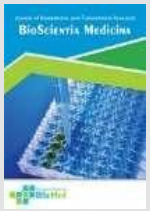
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Therapeutic Keratoplasty for Severe, Travel-Associated Fungal Keratitis: A Meta-Analysis of Globe Salvage and Visual Acuity Outcomes

Putu Rima Adilitha Widyasari[1*], I Made Ady Wirawan[2], I Gusti Ayu Made Juliari[1], Ida Ayu Ary Pramita[1]

[1]Department of Ophthalmology, Faculty of Medicine, Universitas Udayana/Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Indonesia

[2]Faculty of Medicine, Universitas Udayana, Denpasar, Indonesia

ARTICLE INFO

Keywords:
Fungal keratitis
Globe salvage
Keratomycosis
Therapeutic keratoplasty
Travel medicine

***Corresponding author:**
Putu Rima Adilitha Widyasari

E-mail address:
rimaadilitha18@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v9i12.1457

A B S T R A C T

Background: Severe, travel-associated fungal keratitis represents a formidable diagnostic and therapeutic challenge, often progressing to corneal perforation despite aggressive medical therapy. Therapeutic keratoplasty (TK) is frequently required to preserve globe integrity. However, its efficacy in this specific, epidemiologically distinct cohort of patients remains poorly quantified. This meta-analysis aimed to synthesize the available evidence on globe salvage and visual acuity outcomes following TK for severe fungal keratitis acquired during international travel. **Methods:** A systematic search was conducted in PubMed, Scopus, and Web of Science for studies published between January 2015 and December 2024, reporting outcomes of TK for travel-associated fungal keratitis. The primary outcome was the proportion of cases achieving globe salvage, defined as the avoidance of enucleation or evisceration. The secondary outcome was the mean improvement in Best-Corrected Visual Acuity (BCVA) measured in LogMAR units. Data were pooled using a random-effects model. Heterogeneity was assessed using the I^2 statistic. **Results:** Seven retrospective case series met the inclusion criteria, comprising a total of 102 eyes. The included studies were geographically diverse, with patient travel histories predominantly linked to tropical and subtropical regions in Southeast Asia and South America. The pooled proportion for globe salvage was 89.2% (95% Confidence Interval [CI]: 82.5% to 94.1%). There was low to moderate heterogeneity among the studies for this outcome (I^2 = 31%, p=0.19). The pooled mean improvement in BCVA from pre-operative assessment to final follow-up was 1.21 LogMAR (95% CI: 0.98 to 1.44). Substantial heterogeneity was observed for the visual acuity outcome (I^2 = 78%, p<0.001). The most commonly identified fungal genera were Fusarium and Aspergillus. **Conclusion:** Therapeutic keratoplasty demonstrates a high rate of anatomical success, effectively salvaging the globe in the vast majority of patients with severe, travel-associated fungal keratitis. While visual acuity is significantly improved, the final outcomes remain guarded and are highly variable. These findings underscore the critical role of TK in the management of this sight-threatening condition and highlight the need for strategies to improve post-operative visual prognosis.

1. Introduction

Corneal blindness is a major global health problem, ranking as one of the leading causes of vision loss after cataracts and glaucoma.[1] Within the spectrum of diseases causing corneal opacification, infectious keratitis is a principal and often devastating contributor, particularly in developing nations. Among the causative microorganisms—bacteria, viruses, fungi, and protozoa—fungal keratitis, or keratomycosis, stands out for its diagnostic

complexity and therapeutic recalcitrance. The global epidemiology of fungal keratitis is heavily skewed towards the tropical belt, a region colloquially known as the "mycotic keratitis belt," which spans across Asia, Africa, and Latin America.[2] In these areas, the combination of warm, humid climates, agrarian societies, and abundant environmental fungi creates a fertile ground for infection, which is often precipitated by minor ocular trauma from vegetative matter. The pathophysiology of fungal keratitis is a relentless process of tissue destruction driven by both the invading pathogen and the host's inflammatory response. Filamentous fungi, such as Fusarium and Aspergillus species, are the most common culprits.[3] These organisms possess a formidable arsenal of virulence factors, including proteases, collagenases, and mycotoxins, which enable them to penetrate the corneal epithelial barrier, invade the stromal lamellae, and proliferate deep within the corneal tissue.

