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Original Article

Preoperative and postoperative risk factors for persistent dry eye after corneal refractive surgery in ultra-high myopia: a retrospective cohort study

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Abstract: Objective: To identify risk factors for persistent dry eye after refractive surgery in patients with ultra-high myopia and their prognostic value. Methods: Data from 260 patients were analyzed. Least absolute shrinkage and selection operator regression screened preoperative variables. Random forest, Extreme Gradient Boosting, multivariate logistic regression, mediation, and interaction analyses were used to identify predictors and mechanisms of persistent dry eye (≥ 3 months). Results: Persistent dry eye occurred in 33.1% of patients (86/260). Eight preoperative predictors were identified. Elevated Ocular Surface Disease Index (OSDI) (odds ratio [OR] = 1.483) and corneal fluorescein staining (CFS) (OR = 7.154) were independent risk factors; prolonged tear film breakup time (TBUT) (OR = 0.292), no systemic history (OR = 0.042), and normal meibomian gland dysfunction (MGD) (OR = 0.042) were protective. Age and Schirmer test were marginally significant. Medication adherence fully mediated the effect of age on dry eye duration, while ocular inflammation partly mediated the effect of photorefractive keratectomy surgery. A significant synergistic interaction was found between postoperative inflammation and medication adherence ($P < 0.05$). Conclusion: Persistent dry eye after refractive surgery for ultra-high myopia is influenced by multiple factors. Preoperative OSDI, CFS, TBUT, systemic history, MGD, daily screen time, medication adherence, and inflammation play important roles. Individualized perioperative management targeting these factors may improve prognosis.

Keywords: Ultra-high myopia, refractive surgery, postoperative dry eye, prognosis

Introduction

Ultra-high myopia usually refers to a myopia degree of ≥ -10.00 diopters (D) [1]. As a type of refractive error with a high worldwide incidence, it not only seriously affects the visual quality and daily life of patients but also easily causes a series of blinding fundus complications such as retinal detachment and maculopathy, making it an urgent visual public health problem [2, 3]. With the rapid development of refractive surgery technology, all-femtosecond laser small-incision lenticule extraction (SMILE) [4] has become a mainstream correction option [5] for patients with ultra-high myopia because of its advantages of minimal trauma, rapid postoperative recovery, and a wide correction range. However, the prevention and control of postoperative complications is still the focus of clinical attention. As one of the most common complications after refractive surgery, dry eye has an incidence of 30%-70% [6]. It not only causes dry eye, foreign body sensation, burning sensation, and other discomfort symptoms but also affects postoperative visual stability, reduces patient satisfaction with surgery, and may even require long-term intervention. Therefore, it is of great clinical value to clarify its risk factors and effect on prognosis [7].

At present, research on dry eye after refractive surgery has made some progress, but there are still many shortcomings. First, existing studies focus on the observation of short-term (within 1 year) complications [8], whereas the effect of surgical trauma on corneal nerves and tear film function in patients with ultra-high myopia may be long-term [9]. Data on the correlation between long-term visual stability and the occurrence of dry eye during long-term follow-up are relatively scarce [10]. Second, the analysis of

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risk factors for postoperative dry eye is mostly limited to single variables or traditional regression models, lacking accurate screening and joint validation using multiple algorithms. In addition, research on preoperative indicators such as corneal thickness, tear film breakup time (TBUT), and history of blepharitis, as well as postoperative variables such as medication adherence and eye-use habits, remain insufficient [11, 12]. At the same time, most existing studies focus on the identification of risk factors, whereas the mechanisms through which dry eye affects patient prognosis, such as visual acuity fluctuations and recurrence of complications, have been less explored. In particular, the analysis of mediation effect and interaction effect is lacking, making it difficult to clarify the action path and synergistic effect among the factors [13].

Based on the above research gaps, this study used a retrospective cohort design to systematically explore the risk factors for dry eye after refractive surgery in patients with ultra-high myopia and its effect on prognosis, so as to provide a scientific reference for the clinical development of individualized preoperative evaluation plan, early prevention and control strategies for postoperative dry eye, and prognostic improvement measures. This will improve the long-term safety and patient satisfaction of refractive surgery in patients with ultra-high myopia.

Patients and methods

General information

This study was a single-center retrospective cohort study, including 260 adult patients (260 eyes) who underwent refractive surgery in the Department of Ophthalmology of Xining First People's Hospital from January 2020 to December 2023. All patients had ultra-high myopia (spherical equivalent refractive error ≤ -10.00 D). The surgical methods included all-femtosecond laser SMILE, femtosecond laser-assisted laser *in situ* keratomileusis (FS-LASIK), and excimer laser photorefractive keratectomy (PRK). See **Table 1** for patient information. The study protocol was approved by the Ethics Committee of Xining First People's Hospital (2026-005). Due to the retrospective nature of the study and the use of de-identified existing data, the requirement for individual informed consent was waived.

Inclusion criteria: ① age ≥ 18 years; ② spherical equivalent refractive error ≤ -10.00 D; ③ underwent SMILE, FS-LASIK, or PRK; ④ complete postoperative follow-up data were available. Given the different pathophysiologic mechanisms of corneal nerve injury and inflammation between surface ablation (PRK) and flap-based procedures (SMILE and FS-LASIK), the surgical method was included as a key covariate, and subgroup analyses were performed. Exclusion criteria: ① previous history of ocular surgery or trauma; ② glaucoma, retinopathy, or other ocular diseases; ③ serious systemic diseases (such as uncontrolled diabetes or autoimmune diseases); ④ other severe ocular diseases or serious systemic diseases; ⑤ missing or incomplete postoperative follow-up data.

Data collection and standardization

All clinical data in this study were obtained from the electronic medical record system of the Department of Ophthalmology of Xining First People's Hospital and were independently extracted by two ophthalmologists who had received standardized training. The extracted data included general demographic characteristics, preoperative ocular surface and systemic conditions, surgery-related parameters, postoperative follow-up indicators, and other relevant variables.

