

A multicenter retrospective study of non-traumatic corneal perforation: etiology, disease course, clinical manifestations, and treatment strategies

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Abstract

• **AIM:** To analyze the etiologies, disease course, clinical characteristics, and surgical management patterns of non-traumatic corneal perforation in China.

• **METHODS:** This multicenter, retrospective study reviewed medical records from patients with non-traumatic corneal perforation treated at 16 tertiary hospitals in China from 2019 to 2021. Data collected included demographics, etiology, disease duration, perforation location, visual acuity

on admission, and surgical procedures.

• **RESULTS:** A total of 796 eyes from 791 patients were included, comprising 271 women (34.2%) and 520 men (65.7%), with a mean age of 58.4 ± 15.6 y (range, 0.38–92y). Infectious keratitis was the leading cause (62.6%), followed by postoperative complications (12.8%) and autoimmune diseases (8.7%). Fungal infections were more prevalent in rural areas, while autoimmune-related perforations were more common in females. Autoimmune cases more frequently presented with a chronic disease course and better visual acuity at admission compared to infectious causes ($P < 0.001$). Among infectious causes, viral keratitis exhibited the highest proportion of chronic cases (65.7%). Perforation location varied significantly by etiology, with infectious cases predominantly central and autoimmune cases more often peripheral or limbal ($P < 0.001$). Overall, 88.3% of eyes presented with poor visual acuity on admission. Most eyes (90.0%) required surgical intervention. Penetrating keratoplasty was the most common procedure, especially for central perforations, while lamellar keratoplasty was preferred for peripheral and autoimmune-related cases.

• **CONCLUSION:** This nationwide, multicenter study provides a comprehensive epidemiologic characterization of non-traumatic corneal perforation. Infectious keratitis was identified as the predominant etiology. Distinct patterns in disease progression, perforation location, and surgical intervention were observed across etiologic subgroups. These findings underscore the relevance of etiology-stratified assessment and support the need for tailored clinical management strategies.

• **KEYWORDS:** corneal perforation; non-traumatic ocular disease; infectious keratitis; autoimmune eye disease

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INTRODUCTION

Non-traumatic corneal perforation arises from various corneal disorders, broadly classified as infectious or non-infectious. Infectious causes, such as bacterial, viral, and fungal keratitis, are often linked to demographic, systemic, and ocular risk factors, while non-infectious causes generally result from ocular surface disorders or autoimmune conditions^[1-6].

Although rare in developed countries, corneal perforation remains a leading cause of urgent surgical intervention in developing regions^[7], as it can lead to permanent vision loss and significantly diminish quality of life^[8-10]. Early recognition and timely treatment are essential for preserving corneal integrity and functional vision, as delayed intervention may result in further damage and complications^[10-13].

Treatment options range from medical management to surgical interventions, including conjunctival flap cover^[14], amniotic membrane transplantation (AMT)^[15-16], lamellar keratoplasty (LK)^[17], deep anterior lamellar keratoplasty (DALK)^[18], and penetrating keratoplasty (PK)^[19], with the choice of treatment largely depending on the size, location of the perforation, and underlying disease status^[6,20]. Although numerous studies have explored the etiology of corneal perforation, most have been limited by small patient cohorts or a single-center focus due to the rarity of the condition^[21-26].

To gain a clearer understanding of the etiology of non-traumatic corneal perforation and differentiate between various types, we conducted a retrospective study on patients hospitalized at 16 hospitals across China from 2019 to 2021. This study explores the primary causes, disease duration, clinical manifestations, treatments, and risk factors associated with poorer visual acuity (VA) on admission, offering a more reliable understanding of corneal perforation and valuable insights for preventing poor visual outcomes.

PARTICIPANTS AND METHODS

Ethical Approval This retrospective, observational study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of the Eye Hospital of Wenzhou Medical University (Approval No. 2020-217-K-197), and a waiver of informed consent was granted due to the retrospective nature of the study and the use of anonymized clinical data. The participating centers in this study were: Affiliated Eye Hospital of Nanchang University, Dalian No.3 People's Hospital, Eye Hospital of Wenzhou Medical University, Ningbo Eye Hospital, People's Hospital of Ningxia Hui Autonomous Region, Renmin Hospital of Wuhan University, Shanxi Eye Hospital, Sichuan Provincial People's Hospital, The Affiliated Eye Hospital of Nanjing Medical University, The First Affiliated Hospital of Chongqing Medical University, The First Affiliated Hospital of Fujian Medical University, The Second Hospital & Clinical Medical School of Lanzhou University, The Second People's Hospital of Yunnan Province, The Second Xiangya Hospital of Central South University, Tianjin Medical University Eye Hospital, and The Xi'an No.1 Hospital.

This retrospective study reviewed inpatient medical records of 796 eyes from 791 patients diagnosed with non-traumatic corneal perforation across 16 tertiary hospitals in China (5 in

the east, 5 in the central, 5 in the west, and 1 in the northeast) between January 2019 and December 2021. Patients with incomplete data or with trauma as the primary contributing factor were excluded. For individuals with multiple perforation episodes in the same eye, each episode was analyzed independently; bilateral cases were also included. Diagnoses were based on clinical history, presenting signs and symptoms, slit-lamp examination, and microbiological testing including smear and culture.