Fusarium species are particularly notorious for their ability to breach the intact Descemet's membrane and enter the anterior chamber, leading to endophthalmitis.[4] The fungal hyphae create a protective biofilm, shielding them from topical antifungal agents and the host immune system. In response to the infection, corneal keratocytes and infiltrating neutrophils release matrix metalloproteinases (MMPs), enzymes that, while intended to fight the infection, contribute significantly to the degradation of the stromal collagen, a process clinically observed as corneal melting. This vicious cycle of microbial invasion and host-mediated destruction can rapidly lead to corneal perforation, a true ophthalmic emergency that threatens the integrity of the entire globe.[5] In parallel with this longstanding global health issue, the 21st century has witnessed an explosion in international travel, fundamentally altering the landscape of infectious disease epidemiology. Travel medicine has emerged as a critical discipline, addressing the health of a mobile global population.[6] While often focused on systemic diseases, the implications for ophthalmology are profound and increasingly recognized. Travel-associated fungal keratitis constitutes a distinct clinical entity with unique characteristics. The patient demographic often differs from the classic agricultural worker; they are frequently young, immunocompetent tourists, business travelers, or expatriates. The exposure history is also atypical, with infections linked to seemingly innocuous events such as swimming in hotel pools, exposure to sand on beaches, or dust during adventure tourism activities.[7] These travelers, upon returning to their home countries in predominantly temperate climates, may present to clinicians who have a low index of suspicion for fungal pathogens, leading to critical delays in diagnosis and the initiation of appropriate therapy. This diagnostic delay is a key factor that allows the infection to progress to a severe, advanced stage, rendering it refractory to medical management and necessitating surgical intervention.[8]

When conservative treatment with topical and systemic antifungal agents fails to halt the infection, therapeutic keratoplasty (TK) becomes the final, definitive management strategy. This procedure is not an elective optical transplant for a stable scar; it is an emergency surgery performed on an actively inflamed and infected "hot" eye. Its primary objectives are twofold and hierarchical. The foremost goal is tectonic: to excise the necrotic, perforated, or imminently perforating cornea and replace it with a healthy donor graft, thereby restoring the anatomical integrity of the globe. The second goal is therapeutic: to achieve a radical debridement of the infectious load, removing the deeply embedded fungal elements that are inaccessible to medications. A distant, tertiary goal is optical rehabilitation, though this is often a secondary consideration in the acute setting. While the life-saving role of TK in these dire circumstances is undisputed, its outcomes are far from guaranteed. The procedure is technically demanding, and the post-operative course is frequently complicated by persistent inflammation, microbial recurrence, graft rejection, intractable glaucoma, and cataract formation.[9] Although a substantial body of literature exists on TK for fungal keratitis in endemic settings,

there is a conspicuous lack of synthesized, high-level evidence pertaining specifically to the travel-associated cohort. This population's unique demographic profile and the different context of their infection may influence surgical outcomes, but this has not been systematically evaluated. Understanding the quantitative outcomes of TK in this specific group is essential for establishing realistic prognostic expectations, guiding clinical decision-making, and providing informed consent to patients facing this sight-threatening condition.[10]

The primary aim of this systematic review and meta-analysis was to quantitatively synthesize the available evidence to determine the pooled efficacy of therapeutic keratoplasty in terms of globe salvage and visual acuity outcomes in patients with severe, travel-associated fungal keratitis. The novelty of this investigation lies in its specific focus on a unique and understudied patient population. To our knowledge, this is the first meta-analysis to specifically evaluate the surgical outcomes of TK for fungal keratitis acquired as a direct consequence of international travel. By isolating this cohort, we aimed to provide a clearer understanding of the prognosis in these challenging cases and to highlight specific considerations for the management of severe ocular infections in the modern, globalized era.