Main outcome measures [14]: The primary outcome was persistent postoperative dry eye, defined as the presence of dry eye symptoms (e.g., dryness and foreign body sensation) combined with objective signs (TBUT ≤ 5 seconds or corneal fluorescein staining [CFS] score ≥ 2) lasting for ≥ 3 months after surgery (binary: yes/no). This definition distinguishes persistent cases from transient postoperative dry eye.

Preoperative predictors included age, body mass index, Ocular Surface Disease Index (OSDI), TBUT, Schirmer test value, CFS score, central corneal thickness, intraocular pressure, duration of contact lens wear, surgical method, systemic history, medication history, and meibomian gland dysfunction (MGD).

Postoperative prognostic variables included daily screen time, living environment, degree of ocular inflammation, medication adherence, sleep quality, postoperative complications, and other relevant variables.

Table 1. Baseline characteristics of patients

Variable	Level	Dry eye group (n = 86)	Normal group (n = 174)	Test statistic	*P* value
Continuous variables (mean ± standard deviation)				t value	
Age (years)		32.16 ± 5.38	29.86 ± 5.76	-3.10	0.002
BMI (kg/m^2)		23.01 ± 3.12	21.91 ± 2.87	-2.84	0.005
OSDI score		25.36 ± 8.21	14.86 ± 5.50	-12.22	< 0.001
TBUT (seconds)		5.84 ± 2.07	10.27 ± 2.31	15.03	< 0.001
Schirmer test (mm/5 min)		8.24 ± 2.64	12.98 ± 3.02	12.42	< 0.001
CFS score		2.57 ± 1.13	1.02 ± 0.79	-12.82	< 0.001
Postoperative residual spherical equivalent (diopters)		-5.30 ± 1.84	-4.52 ± 1.96	3.05	0.002
CCT (μm)		521.87 ± 30.83	528.38 ± 29.85	1.64	0.103
IOP (mmHg)		15.17 ± 1.87	15.16 ± 2.15	-0.04	0.968
Contact lens wear duration (years)		6.00 ± 4.70	2.52 ± 3.27	-6.95	< 0.001
Ablation depth (μm)		81.19 ± 14.03	68.41 ± 14.93	-6.62	0.001
Suction time (seconds)		25.59 ± 5.31	21.38 ± 4.54	-6.65	< 0.001
Daily screen time (hours)		5.84 ± 2.10	4.33 ± 1.92	-5.76	< 0.001
Recovery rate (%)		69.77 ± 9.58	90.12 ± 7.21	19.14	< 0.001
Flap thickness (μm)		109.05 ± 10.69	100.30 ± 9.09	-4.52	0.001
Categorical variables, n (%)				X^2	*P* value
Gender	Male	36 (41.9)	90 (51.7)	2.24	0.134
	Female	50 (58.1)	84 (48.3)		
Smoking history	No	68 (79.1)	136 (78.2)	0.03	0.867
	Yes	18 (20.9)	38 (21.8)		
Systemic history	Allergy	24 (27.9)	30 (17.2)	9.68	0.008
	None	50 (58.1)	133 (76.4)		
	Autoimmune disease	12 (14.0)	11 (6.3)		
Medication use history	Antidepressants	10 (11.6)	11 (6.3)	15.84	< 0.001
	Antihistamines	18 (20.9)	11 (6.3)		
	None	58 (67.4)	152 (87.4)		
MGD	Dysfunction	61 (70.9)	48 (27.6)	44.41	< 0.001
	Normal	25 (29.1)	126 (72.4)		
Contact lens history	No	29 (33.7)	100 (57.5)	12.99	< 0.001
	Yes	57 (66.3)	74 (42.5)		
Surgical procedure	FS-LASIK	42 (48.8)	64 (36.8)	12.01	0.002
	PRK	27 (31.4)	38 (21.8)		
	SMILE	17 (19.8)	72 (41.4)		
Postoperative complications	No	64 (74.4)	159 (91.4)	13.56	< 0.001
	Yes	22 (25.6)	15 (8.6)		
Surgeon group	A	44 (51.2)	79 (45.4)	0.77	0.381
	B	42 (48.8)	95 (54.6)		
Ocular inflammation	Mild	30 (34.9)	105 (60.3)	15.54	< 0.001
	Moderate	46 (53.5)	53 (30.5)		
	Severe	10 (11.6)	16 (9.2)		
Medication adherence level	Irregular	32 (37.2)	28 (16.1)	14.46	< 0.001
	Regular	54 (62.8)	146 (83.9)		
Living environment type	Dry/polluted	28 (32.6)	29 (16.7)	13.97	0.001
	Air-conditioned	29 (33.7)	46 (26.4)		
	Normal	29 (33.7)	99 (56.9)		
Sleep quality	Poor (late sleep/insomnia)	52 (60.5)	58 (33.3)	17.36	< 0.001
	Good	34 (39.5)	116 (66.7)		
Visual symptoms	Fluctuating vision	35 (40.7)	35 (20.1)	60.82	< 0.001
	None	21 (24.4)	127 (73.0)		
	Glare	30 (34.9)	12 (6.9)		
Patient satisfaction	Dissatisfied	19 (22.1)	21 (12.1)	13.66	0.001
	Satisfied	40 (46.5)	122 (70.1)		
	Neutral	27 (31.4)	31 (17.8)		

Note: Postoperative residual spherical equivalent refers to postoperative refractive status. The inclusion criterion was preoperative spherical equivalent refractive error ≤ -10.00 diopters, with a mean preoperative spherical equivalent of -11.45 ± 1.52 diopters in the entire cohort. Abbreviations: BMI, body mass index; OSDI, Ocular Surface Disease Index; TBUT, tear film breakup time; CFS, corneal fluorescein staining; CCT, central corneal thickness; IOP, intraocular pressure; MGD, meibomian gland dysfunction; FS-LASIK, femtosecond laser-assisted laser in situ keratomileusis; PRK, photorefractive keratectomy; SMILE, small-incision lenticule extraction.

