WM. Corneal endothelium and postoperative outcomes 15 years after penetrating keratoplasty. Am J Ophthalmol. 2005;139(2):311–9.

10. Thompson RW Jr, Price MO, Bowers PJ, et al. Long-term graft survival after penetrating keratoplasty. Ophthalmology. 2003;110(7):1396–402.

11. Barraquer RI, Pareja-Aricò L, Gómez-Benlloch A, et al. Risk factors for graft failure after penetrating keratoplasty. Medicine. 2019;98(17): e15274.

12. Hicks CR, MacVie O, Crawford GJ, et al. A risk score as part of an evidence-based approach to the selection of corneal replacement surgery. Cornea. 2005;24(5):523–30.

13. Shiuey EJ, Zhang Q, Rapuano CJ, et al. Development of a nomogram to predict graft survival after penetrating keratoplasty. Am J Ophthalmol. 2021;226:32–41.

14. Liu Y, Li X, Li W, et al. Systematic review and meta-analysis of femtosecond laser–enabled keratoplasty versus conventional penetrating keratoplasty. Eur J Ophthalmol. 2021;31(3):976–87.

15. Anshu A, Li L, Htoon HM, et al. Long-term review of penetrating keratoplasty: a 20-year review in Asian eyes. Am J Ophthalmol. 2021;224:254–66.

16. Kamiya K, Kobashi H, Shimizu K, et al. Clinical outcomes of penetrating keratoplasty performed with the VisuMax femtosecond laser system and comparison with conventional penetrating keratoplasty. PLoS One. 2014;9(8): e105464.

17. Gaster RN, Dumitrascu O, Rabinowitz YS. Penetrating keratoplasty using femtosecond laser-enabled keratoplasty with zig-zag incisions versus a mechanical trephine in patients with keratoconus. Br J Ophthalmol. 2012;96:1195–9.

18. Chamberlain WD, Rush SW, Mathers WD, et al. Comparison of femtosecond laser-assisted keratoplasty versus conventional penetrating keratoplasty. Ophthalmology. 2011;118(3):486–91.

19. van Rij G, Saelens IEY, Bartels MC. Femtosecond laser versus manual dissection for top hat penetrating keratoplasty. Br J Ophthalmol. 2010;94(1):139.

20. Kwon HY, Hyon JY, Jeon HS. Effect of donor age on graft survival in primary penetrating keratoplasty with imported donor corneas. Korean J Ophthalmol. 2020;34(1):35–45.

21. Sugar A, Gal RL, Kollman C, et al. Factors associated with corneal graft survival in the cornea donor study. JAMA Ophthalmol. 2015;133(3):246–54.

22. Alice LY, Kaiser M, Schaumberger M, et al. Donor-related risk factors and preoperative recipient-related risk factors for graft failure. Cornea. 2014;33(11):1149–56.

23. Alio JL, Montesel A, El Sayyad F, et al. Corneal graft failure: an update. Br J Ophthalmol. 2020;105:1049–58.

24. Cherkas E, Cinar Y, Zhang Q, et al. Development of a nomogram to predict graft survival after Descemet stripping endothelial keratoplasty. Cornea. 2022;42(1):20–6.

25. Arnalich-Montiel F, de-Arriba-Palomero P, Muriel A, et al. A risk prediction model for endothelial keratoplasty after uncomplicated cataract surgery in Fuchs endothelial corneal dystrophy. Am J Ophthalmol. 2021;231:70–8.