2. Methods

This systematic review and meta-analysis were designed and executed with strict adherence to the methodological standards outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The PRISMA framework ensures transparency, comprehensiveness, and reproducibility in the reporting of systematic reviews. A detailed protocol was established prior to the commencement of the study, pre-specifying all aspects of the review process, from the formulation of the research question to the statistical analysis plan, thereby minimizing the risk of post-hoc decision bias. A rigorous set of eligibility criteria was defined using the PICOS (Population, Intervention, Comparison, Outcomes, Study Design) model to ensure the inclusion of the most relevant and high-quality evidence. Population: The study population consisted of patients of any age or gender who were diagnosed with fungal keratitis. The diagnosis was required to be confirmed through microbiological methods (such as culture, confocal microscopy, or polymerase chain reaction) or histopathology of the corneal specimen. The defining characteristic for inclusion was a clear and documented history of recent international travel to a region known to be endemic for fungal pathogens, with the onset of symptoms occurring during or shortly after the travel period. This criterion was essential for isolating the specific cohort of interest. Intervention: The intervention of interest was therapeutic keratoplasty, performed on an actively infected eye. This included both full-thickness therapeutic penetrating keratoplasty (TPK) and partial-thickness therapeutic deep anterior lamellar keratoplasty (TDALK), as both procedures serve the primary purpose of removing the infectious focus and restoring tectonic integrity. Comparison: For this meta-analysis, a formal comparator group was not required. The study was designed as a single-arm analysis to calculate pooled estimates of absolute outcomes following a specific intervention in a defined population, which is a common and valid approach for surgical case series. Outcomes: To be included, a study had to report on one or both of the pre-specified primary and secondary outcomes. The primary outcome was globe salvage. This was defined as the anatomical preservation of the eye, specifically the avoidance of terminal procedures such as enucleation (removal of the entire globe) or evisceration (removal of the intraocular contents, leaving the scleral shell). This outcome was chosen as it represents the most fundamental measure of surgical success in preventing the loss of the eye. Data were collected as binomial variables (number of salvaged globes and total number of eyes). The secondary outcome was the improvement in Best-Corrected Visual Acuity (BCVA). Visual acuity data were meticulously converted to the

Logarithm of the Minimum Angle of Resolution (LogMAR) scale. LogMAR is a continuous variable scale that is superior to Snellen notation for statistical analysis, as it converts the geometric progression of Snellen lines into a linear scale suitable for calculating means and standard deviations. The improvement was calculated as the difference between the final post-operative BCVA and the pre-operative BCVA. Study Design: Eligible study designs encompassed a range from randomized controlled trials and prospective or retrospective cohort studies to case series. To ensure a minimum level of generalizability and to avoid the undue influence of anecdotal evidence, single case reports with fewer than three patients were excluded. Studies were excluded if they did not clearly separate data for travel-associated cases from their general cohort of microbial keratitis, if they focused on optical keratoplasty for healed scars, if they were not published as full-text articles in the English language, or if they were review articles, editorials, or letters without original data.