Multiple imputation was used to handle missing values, with five imputations performed to reduce data bias. Continuous variables were standardized using Z-score normalization to eliminate dimensional differences and facilitate subsequent model construction.

Model building method

A least absolute shrinkage and selection operator (LASSO) regression model was first used to regularize and screen preoperative candidate variables. The optimal regularization parameter (λ) was determined through 10-fold cross-validation (CV), and the coefficients of redundant variables were reduced to zero to achieve variable selection and prevent overfitting. Based on the selected core variables, a random forest prediction model was further constructed. The Gini coefficient was used to evaluate the importance of each variable, and the area under the receiver operating characteristic (ROC) curve (AUC) was used to evaluate model performance. At the same time, a multivariable logistic regression model was used to identify independent risk factors for postoperative dry eye, and effect sizes were expressed as odds ratio (OR) and 95% confidence intervals (CIs).

Based on postoperative indicators, random forest and Extreme Gradient Boosting (XGBoost) prognostic models were constructed. The Gini coefficient and gain value were used to evaluate variable importance, and the ROC curve was used to assess the discrimination ability of the models for persistent postoperative dry eye lasting ≥ 3 months. Furthermore, mediation analysis was used to explore the pathways through which age and surgical method affected dry eye duration by medication adherence and ocular inflammation. Interaction analysis was performed to clarify the synergistic effect of ocular inflammation and medication adherence on the prognosis of postoperative dry eye.

Statistical methods

All statistical analyses were performed using SPSS 26.0 and R 4.2.1. Continuous variables were presented as mean ± standard deviation, and categorical variables as number (%). A two-sided significance level (alpha) of 0.05 was used for all tests.

Missing data handling: Missing values in preoperative and postoperative variables (overall missing rate < 8%) were imputed using the multivariate imputation by chained equations algorithm (R package mice, version 3.14.0). Five imputed datasets were generated, with 20 iterations per dataset. The imputation model included all variables listed in **Table 1** plus the outcome (persistent dry eye). Results were pooled using Rubin's rules.

Variable selection (LASSO regression): LASSO regression with L1 penalty was applied to the 13 preoperative candidate variables. The optimal regularization parameter λ was determined by 10-fold CV minimizing the binomial deviance. The "1-standard error" rule was also examined for model parsimony, but the λ that gave the minimum CV deviance was chosen for final variable selection. All continuous predictors were Z-score standardized before LASSO to ensure coefficient comparability. The analysis was performed using the glmnet package (version 4.1-4) in R.

Random forest (preoperative prediction model): A random forest classifier was built on the 8 variables selected by LASSO. The model was trained using the randomForest package (version 4.7-1.1) with the following parameters: number of trees = 1000, mtry = $\sqrt{P}$ = 3 (where P = number of predictors), minimum node size = 5. Variable importance was assessed by the mean decrease in Gini index averaged over all trees. Model discrimination was evaluated by the AUC calculated on the out-of-bag samples, not on the training set, to reduce overfitting.

Multivariate logistic regression: To identify independent risk factors for persistent dry eye, a multivariate logistic regression model was fitted using the same 8 LASSO-selected variables. The model was estimated by maximum likelihood with a logit link function. Wald χ^2 tests were used to calculate P-values for each coefficient. No stepwise selection was applied because variable selection had already been performed by LASSO. Model calibration was assessed by the Hosmer-Lemeshow goodness-of-fit test (P = 0.43, indicating adequate calibration). Results are reported as ORs with 95% CIs derived from profile likelihood.

Postoperative prognostic modeling (random forest and XGBoost):

Random forest: Using the same randomForest parameters as above (ntree = 1000, mtry =

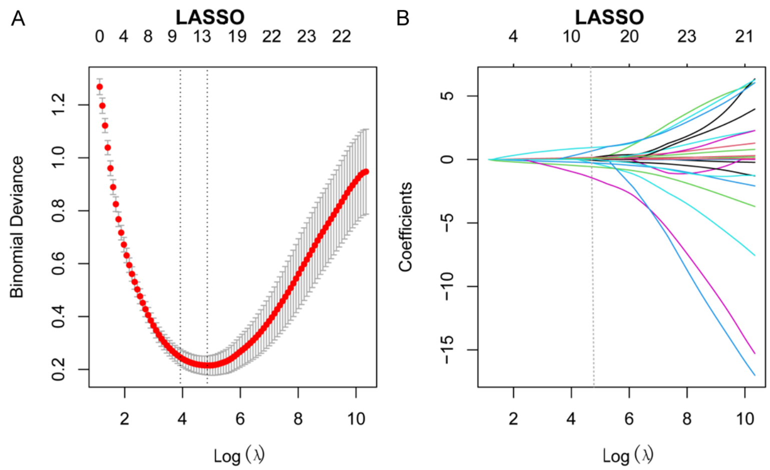

Figure 1. Visualization of LASSO regression screening results. A. CV curve of binomial deviance versus log(λ). The red curve represents the mean binomial deviance, and the gray bars represent the standard error. The two vertical dashed lines indicate the optimal λ (λ = 0.007781136, log(λ) ≈ 4.5) and the λ value selected according to the 1-standard error criterion, respectively. B. Coefficient path plot of the LASSO regression model. Each colored curve represents the trajectory of a candidate variable coefficient as a function of log(λ). At the optimal λ, only eight variables retained non-zero coefficients and were identified as the core predictors of postoperative dry eye. Abbreviations: LASSO, least absolute shrinkage and selection operator; CV, cross-validation.