Patient demographic characteristics, including age, sex, and region, along with clinical data covering primary cause of corneal perforation, disease duration, VA on admission, perforation location, ocular and systemic history, and treatment, were retrospectively reviewed from medical charts. Visual outcomes on admission were assessed in relation to various systemic and ocular diagnoses, as well as demographic characteristics, using VA on admission as the dependent variable.

Each patient underwent a detailed evaluation, encompassing medical history, measurement of VA, anterior segment biomicroscopy, and posterior pole examination when applicable on admission. Upon admission to the hospital, treatment was initiated with the primary aims of restoring functional VA, maintaining ocular integrity, and mitigating further complications. Cases of persistent or refractory perforation were addressed with a stepwise therapeutic approach until clinical stabilization was achieved. For cases unresponsive to conventional management or where progression could not be controlled, enucleation was considered to prevent further disease advancement. Treatment strategies were individualized by cornea specialists, incorporating additional therapies as dictated by specific etiologies. In instances where infectious signs presented without a clear etiology, corneal scraping was conducted for pathogen identification. Cases with unidentified etiologies initially received broad-spectrum antibiotics, antivirals, or antifungals, with subsequent modifications based on antibiogram results when available. For patients with systemic autoimmune involvement, referral to a rheumatology specialist was recommended following initial management of corneal perforation, while those with ocular-limited autoimmune conditions received targeted therapies, including corticosteroids, immunosuppressants, or biologic agents as appropriate. Procedures such as AMT, conjunctival flap cover, and various forms of corneal transplantation were performed under general anesthesia.

Primary diseases of corneal perforation were classified into: 1) infectious keratitis, including bacterial infection (Figure 1A), fungal infection (Figure 1B), viral infection (Figure 1C), mixed infection, infection with unknown reason; 2) autoimmune disease, including Mooren's ulcer (Figure 1D),

corneal marginal ulcer (Figure 1E), Sjögren syndrome (SS), Steven Johnson, ocular graft versus host disease (oGVHD), rheumatoid arthritis (RA), ankylosing spondylitis (AS), systemic lupus erythematosus (SLE); 3) others, including endophthalmitis, band keratopathy, adherent corneal leucoma, blepharokeratoconjunctivitis (BKC; Figure 1F), keratoconus, lagophthalmos, neurotrophic keratitis (NK), trichiasis, tumor, chemical burn, thermal burn; 4) after surgery, including post-ptyerygium excision, post-conjunctival tumor excision, post-corneal suturing, post-conjunctival flap cover, post-AMT, corneal transplant rejection; 5) multiple factors. The primary etiology was determined based on the admission diagnosis, chief complaint, and documented disease history. Cases in which more than one factor contributed and no dominant cause could be confidently determined were classified as multiple factors. Disease duration was defined based on the patient's medical history and categorized into three stages: acute (≤ 1 mo), sub-acute (1 to 3mo), and chronic (> 3 mo). Urban or city region classification is according to the location of address of the patient. VA was measured with decimal VA and was converted to the logarithmic scale of the minimum angle of resolution (logMAR) for statistical analysis. Hand motion, counting finger, light perception, and no light perception were calculated using logMAR 1.85, 2.30, 2.80, and 2.90, respectively, based on a previous report^[27]. Poor VA was defined as a logMAR > 1.0 . Perforation characteristics were analyzed based on location (Figure 2), classified from center to periphery as central (within 4 mm of the central cornea), paracentral (4 to 7 mm), peripheral (7 to 11 mm), and limbal^[28]. Location classifications were determined from descriptions in medical records and anterior segment photographs of the patients.

Statistical Analysis All data are expressed as the mean \pm standard deviation, except for VA, which is presented as the median and interquartile range (IQR). Comparisons primarily focused on the etiological types within non-traumatic perforations, specifically contrasting infectious keratitis and autoimmune disease. Additionally, detailed analyses were conducted within the infectious keratitis group to examine differences among bacterial, fungal, and viral etiologies. The logMAR on admission were compared between the autoimmune and infectious groups, as well as among different infection types, using the Wilcoxon rank-sum (Mann-Whitney) test. The Chi-square test was used to compare sex distribution, rural versus urban distribution, disease duration, perforation location, incidence of poor VA across groups, and the distribution of surgical procedures (PK, DALK, and LK) across perforation locations between infectious and autoimmune corneal perforations, as well as among different infection types. The unpaired *t*-test was used to compare age between the non-