$\sqrt{(11)}$ ≈ 3, nodesize = 5) on the 11 postoperative variables. The out-of-bag AUC was reported.

XGBoost: The model was built using the xgboost package (version 1.6.0.1) with the following tuned parameters: learning rate (eta) = 0.1, maximum tree depth = 4, number of boosting rounds = 150 (determined by early stopping with a 10-fold CV, stopping criterion = 10 rounds without improvement), subsample = 0.8, colsample_bytree = 0.8. The evaluation metric was binary logistic loss (logloss). Variable importance was measured by gain (the average improvement in model performance when a variable was used in a split).

Mediation analysis: The mediating role of medication adherence (for age) and ocular inflammation (for PRK surgery) was tested using the causal mediation framework (Imai et al., 2010) implemented in the R package mediation (version 4.5.0). Quasi-Bayesian Monte Carlo simulations with 1000 bootstrap resamples were used to estimate average causal mediation effects (ACME), average direct effects (ADE), and total effects. All models included the same set of covariates listed in **Table 1** as confounders. A mediation effect was considered significant if the 95% CI for ACME (based on the bootstrap percentile method) did not include zero.

Interaction analysis: The interaction between postoperative ocular inflammation (ordinal: mild, moderate, severe) and medication adherence (binary: regular vs. irregular) on persistent dry eye (≥ 3 months) was examined by adding their product term to a logistic regression model that also included all postoperative variables. The significance of the interaction was tested using the likelihood ratio test comparing models with and without the interaction term. *Post-hoc* simple slopes analysis was performed to estimate the effect of medication adherence at each level of inflammation, with *P*-values adjusted for multiple comparisons using the Bonferroni correction.

All code and output are available from the corresponding author upon reasonable request.

Results

LASSO regression results

To avoid the risk of multicollinearity and overfitting, a LASSO regression model was used to screen candidate predictors. By introducing an L1 regularization term, the model shrinks some variable coefficients to zero, thereby achieving variable selection and feature reduction. In this study, 10-fold CV was used to determine λ, and binomial deviance was used as the model performance evaluation metric. As shown in **Figure 1A**, the binomial deviance reached its minimum value when λ = 0.007781136 (log(λ) ≈ 4.5), which was therefore selected as the optimal regularization parameter. At the same time, the λ value under the 1-standard error criterion was also identified to evaluate model robustness. At the optimal λ, the model maintained predictive performance while achieving variable selection and reducing overfitting.

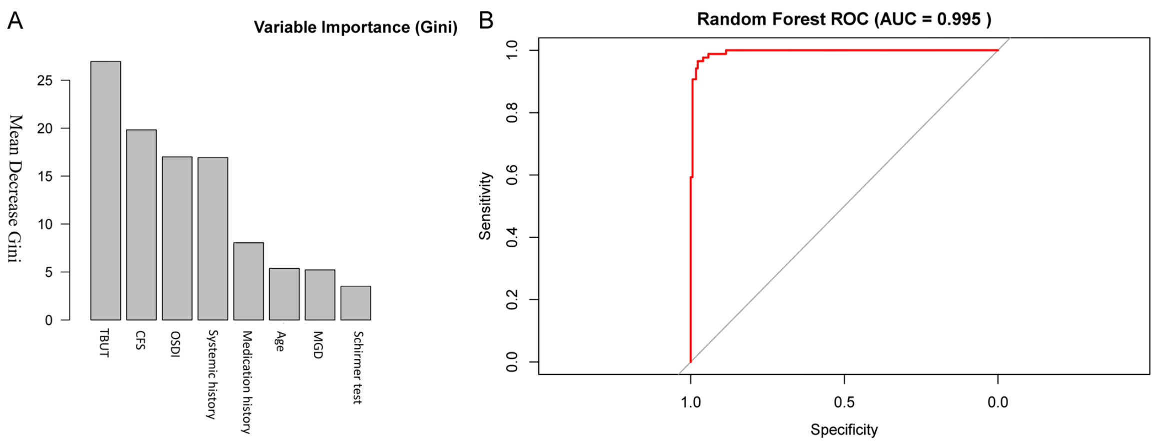

Figure 2. Results of the random forest model constructed using preoperative predictors. A. Variable importance ranking based on the mean decrease in Gini index, showing the contribution of each preoperative predictor to the prediction of postoperative dry eye. Variables are ranked from highest to lowest importance. B. ROC curve of the random forest model. The AUC was 0.995, indicating excellent discriminative performance for predicting postoperative dry eye. Abbreviations: TBUT, tear film breakup time; CFS, corneal fluorescein staining; OSDI, Ocular Surface Disease Index; MGD, meibomian gland dysfunction; ROC, receiver operating characteristic; AUC, area under the curve.

Figure 1B shows the coefficient path plot of the LASSO regression model, illustrating the trajectories of candidate variable coefficients as a function of log(λ). When the λ value was large (log(λ) was small), the coefficients of most variables were shrunk to zero. As the λ value decreased (log(λ) increased), the coefficients of more variables gradually deviated from zero. At the optimal λ (λ = 0.007781136), only eight variables retained non-zero coefficients: age, systemic history, medication history, OSDI, TBUT, Schirmer test value, CFS, MGD.

Preoperative random forest model construction

Based on the eight preoperative variables selected by LASSO regression (age, systemic history, medication history, OSDI, TBUT, Schirmer test value, CFS score, and MGD), a random forest prediction model was constructed to further evaluate variable importance and overall model performance. The variable importance ranking based on the mean decrease in Gini index is shown in **Figure 2A**. TBUT was the most important preoperative indicator of postoperative dry eye. CFS score, OSDI, and systemic history ranked next and also showed relatively high importance. Age, medication history, MGD, and Schirmer test value were relatively less important but still contributed to model prediction. The ROC curve of the random forest model, based on out-of-bag (OOB) predictions, is shown in **Figure 2B**. The model achieved an out-of-bag AUC of 0.995, indicating excellent discriminative performance (**Figure 2B**). However, given that several predictors (OSDI, TBUT, and CFS) are components of the dry eye diagnostic criteria, this high AUC value should be interpreted with caution, as it may reflect conceptual overlap rather than true prognostic value. The primary purpose of this model was variable selection and hypothesis generation rather than clinical deployment as a standalone predictive tool.

Logistic regression results

Multivariable logistic regression analysis was performed using the eight variables selected by LASSO regression. The results showed that a higher OSDI score (OR = 1.483, $P < 0.001$) and a higher CFS score (OR = 7.154, P = 0.002) were independent risk factors for persistent postoperative dry eye. In contrast, a longer TBUT (OR = 0.292, $P < 0.001$), absence of systemic history (OR = 0.042, 95% CI: 0.001-0.510, P = 0.028), and normal MGD status (OR = 0.042, P = 0.006) were identified as independent protective factors. Age (OR = 1.239, 95% CI: 1.011-1.588, P = 0.055) and Schirmer test value (OR = 0.669, 95% CI: 0.417-0.963, P = 0.052) showed borderline statistical significance (**Table 2**).

Table 2. Results of multivariable logistic regression analysis

Variable	Coefficient	Std. Error	z-value	*P* value	OR (95% CI)
Intercept	0.3074	4.4818	0.069	0.945	1.360 (0.00-12236.94)
Age (years)	0.2146	0.1120	1.915	0.055	1.239 (0.995-1.543)
Systemic history					
Allergy history (ref.)					
None	-3.1777	1.4486	-2.194	0.028	0.042 (0.001-0.510)
Autoimmune disease	-2.7809	2.2598	-1.231	0.219	0.062 (0.000-3.607)
Medication history					
Antidepressants (ref.)					
Antihistamines	1.0011	2.3565	0.425	0.671	2.721 (0.017-275.201)
None	-1.5306	1.5717	-0.974	0.330	0.216 (0.009-6.377)
OSDI score	0.3943	0.1135	3.474	< 0.001	1.483 (1.234-1.951)
TBUT (seconds)	-1.2323	0.3459	-3.563	< 0.001	0.292 (0.120-0.496)
Schirmer test (mm/5 min)	-0.4024	0.2074	-1.940	0.052	0.669 (0.445-1.004)
CFS score	1.9677	0.6322	3.113	0.002	7.154 (2.544-32.572)
MGD status					
Dysfunction (ref.)					
Normal	-3.1640	1.1522	-2.746	0.006	0.042 (0.003-0.311)

Note: Multivariable logistic regression analysis was performed to identify independent risk factors for persistent postoperative dry eye. Reference categories for categorical variables are indicated in parentheses. Allergy history, antidepressant use, and MGD dysfunction status served as the reference categories. $P < 0.05$ was considered statistically significant. Abbreviations: Std. Error, standard error; OSDI, Ocular Surface Disease Index; TBUT, tear film breakup time; CFS, corneal fluorescein staining; MGD, meibomian gland dysfunction; OR, odds ratio; CI, confidence interval.

Results of random forest analysis of postoperative indicators

As shown in **Figure 3A**, daily screen time was the most important postoperative predictor, followed by living environment, ocular inflammation, and medication adherence. The partial dependence plot (**Figure 3B**) demonstrated that the predicted probability of persistent postoperative dry eye increased markedly when daily screen time exceeded approximately 6 hours. The ROC curve (**Figure 3C**) showed excellent discriminative performance, with an AUC of 0.997.

XGBoost model results

In the XGBoost prognostic model constructed using postoperative indicators, feature importance ranking based on gain showed that daily screen time had substantially greater importance than the other variables and was the most important postoperative predictor of persistent postoperative dry eye (≥ 3 months) (**Figure 4A**). Ocular inflammation, living environment, medication adherence, and sleep quality ranked next in importance, whereas the remaining variables showed relatively lower importance. Model performance was evaluated using ROC curve analysis. As shown in **Figure 4B**, the model achieved an AUC of 0.951, indicating good discriminative performance for predicting persistent postoperative dry eye (≥ 3 months).

Mediation effect analysis

Mediation analysis identified two important pathways underlying persistent postoperative dry eye (≥ 3 months). The effect of age on persistent postoperative dry eye was fully mediated by medication adherence. Older age was associated with poorer medication adherence, which in turn increased the risk of persistent postoperative dry eye. As shown in **Figure 5A**, the indirect effect (ACME = -0.0050, $P < 0.05$) and total effect (-0.0050, $P < 0.05$) were statistically significant, whereas the direct effect was not significant. The corresponding mediation pathway is illustrated in **Figure 5B**. Compared to the other surgical procedures, the effect of PRK on persistent postoperative dry eye was partially mediated by ocular inflammation. PRK was associated with increased post-