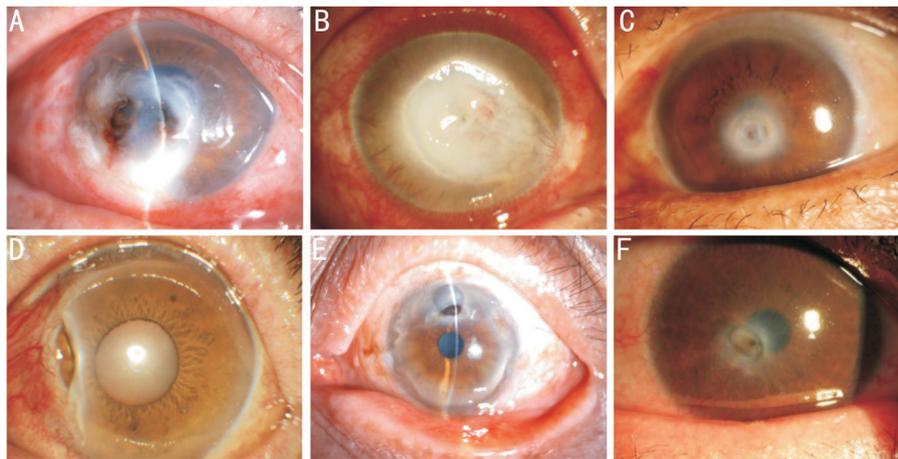


Figure 1 Typical images of corneal perforation caused by different etiologies A: Bacterial infection; B: Fungal infection; C: Viral infection; D: Mooren's ulcer; E: Corneal marginal ulcer; F: Blepharokeratoconjunctivitis (BKC).

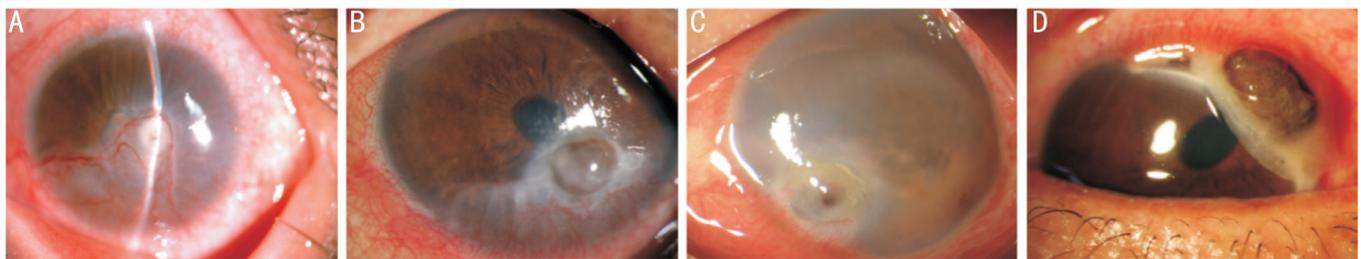


Figure 2 Classification of corneal perforation locations A: Central perforation: within 4 mm of the central cornea; B: Paracentral perforation: 4 to 7 mm; C: Peripheral perforation: 7 to 11 mm; D: Limbal perforation.

infectious and infectious groups, as well as between infections of unknown etiology and those with a defined infectious cause. Fisher's exact test examined differences in corneal transplantation types between infection- and autoimmune-related perforations. Stepwise multivariate linear regression analyses were conducted to assess the associations between the logMAR value on admission and factors including diabetes, hypertension, RA, sex, age, presence of infection, and disease duration. Additionally, a binary logistic regression analysis was performed to explore factors associated with the need for surgical intervention. Variables entered into the model included age, sex, logMAR value on admission, etiology, perforation location, and disease duration. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A P -value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics, Version 27 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 796 eyes from 791 patients were included, comprising 271 women (34.3%) and 520 men (65.7%), with a mean age of 58.3 ± 15.6 y (range, 0.38–92y). The etiologies of corneal perforation are summarized in Table 1. Five patients presented with bilateral perforation, including two due to Mooren's ulcer, two due to bilateral bacterial keratitis, and one with an unclassified cause. The most common systemic comorbidities were hypertension (18.4%) and diabetes

mellitus (6.2%). Among the 796 eyes, 46 (5.8%) had multiple contributing etiologies. A significant sex-based difference was observed: infectious keratitis was more common in males, whereas autoimmune-related perforations were more frequently noted in females ($P < 0.001$). Although no significant difference was found in the overall distribution of infectious versus autoimmune causes between rural and urban regions ($P = 0.366$), fungal infections were predominant in rural areas, accounting for 85.9% of infectious cases.

Table 2 presents the distribution of disease duration across etiologies of corneal perforation. Both infectious keratitis and autoimmune-related perforations commonly occurred in the chronic phase; however, their distributions differed significantly ($P = 0.042$). Autoimmune-related perforations were more frequently chronic (58.5%) compared to infectious cases (43.8%), while infectious keratitis showed higher proportions in the acute (32.6%) and subacute (23.4%) phases than autoimmune causes (28.5% and 12.8%, respectively). This suggests that infectious etiologies are more likely to result in earlier-onset perforation. Notably, Mooren's ulcer was predominantly associated with a chronic course (85.7%). No significant difference in disease duration distribution was observed between bacterial and fungal perforations ($P = 0.247$). In contrast, viral infections differed significantly from both bacterial ($P = 0.001$) and fungal infections ($P < 0.001$), with a marked tendency toward chronic presentation. In addition,

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Table 1 Primary causes of corneal perforation