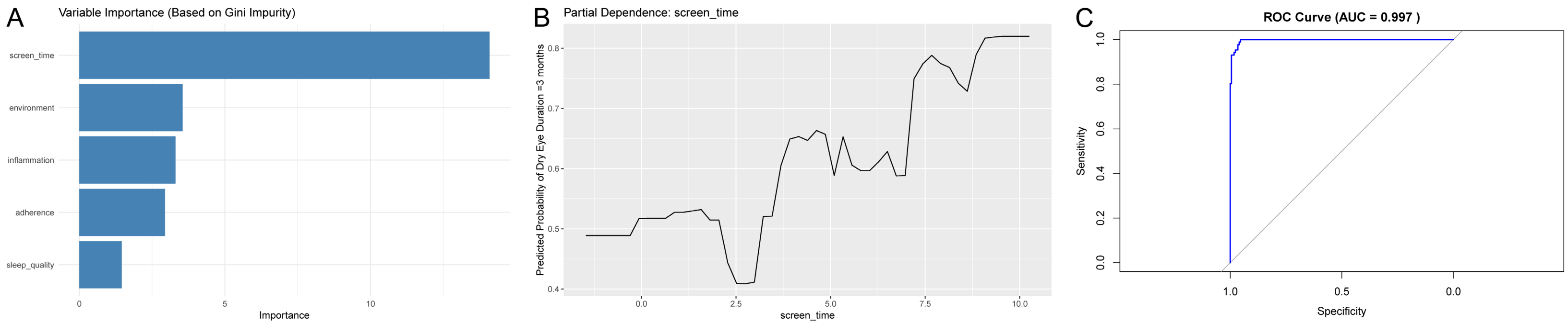

Figure 3. Random forest prognostic model for predicting persistent postoperative dry eye (≥ 3 months) using postoperative predictors. A. Variable importance ranking based on the mean decrease in Gini index, showing the contribution of each postoperative predictor to the prediction of persistent postoperative dry eye (≥ 3 months). Variables are ranked from highest to lowest importance. B. Partial dependence plot showing the relationship between daily screen time and the predictive probability of persistent postoperative dry eye. The predictive probability increased markedly when daily screen time exceeded approximately 6 hours. C. ROC curve of the random forest model. The AUC was 0.997, indicating excellent discriminative performance for predicting persistent postoperative dry eye (≥ 3 months). Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve.

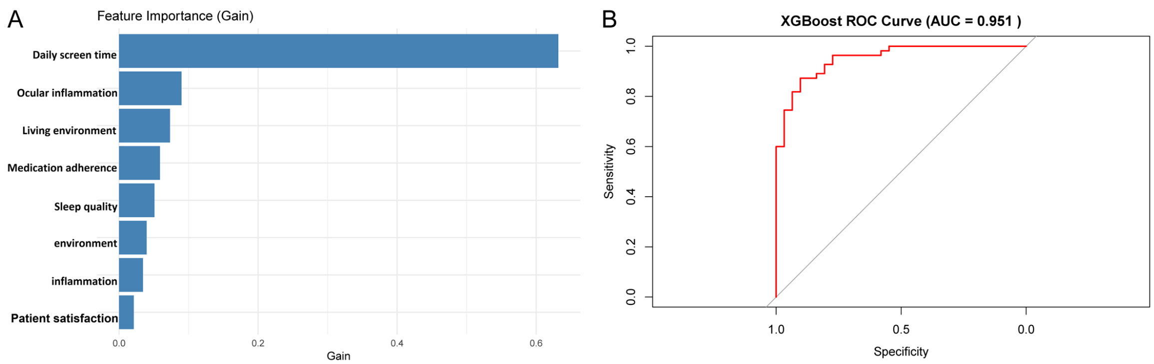

Figure 4. XGBoost prognostic model for predicting persistent postoperative dry eye (≥ 3 months) using postoperative predictors. A. Feature importance ranking based on gain, showing the contribution of each postoperative predictor to the prediction of persistent postoperative dry eye (≥ 3 months). Variables are ranked from highest to lowest importance. B. ROC curve of the XGBoost model. The AUC was 0.951, indicating good discriminative performance for predicting persistent postoperative dry eye (≥ 3 months). Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; XGBoost, Extreme Gradient Boosting.

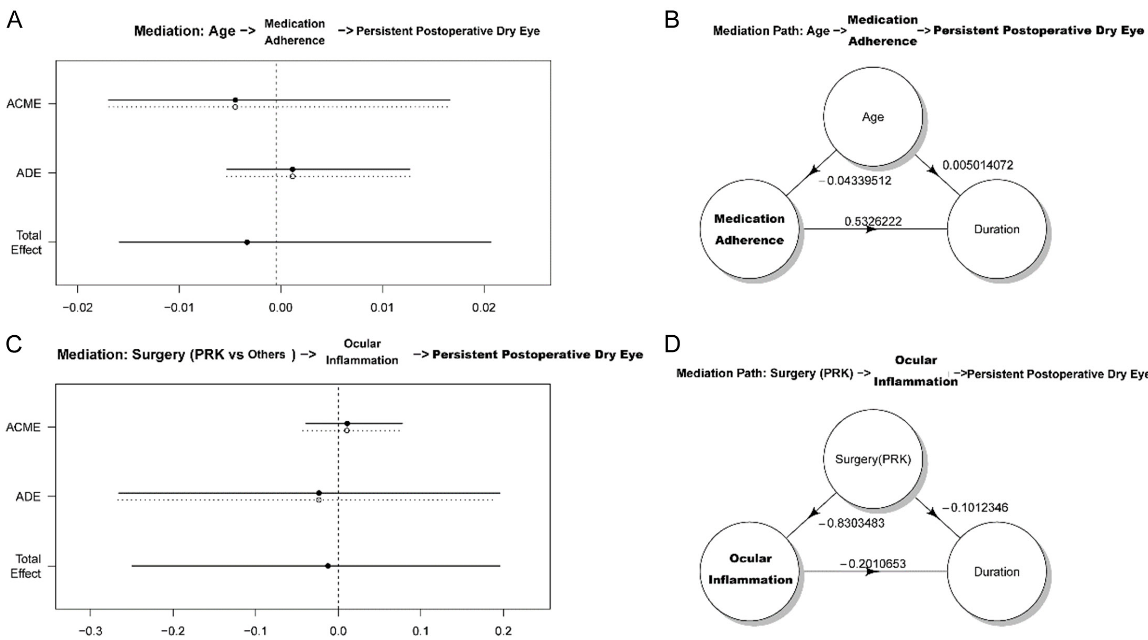

Figure 5. Mediation analysis of persistent postoperative dry eye (≥ 3 months). A. Decomposition of the mediating effect of age on persistent postoperative dry eye through medication adherence, showing the ACME, ADE, total effect, and their 95% CIs. B. Mediation pathway illustrating the relationship among age, medication adherence, and persistent postoperative dry eye. Regression coefficients for each pathway are shown. C. Decomposition of the mediation effect of surgical procedure (PRK versus other procedures) on persistent postoperative dry eye through ocular inflammation, showing the ACME, ADE, total effect, and their 95% CIs. D. Mediation pathway illustrating the relationship among PRK, ocular inflammation, and persistent postoperative dry eye. Regression coefficients for each pathway are shown. Abbreviations: ACME, average causal mediation effect; ADE, average direct effect; CI, confidence interval; PRK, photorefractive keratectomy.

operative ocular inflammation, which subsequently increased the risk of persistent postoperative dry eye. As shown in **Figure 5C**, the indirect effect (ACME = 0.0201, $P < 0.05$), direct effect (ADE = -0.0830, $P < 0.05$), and total effect (-0.1012, $P < 0.05$) were all statistically significant. The corresponding mediation pathway is presented in **Figure 5D**. These findings suggest that medication adherence and ocular inflammation play important mediating

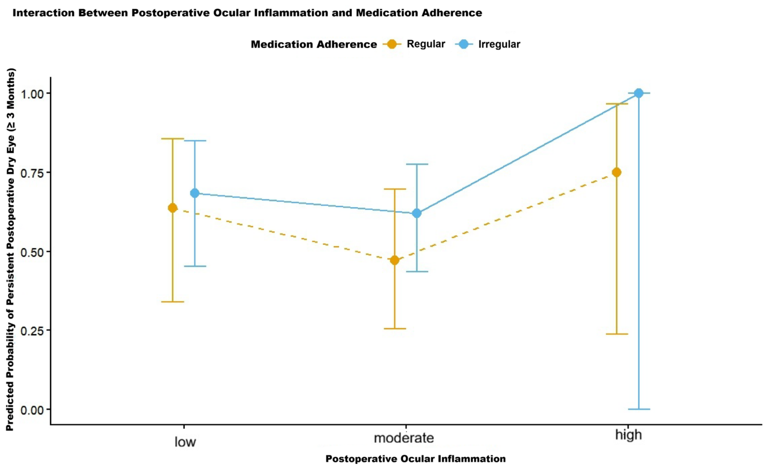

Figure 6. Interaction effect of postoperative ocular inflammation and medication adherence on persistent postoperative dry eye (≥ 3 months). The figure shows the relationship between postoperative ocular inflammation and the predicted probability of persistent postoperative dry eye (≥ 3 months) according to medication adherence status. The orange dashed line represents regular medication adherence, and the blue solid line represents irregular medication adherence. Error bars indicate 95% confidence intervals. The divergence of the two curves suggests a significant interaction between postoperative ocular inflammation and medication adherence, indicating that the effect of medication adherence on the risk of persistent postoperative dry eye becomes more pronounced under conditions of moderate-to-severe inflammation.

roles in the associations of age and surgical procedure with persistent postoperative dry eye, respectively.

Interaction results

The interaction analysis showed a significant interaction between postoperative ocular inflammation and medication adherence with respect to the predicted probability of persistent postoperative dry eye (≥ 3 months) (**Figure 6**, $P < 0.05$). Among patients with poor medication adherence, the predicted probability showed a non-linear pattern: it decreased slightly from mild to moderate inflammation but then rose sharply when inflammation progressed to severe. As shown in **Figure 6**, the difference between regular and irregular medication adherence became more pronounced with increasing severity of postoperative ocular inflammation. This non-linear interaction suggested that the synergistic effect of poor adherence and inflammation is most pronounced only under severe inflammatory conditions, whereas the effect appears attenuated at moderate inflammation levels, possibly due to other competing mechanisms. The synergistic effect of these two factors jointly influenced the risk of persistent postoperative dry eye.

Discussion

In this study, patients with ultra-high myopia undergoing refractive surgery were selected as the research subjects, and the core influencing factors for postoperative dry eye were screened through multi-model joint analysis. The action pathways and synergistic effects of relevant variables on the duration of dry eye were further explored, aiming to provide references for the prevention and control of postoperative dry eye in clinical practice. The results showed that eight preoperative indicators screened by LASSO regression, including age, systemic history, and OSDI, could effectively predict the occurrence of postoperative dry eye, among which TBUT was the most critical preoperative predictor. Multivariate logistic regression further confirmed that increased OSDI and CFS scores were independent risk factors for postoperative dry eye, while prolonged TBUT, no systemic history, and normal meibomian gland function were independent protective factors. In the analysis of postoperative indicators, both random forest and XGBoost models suggested that daily screen time was the core indicator for predicting persistent postoperative dry eye (≥ 3 months). Mediation analysis found that medication adherence and ocular inflammation mediated the effects of age and PRK surgery on persistent postoperative dry eye, respectively. The interaction effect confirmed that ocular inflammation and medication adherence had a synergistic effect on the prognosis of postoperative dry eye. The above results, to a certain extent, reveal the patterns underlying the occurrence and persistence of dry eye after refractive surgery in patients with ultra-high myopia and are also consistent with current knowledge regarding dry eye after refractive surgery [15].