Parameters	Number of eyes	Age	Male ratio	Rural region
Infectious keratitis	499 (62.6%)	59.3±14.9	345 (69.1%)	361 (72.3%)
Bacteria	93 (11.6%)	58.7±14.9	66 (70.9%)	58 (62.3%)
Fungi	64 (8.0%)	59.1±12.5	47 (73.4%)	55 (85.9%)
Virus	114 (14.3%)	55.5±15.4	81 (71.0%)	81 (71.0%)
Mixed	15 (1.8%)	63.7±11.7	12 (80.0%)	11 (73.3%)
Unknown	213 (26.7%)	61.2±15.2	139 (65.2%)	156 (73.2%)
Autoimmune disease	70 (8.7%)	57.8±13.2	25 (35.7%)	47 (67.1%)
Mooren's ulcer	14 (1.7%)	53.2±12.5	7 (50.0%)	8 (57.1%)
Corneal marginal ulcer	12 (1.5%)	60.8±14.0	7 (58.3%)	4 (33.3%)
SS	6 (0.7%)	67.3±11.1	1 (16.6%)	4 (66.6%)
Steven Johnson	1 (0.1%)	23	1 (100%)	1 (100%)
oGVHD	4 (0.5%)	48.5±10.3	2 (50.0%)	3 (75.0%)
RA	31 (3.8%)	59.6±10.5	7 (22.5%)	22 (70.9%)
AS	1 (0.1%)	69	0	1 (100%)
SLE	1 (0.1%)	30	0	0
Others	79 (9.9%)	52.5±19.9	53 (67.0%)	48 (60.7%)
Endophthalmitis	12 (1.5%)	61.3±15.9	7 (58.3%)	9 (75.0%)
Band keratopathy	2 (0.2%)	54.5±31.8	1 (50.0%)	0
Adherent corneal leucoma	6 (0.7%)	64.0±18.2	4 (66.6%)	3 (50.0%)
BKC	15 (1.8%)	34.1±21.7	5 (33.3%)	8 (53.3%)
Keratoconus	1 (0.1%)	0.38	1 (100%)	0
Lagophthalmos	17 (2.1%)	57.4±12.4	13 (76.4%)	11 (64.7%)
NK	2 (0.2%)	69.5±16.3	2 (100%)	2 (100%)
Trichiasis	5 (0.6%)	56.6±25.8	2 (40.0%)	4 (80.0%)
Tumor	1 (0.1%)	92	1 (100%)	0
Chemical burn	11 (1.3%)	53.1±10.8	10 (90.9%)	7 (63.6%)
Thermal burn	7 (0.8%)	48.1±4.5	7 (100%)	4 (57.1%)
After surgery	102 (12.8%)	58.9±14.3	71 (69.6%)	71 (69.6%)
Post-pterygium excision	6 (0.7%)	68.7±4.1	4 (66.7%)	4 (66.6%)
Post-conjunctival tumor excision	1 (0.1%)	63	1 (100%)	0
Post-corneal suturing	3 (0.3%)	67.0±13.9	1 (33.3%)	2 (66.6%)
Corneal transplant rejection	61 (7.6%)	56.6±15.9	42 (68.8%)	45 (73.7%)
Postoperative progression of underlying disease (post-conjunctival flap cover & post-AMT)	31 (3.8%)	60.42±11.2	23 (74.1%)	20 (64.5%)
Multiple factors	46 (5.8%)	58.0±18.4	29 (63.0%)	34 (73.9%)
Total	796 (100%)	58.3±15.6	523 (65.7%)	561 (70.4%)

SD: Standard deviations; SS: Sjögren syndrome; oGVHD: Ocular graft versus host disease; RA: Rheumatoid arthritis; AS: Ankylosing spondylitis; SLE: Systemic lupus erythematosus; BKC: Blepharokeratoconjunctivitis; NK: Neurotrophic keratitis; AMT: Amniotic membrane transplantation.

BKC-related perforations also demonstrated a predominantly chronic course. Among 15 BKC cases, 11 patients presented more than 3mo after symptom onset, consistent with the chronic, relapsing nature of this ocular surface inflammatory disorder. Only four patients presented within 1mo. None of the BKC cases had associated systemic autoimmune disease or other ocular comorbidities. These findings are consistent with the chronic inflammatory nature of BKC and suggest that sustained ocular surface inflammation may play a major role in the development of perforation. However, we cannot rule

out the possibility that delayed referral or suboptimal early management contributed to disease progression in some cases. The median VA on admission was 3.00 logMAR (Snellen equivalent of hand motion; range, 20/40 to no light perception), and remained unchanged at discharge. This is because 90.0% (716/796) of eyes underwent surgical intervention and most patients were discharged within 5–10d postoperatively, discharge VA reflects the early postoperative period rather than long-term outcomes. During this stage, graft opacity and pre-existing ocular conditions may limit visual recovery; therefore,

Table 2 Disease duration of corneal perforation

n (%)