The occurrence of dry eye after refractive surgery is closely related to corneal nerve injury and tear film stability decline, which is also the core mechanism generally recognized in previous studies [16]. This study found that TBUT and meibomian gland functional status were important influencing factors for postoperative dry eye. This is because MGD directly leads to abnormal secretion of the tear lipid layer, and reduced TBUT is a direct manifestation of decreased tear film stability [17]. Both factors further aggravate ocular surface dryness on the basis of corneal microdamage caused by refractive surgery, which is consistent with the findings of many studies on the risk factors for dry eye after refractive surgery [18]. As a comprehensive assessment index of ocular surface discomfort symptoms [19], an elevated OSDI score reflects the presence of ocular surface dysfunction before surgery. Such patients have lower ocular surface tolerance and a higher risk of postoperative dry eye, which also provides a clear reference for preoperative ocular surface evaluation. Postoperative screen time was identified as the core influencing factor for the persistence of dry eye, which is also consistent with clinical practice. Long-term use of electronic screens leads to reduced blink frequency and excessive tear evaporation. At the same time, blue light emitted from screens may aggravate ocular surface inflammation, thereby delaying the relief of dry eye symptoms. This result further confirms the importance of appropriate postoperative eye-use habits for the prevention and control of dry eye [20].

Based on the identification of risk factors, this study further explored the mechanisms underlying the relationships among variables, and found that the effect of age on persistent postoperative dry eye was fully mediated by medication adherence. This may be because older patients pay less attention to postoperative medication and have relatively lower adherence, while irregular medication directly affects the control of ocular surface inflammation and corneal repair, ultimately leading to prolonged dry eye symptoms [21]. PRK surgery partially mediates its effect on persistent postoperative dry eye through ocular inflammation [22]. This may be because PRK does not involve corneal flap creation, the corneal epithelial healing process is longer, or the postoperative ocular inflammatory response is more pronounced. Persistent inflammation further damages the ocular surface microenvironment and aggravates dry eye. At the same time, interaction analysis of ocular inflammation and medication adherence showed that the effect of medication adherence on persistent postoperative dry eye was amplified under conditions of moderate-to-severe inflammation. This finding provides important support for intervention strategies for postoperative dry eye, suggesting that clinical intervention should not focus on a single factor and that individualized management plans should be developed according to the ocular status of patients. In addition, a multimodel analytical approach combining LASSO regression, random forest, and logistic regression was used in this study, which effectively reduced the problem of multicollinearity associated with a single regression model and improved the accuracy of risk factor screening. Meanwhile, random forest and XGBoost models were constructed for postoperative verification, which also made the screening results of postoperative prognostic indicators more reliable.

Our finding that preoperative TBUT and MGD were key predictors is consistent with the findings of Zhao et al. [16] and Tuisku et al. [23] in the LASIK population. However, unlike Wang et al. [15], who focused on dry eye incidence within 12 months after surgery, our study specifically addressed persistent postoperative dry eye (≥ 3 months) and identified screen time as a dominant modifiable factor, which is consistent with the computer vision syndrome literature reported by Portello et al. [20].

Nevertheless, this study still has several limitations, and the generalizability of its conclusions is limited. This study was a single-center retrospective cohort study. The sample size of 260 patients was relatively limited, and all participants were recruited from the Department of ophthalmology of Xining First People's Hospital. There was a certain degree of homogeneity in patient baseline characteristics and surgical procedures, which may have introduced selection bias, making it difficult to directly generalize the findings to patients undergoing refractive surgery at other medical centers. Second, the retrospective nature of the study meant that the data relied on electronic medical records. Some postoperative variables, such as sleep quality and living environment, were assessed using qualitative or semi-quantitative measures and lacked more objective quantitative indicators, which may have introduced measurement bias. In addition, the mediation analysis only explored the pathways of age → medication adherence → postoperative dry eye and PRK → ocular inflammation → postoperative dry eye and did not further evaluate potential mediation relationships involving other core variables. Similarly, the interaction analysis only examined the synergistic effect of ocular inflammation and medication adherence, whereas interactions among other variables have not yet been explored, and the underlying mechanisms require further investigation. We acknowledge the concern regarding the high AUC (0.995) achieved by the preoperative random forest model. This likely results from the fact that the predictors (e.g., OSDI, TBUT, CFS) are also components of the diagnostic criteria for dry eye. Therefore, the model's performance reflects a tautological relationship rather than the discovery of novel biomarkers. Our analysis should therefore be interpreted as a risk factor identification study, not a validated clinical prediction tool. Future prospective studies with independent validation cohorts are needed.

Based on the results and limitations of this study, the perioperative management of refractive surgery for ultra-high myopia can be targeted and optimized in clinical practice. Preoperative comprehensive assessment of ocular surface function should be strengthened. For patients with MGD, shortened TBUT, and elevated OSDI, pretreatment measures such as meibomian gland hot compresses, artificial tear moistening, and anti-inflammatory treatment should be administered in advance to improve the baseline status of the ocular surface. Postoperatively, it is necessary to focus on guiding patients to reduce electronic screen use and to strengthen the monitoring of ocular inflammation, especially for patients undergoing PRK, with timely adjustment of the anti-inflammatory regimen. In addition, when patients present with moderate to severe ocular inflammation, it is important to reinforce education on medication adherence and improve patient compliance through personalized medication guidance, so as to reduce delays in the resolution of dry eye symptoms. In future studies, the sample size could be further expanded, and a multicenter prospective cohort study could be conducted to reduce bias and improve the generalizability of the findings. More potential influencing factors could also be included to improve the analysis of mediating and interaction effects, thereby providing a more comprehensive understanding of the mechanisms underlying the occurrence and persistence of postoperative dry eye. At the same time, a simple and practical clinical risk assessment model could be constructed based on the core indicators identified in this study, offering a more direct tool for preoperative risk stratification and postoperative individualized prevention and management.

In general, this study preliminarily clarified the core influencing factors and part of the mechanism of dry eye after refractive surgery for ultra-high myopia through multi-model joint analysis, and provided some references for the early prevention and control of dry eye after refractive surgery in clinical practice. However, due to the study design and sample size, the relevant conclusions still need to be verified and improved by more high-quality studies. In the future, more in-depth exploration should be carried out around the long-term prevention and control of dry eye after refractive surgery, in order to further improve long-term safety and patient satisfaction with refractive surgery for ultra-high myopia.

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Disclosure of conflict of interest

None.

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