Parameters	Acute	Sub-acute	Chronic
Infectious keratitis	163 (32.6%)	117 (23.4%)	219 (43.8%)
Bacteria	30 (32.2%)	25 (26.8%)	38 (40.8%)
Fungi	19 (29.6%)	25 (39.0%)	20 (31.2%)
Virus	19 (16.6%)	20 (17.5%)	75 (65.7%)
Mixed	6 (40%)	3 (20%)	6 (40%)
Unknown	89 (41.7%)	44 (20.6%)	80 (37.5)
Autoimmune disease	20 (28.5%)	9 (12.8%)	41 (58.5%)
Mooren's ulcer	1 (7.1%)	1 (7.1%)	12 (85.7%)
Corneal marginal ulcer	4 (33.3%)	2 (16.6%)	6 (50%)
SS	3 (50%)	0	3 (50%)
Steven Johnson	0	1 (100%)	0
oGVHD	2 (50%)	0	2 (50%)
RA	10 (32.2%)	5 (16.1%)	16 (51.6%)
AS	0	0	1 (100%)
SLE	0	0	1 (100%)
Others	29 (36.7%)	17 (21.5%)	33 (41.7%)
Endophthalmitis	6 (50%)	2 (16.6%)	4 (33.3%)
Band keratopathy	1 (50%)	1 (50%)	0
Adherent corneal leucoma	2 (33.3%)	1 (16.6%)	3 (50%)
BKC	4 (26.6%)	0	11 (73.3%)
Keratoconus	1 (100%)	0	0
Lagophthalmos	8 (47%)	3 (17.6%)	6 (35.2%)
NK	1 (50%)	0	1 (50%)
Trichiasis	0	2 (40%)	3 (60%)
Tumor	0	0	1 (100%)
Chemical burn	3 (27.2%)	5 (45.4%)	3 (27.2%)
Thermal burn	3 (42.8%)	3 (42.8%)	1 (14.2%)
After surgery	48 (47%)	22 (21.5%)	32 (31.3%)
Post-ptyerygium excision	4 (66.6%)	1 (16.6%)	1 (16.6%)
Post-conjunctival tumor excision	1 (100%)	0	0
Post-corneal suturing	3 (100%)	0	0
Corneal transplant rejection	26 (42.6%)	12 (19.6%)	23 (37.7%)
Postoperative progression of underlying disease (post-conjunctival flap cover & post-AMT)	14 (45.1%)	9 (29.0%)	8 (25.8%)
Multiple factors	19 (41.3%)	11 (23.9%)	16 (34.7%)
Total	279 (35.0%)	176 (22.1%)	341 (42.8%)

SS: Sjögren syndrome; oGVHD: Ocular graft versus host disease; RA: Rheumatoid arthritis; AS: Ankylosing spondylitis; SLE: Systemic lupus erythematosus; BKC: Blepharokeratoconjunctivitis; NK: Neurotrophic keratitis; AMT: Amniotic membrane transplantation.

discharge VA does not represent the final prognosis. Patients with autoimmune-related perforations had significantly better VA at presentation than those with infectious causes [median logMAR 2.3 (IQR, 1.0–3.0) vs 3.0 (IQR, 3.0–4.0); $P<0.001$]. Among infectious subtypes, presenting VA differed significantly between bacterial and viral infections [median logMAR 4.0 (IQR, 3.0–4.0) vs 3.0 (IQR, 2.9–4.0); $P=0.001$] and between fungal and viral infections [3.0 (IQR, 3.0–4.0) vs 3.0 (IQR, 2.9–4.0); $P=0.014$]. Viral infections showed better presenting VA compared with both bacterial and fungal infections, while fungal and bacterial groups exhibited

comparable VA ($P=0.37$). Among infectious subtypes, VA differed significantly between bacterial and viral groups [median logMAR 4.0 (IQR, 3.0–4.0) vs 3.0 (IQR, 2.9–4.0); $P<0.01$], with viral infections associated with better presenting VA. No significant differences were observed between the fungal and bacterial groups ($P>0.05$) or between the fungal and viral groups ($P>0.05$).

In addition to median VA comparisons, the proportion of patients with poor VA (defined as >1.0 logMAR) was analyzed across etiologic groups (Table 3). The infectious group had a poor VA rate of 90.2%, with bacterial, fungal, and viral

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Table 3 Patients with poor VA more than logMAR 1.0 on admission

Parameters	Eyes (n)	Rate of patients with poor VA more than 1.0
Infectious keratitis	450/499	90.2%
Bacteria	85/93	91.4%
Fungi	59/64	92.2%
Virus	103/114	90.3%
Autoimmune disease	49/70	70.0%
Others	69/79	87.3%
After surgery	98/102	96.1%
Multiple factors	37/46	80.4%
Total	703/796	88.3%

VA: Visual acuity; logMAR: Logarithm of the minimum angle of resolution.

subgroups showing similar rates (91.4%, 92.2%, and 90.3%, respectively). In contrast, the autoimmune disease group had a significantly lower poor VA rate (70.0%), while the post-surgery group exhibited the highest rate (96.1%). Statistically significant differences were found between the infectious and autoimmune groups ($P<0.001$) and between the autoimmune and post-surgical groups ($P<0.001$), whereas the difference between the infectious and post-surgical groups was not statistically significant ($P=0.056$).

A stepwise multivariate linear regression analysis was conducted with logMAR at admission as the dependent variable. After adjusting for other covariates, older age ($B=0.017$, $SE=0.003$, 95%CI: 0.011 to 0.024, $P<0.001$), male sex ($B=0.211$, $SE=0.096$, 95%CI: 0.022 to 0.400, $P=0.028$), and RA ($B=-0.710$, $SE=0.200$, 95%CI: -1.102 to -0.318, $P<0.001$) were independently associated with logMAR values. Increasing age and male sex were associated with higher logMAR scores, indicating worse VA, whereas the presence of RA was associated with lower logMAR scores, suggesting better VA. Diabetes ($P=0.529$), hypertension ($P=0.586$), infection status ($P=0.926$), and disease duration ($P=0.344$) were not statistically significant and were removed from the final model.

The anatomical location of the corneal perforation was central in 298 eyes (37.4%), paracentral in 180 (22.6%), peripheral in 267 (33.5%), and in the limbal region in 31 (3.8%); the location was unclear in 20 eyes (2.5%; Table 4). In the infectious group, most perforations were located centrally (40.8%), particularly in viral infections (45.6%). In contrast, autoimmune-related perforations were more frequently peripheral (48.5%) and showed a higher proportion in the limbal region (14.2%). This distribution difference between infectious and autoimmune groups was statistically significant ($P<0.001$). However, perforation location did not differ significantly among infectious subtypes ($P=0.128$). Perforations due to corneal transplant rejection were most

observed in the peripheral region (39.3%), followed by the central region (27.8%).

A total of 716 eyes (90.0%) with corneal perforation underwent surgical intervention. The most common procedures included corneal transplantation (398 eyes, 55.5%), conjunctival flap (173 eyes, 24.1%), and AMT (146 eyes, 20.3%). Other procedures included evisceration (122 eyes, 17.0%), blepharorrhaphy (55 eyes, 7.6%), sclerocorneal keratoplasty (21 eyes, 2.9%), and corneal suturing (10 eyes, 1.3%). Notably, 90 eyes received both conjunctival flap and AMT, and 2 eyes underwent a combination of conjunctival flap, AMT, and corneal transplantation. Most patients required only one surgical procedure (655 patients, 82.8%), while 55 (6.9%) underwent two procedures and 3 (0.3%) underwent three.

Logistic regression analysis was performed to identify factors associated with surgical intervention. Worse presenting VA was independently associated with the need for surgery (OR=1.27, 95%CI: 1.05–1.53, $P=0.014$). Central/paracentral perforation showed a trend toward significance ($P=0.079$), consistent with its established role as a key surgical indication. Other variables, including age, sex, etiology and disease duration, were not significant predictors. These findings support current clinical practice in which anatomic location and functional severity guide the decision for surgical management.

In this multicenter retrospective study, the most frequently performed surgical interventions following corneal perforation included keratoplasty (400 eyes), conjunctival flap cover (173 eyes), and AMT (146 eyes). Representative images of these procedures, obtained from the participating centers in this study, are shown in Figure 3. Among the 398 eyes that underwent corneal transplantation, PK was the most common (266 eyes, 66.8%), followed by LK (93 eyes, 23.3%), DALK (37 eyes, 9.2%), and limbal stem cell transplantation (LSCT, 4 eyes, 1.0%). One eye received a keratoprosthesis due to bacterial infection. In addition, three eyes underwent combined PK and LSCT—two due to multifactorial causes and one due to bacterial infection.

The type of corneal transplantation differed significantly between infectious and autoimmune etiologies ($P<0.001$): eyes with infectious causes were more likely to receive PK, whereas those with autoimmune causes more often received LK (Table 5).

Table 6 presents the distribution of surgical procedures (PK, DALK, and LK) across perforation locations (central, paracentral, peripheral, and limbal), with a statistically significant association between location and procedure type ($P<0.001$). PK was the most frequently performed procedure for central, paracentral, and peripheral perforations. However, a progressive shift toward greater use of LK was observed as the perforation site moved peripherally, with LK being the

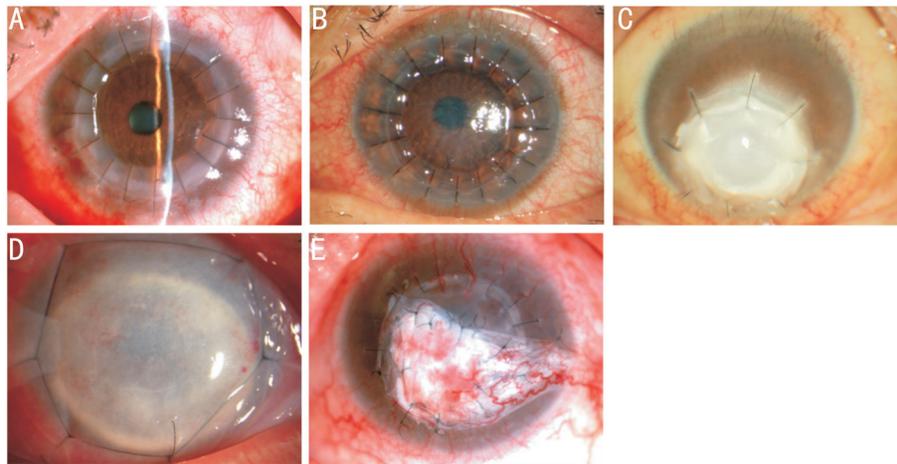


Figure 3 Representative clinical images of major surgical interventions following corneal perforation from participating centers in this multicenter retrospective study A: Penetrating keratoplasty (PK); B: Deep anterior lamellar keratoplasty (DALK); C: Lamellar keratoplasty (LK); D: Amniotic membrane transplantation (AMT); E: Conjunctival flap cover.

Table 4 Perforation location

Parameters	Central	Paracentral	Peripheral	Limbal	Unclear
Infectious keratitis	204 (40.8%)	121 (24.2%)	158 (31.6%)	10 (2.0%)	6 (1.2%)
Bacteria	35 (37.6%)	19 (20.4%)	37 (39.7%)	0	2 (2.1%)
Fungi	28 (43.7%)	12 (18.7%)	22 (34.3%)	0	2 (3.1%)
Virus	52 (45.6%)	32 (28.0%)	28 (24.5%)	2 (1.7%)	0
Autoimmune disease	14 (20.0%)	12 (17.1%)	34 (48.5%)	10 (14.2%)	0
Corneal transplant rejection	17 (27.8%)	13 (21.3%)	24 (39.3%)	2 (3.2%)	5 (8.1%)
Total	298 (37.4%)	180 (22.6%)	267 (33.5%)	31 (3.8%)	20 (2.5%)

Table 5 Types of corneal transplantation for corneal perforations

Parameters	PK	DALK	LK	LSCT	Keratoprosthesis
Infectious keratitis	176	16	49	1	1
Bacteria	36	3	6	1	1
Fungi	27	2	1	0	0
Virus	38	6	5	0	0
Autoimmune disease	12	12	19	1	0
After surgery	43	2	11	0	0
Post-corneal suturing	0	0	2	0	0
Corneal transplant rejection	29	2	4	0	0
Postoperative progression of underlying disease (post-conjunctival flap cover & post-AMT)	14	0	2	0	0
Total	266	37	93	4	1

PK: Penetrating keratoplasty; DALK: Deep anterior lamellar keratoplasty; LK: Lamellar keratoplasty; LSCT: Limbal stem cell transplantation; AMT: Amniotic membrane transplantation.

Table 6 Types of corneal transplantation for different perforation location

Parameters	PK	DALK	LK
Central	113	10	16
Paracentral	58	6	29
Peripheral	86	18	39
Limbal	7	3	9

PK: Penetrating keratoplasty; DALK: Deep anterior lamellar keratoplasty; LK: Lamellar keratoplasty.

predominant procedure for limbal perforations. This trend

highlights the influence of anatomical location on surgical decision-making.

DISCUSSION

Corneal perforation represents a vision-threatening complication of both infectious and immune-mediated corneal diseases^[29]. In advanced stages, structural compromise may necessitate urgent surgical intervention to preserve ocular integrity^[30-32]. Given the clinical severity and potential burden on healthcare resources, characterizing the underlying etiologies and treatment patterns is essential, particularly in

regions with limited access to timely ophthalmic care^[33-34].

This multicenter study involving 791 patients from 16 tertiary hospitals across China identified infectious keratitis as the predominant cause of corneal perforation, with fungal infections disproportionately represented in rural areas. Etiologic patterns showed sex-specific differences: infectious causes were more common in males, while autoimmune-related perforations were more frequently observed in females. A substantial proportion of cases—particularly those involving viral keratitis—had a symptom duration exceeding 3mo, consistent with the typically chronic or recurrent nature of viral corneal disease. Presenting VA was generally worse in infectious cases and was associated with male sex and older age, whereas autoimmune-related perforations, especially those secondary to RA, tended to present with better baseline vision. LK was more frequently employed for peripheral or autoimmune-associated perforations. Additionally, we observed that graft rejection following corneal transplantation occurred more often in the peripheral cornea, suggesting that postoperative follow-up should pay particular attention to the graft margins to enable timely detection and management of complications. These findings underscore the clinical heterogeneity of corneal perforation and highlight the importance of etiology-guided surgical strategies.

We further contextualized our findings with previous reports from both high-income and domestic settings. Takahashi *et al*^[26] reported that infectious etiologies accounted for 36.4% of nontraumatic perforations in Japan, while Lekskul *et al*^[25] reported 39.1% in the United States. In Mexico, Loya-Garcia *et al*^[24] noted a similar rate of approximately 40% in a tertiary ophthalmology center^[24]. In contrast, our study showed a higher rate of infectious causes (62.6%), though lower than the 82.8% reported by Xie *et al*^[21] in Shandong Province in 2007. These discrepancies likely reflect differences in geographic distribution, access to care, and referral patterns. The limited number of standardized multicenter studies makes it difficult to determine whether a true temporal or regional shift has occurred.

The anatomical distribution of perforation sites in our cohort also aligned with findings from Loya-Garcia *et al*^[24], who reported that autoimmune-related perforations, particularly those associated with peripheral ulcerative keratitis, typically involved the peripheral or limbal regions, while infectious perforations were more commonly central. Although RA was a prominent autoimmune cause in our cohort, its proportion was somewhat lower than that reported by Loya-Garcia *et al*^[24], which may be attributed to differences in population size, ethnicity, or treatment accessibility^[35].

Hanada *et al*^[36] emphasized that therapeutic keratoplasty plays a critical role in restoring structural integrity and preserving

the globe in cases of corneal perforation. Lekskul *et al*^[25] further highlighted that the choice of surgical technique should be individualized based on the size and configuration of the perforation as well as the visual potential of the affected eye. In our study, PK was more commonly performed for central perforations, while LK was increasingly used for peripheral and limbal sites. This distribution pattern aligns with current clinical practice, reflecting a surgical preference for tissue-preserving approaches and reduced risk of rejection in anatomically and immunologically high-risk zones^[6,19,24].

Recent research has also focused on BKC-related corneal perforation. Li *et al*^[37] reported 16 adolescent cases caused by severe BKC, demonstrating that chronic lid margin inflammation in young patients may progress to perforation and that small-diameter PK can achieve favorable outcomes. In our BKC subset (15 eyes; mean age 34.1±21.7y), 10 eyes underwent keratoplasty (5 PK, 2 DALK, and 3 LK), and most cases followed a chronic disease course (>3mo in 11 patients; ≤1mo in 4). Compared with Li *et al*'s^[37] younger cohort uniformly treated with small-diameter PK, our findings suggest that BKC-related perforation across a wider age range may require more individualized surgical strategies tailored to perforation characteristics and ocular surface status.

This study offers several notable strengths that extend beyond prior reports. First, it proposes a comprehensive and clinically relevant classification of corneal perforation etiology, particularly highlighting a broad range of postoperative causes—such as post-ptyerygium excision, post-conjunctival tumor excision, post-corneal suturing, graft rejection, and postoperative progression of underlying disease (*e.g.*, following conjunctival flap or AMT). By consolidating these under a distinct “postoperative etiology” category, the study distinguishes between direct surgical complications and disease-related progression after ocular procedures. This novel classification may aid in surgical risk stratification, postoperative monitoring, and patient counseling. Second, the study reveals a strong association between perforation site and surgical choice: central lesions were primarily treated with PK, while peripheral or limbal perforations often received LK. This anatomic-surgical relationship underscores the importance of lesion location in operative planning. Third, regional analysis revealed a disproportionately high burden of fungal keratitis in rural populations, underscoring the need for targeted prevention, earlier diagnosis, and accessible antifungal care in underserved areas. Fourth, analysis of disease duration and presenting VA across etiologic subgroups highlights opportunities for earlier intervention. Notably, patients with viral, autoimmune, or BKC-related perforations frequently presented in the chronic phase, indicating possible delays in diagnosis or referral. Finally, the large-scale, multicenter design

encompassing 16 tertiary hospitals across China enhances the external validity of the findings and provides a valuable snapshot of real-world clinical practice in the management of non-traumatic corneal perforation.

Nevertheless, several limitations should be acknowledged. First, as a retrospective analysis, the study is subject to inherent constraints, including incomplete data capture and potential referral bias across participating centers. Second, due to the observational study design, the findings demonstrate associations rather than causal relationships, and causality cannot be inferred. Third, we were unable to control for several potentially important clinical confounders, such as prior corticosteroid exposure, initial treatment conditions, and time from symptom onset to presentation, which may influence disease severity and clinical outcomes. Fourth, although microbiological testing was performed, a considerable proportion of infectious cases remained culture-negative, likely due to pre-treatment antibiotic use or limited microbiological resources in real-world settings; prospective studies with standardized microbiological sampling protocols and early specimen collection are needed. Fifth, postoperative outcomes (e.g., final VA, graft failure, recurrence, or globe loss) were not analyzed due to heterogeneous and incomplete follow-up data across centers, particularly in emergency surgical cases; this will be addressed in future prospective studies with structured long-term follow-up. Finally, although approaches such as propensity score matching or sensitivity analyses could theoretically reduce selection bias, these methods were not feasible in this dataset due to the heterogeneous real-world nature of multi-center medical records and the lack of standardized baseline variables across hospitals. We acknowledge this as a limitation and have noted it in the revised manuscript; future prospective studies will incorporate more rigorous bias-control methods.

Despite these limitations, the inclusion of unselected real-world cases from 16 tertiary hospitals strengthens the external validity of the study and reflects true clinical practice patterns. Future prospective research with standardized data collection, detailed treatment recording, and unified follow-up protocols is warranted to further refine management strategies and improve visual outcomes, particularly in underserved regions where the burden of corneal perforation remains high.

In conclusion, this multicenter study provides a comprehensive epidemiologic and clinical profile of non-traumatic corneal perforation based on data from 791 patients across 16 tertiary hospitals in China. Infectious keratitis was the most common etiology, with viral infections often associated with chronic or recurrent disease, and fungal cases disproportionately affecting rural populations. Autoimmune-related perforations were more prevalent in female patients, frequently located in the

peripheral or limbal cornea, and generally presented with better VA at admission. The location and etiology of perforation were closely linked to surgical choice: PK was preferred for central lesions, while LK was commonly used for peripheral or autoimmune-associated cases. These findings highlight the clinical heterogeneity of corneal perforation and emphasize the importance of etiology-based treatment strategies, individualized surgical planning, and targeted postoperative surveillance. Moreover, given that poorer presenting VA was the primary predictor for surgical intervention, our findings suggest that earlier referral and timely management may reduce the likelihood of progression to severe perforation requiring surgery. While disease etiology did not independently predict the need for surgical treatment, etiologic recognition remains essential for selecting the appropriate surgical modality and tailoring postoperative care. Future prospective research is needed to evaluate long-term visual outcomes and to inform the development of standardized management algorithms.

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