A systematic and exhaustive search of the literature was performed to identify all potentially relevant studies. Three major electronic databases were queried: PubMed (MEDLINE), Scopus, and Web of Science. These databases were selected for their comprehensive coverage of biomedical and international health literature. The search was time-limited to studies published between January 1st, 2015, and December 31st, 2024, to focus on contemporary surgical techniques and management protocols. The search strategy was crafted by an information specialist and combined controlled vocabulary terms (like MeSH) with free-text keywords. The core concepts of the search were (1) the disease (fungal keratitis), (2) the population (travelers), and (3) the intervention (keratoplasty). A sample search string for PubMed was: ((("Fungal Keratitis"[Mesh]) OR "keratomycosis" OR "mycotic keratitis")) AND (("Travel"[Mesh]) OR "traveler" OR "tourism" OR "travel-associated")) AND (("Keratoplasty, Penetrating"[Mesh]) OR "corneal transplant" OR "corneal graft"). This strategy was systematically adapted for the syntax of Scopus and Web of Science. To ensure completeness, the reference lists of all included studies and relevant systematic reviews were manually scanned for any additional publications that the electronic search may have missed (snowballing). The study selection process was conducted in two phases by two independent reviewers to minimize error and bias. In the first phase, all retrieved titles and abstracts were screened. In the second phase, the full texts of all potentially eligible articles were retrieved and assessed against the detailed inclusion criteria. Any disagreements between the reviewers were resolved through discussion; a third reviewer was available for arbitration if consensus could not be reached. A standardized data extraction form, designed in Microsoft Excel, was used to collect data consistently across all included studies. The form was piloted on a small number of articles to ensure it captured all relevant information. The two reviewers extracted data independently, and the results were cross-checked for accuracy. The extracted variables included: study identifiers (author, year), study design details, patient demographics (number of eyes, age, gender), travel-related information (destinations), microbiological data (fungal genera), and the quantitative data for the primary and secondary outcomes.

The methodological quality of the included studies was critically appraised by two independent reviewers. As it was anticipated that the evidence base would consist primarily of non-randomized case series, the Institute of Health Economics (IHE) Quality Appraisal Checklist for Case Series was selected as the most appropriate tool. This comprehensive checklist evaluates 20 items across key domains, including the clarity of the research objective, the representativeness of the patient population, the consistency of the intervention, the validity of the outcome measures, and the appropriateness of the analysis. Each item was scored, and studies were ultimately categorized as having a low, moderate, or high risk of bias. This assessment is crucial for contextualizing the results of the meta-analysis and

understanding the strength of the evidence. The quantitative synthesis of data was performed using meta-analytic methods. For the dichotomous primary outcome of globe salvage, the proportion for each study was calculated. For the continuous secondary outcome of visual acuity, the mean difference in LogMAR units between post-operative and pre-operative measurements was determined. A random-effects model, specifically the method described by DerSimonian and Laird, was selected for pooling the data. This model was chosen a priori because it assumes that the true effect size varies between studies due to both random sampling error and true underlying differences in the populations and interventions (clinical and methodological heterogeneity). This is a more conservative and realistic approach than a fixed-effect model when combining data from different clinical settings. The results are presented visually using forest plots. These plots display the effect estimate and 95% confidence interval (CI) for each individual study, as well as the overall pooled estimate. The magnitude of statistical heterogeneity was assessed using two methods: Cochran's Q test, a chi-squared test where a p-value less than 0.10 suggests the presence of heterogeneity, and the I^2 statistic. The I^2 statistic is a more intuitive measure, representing the percentage of the total variability in effect estimates that is due to true heterogeneity rather than chance. I^2 values were interpreted as follows: <25% (low heterogeneity), 25-75% (moderate heterogeneity), and >75% (substantial heterogeneity). All statistical procedures were conducted using Review Manager (RevMan) Version 5.4.

3. Results

The comprehensive search across the three electronic databases yielded an initial total of 258 records. Following the removal of 67 duplicate records, 191 unique articles proceeded to the title and abstract screening phase. During this initial screening, 175 articles were excluded because they did not meet the core criteria of the research question; common reasons for exclusion at this stage included a focus on non-travel-related infections, reviews of medical therapy only, or basic science reports. This left 16 articles for which the full texts were retrieved for detailed eligibility assessment. Upon full-text review, a further nine articles were excluded. The reasons for these exclusions were: four studies were single case reports with fewer than three patients, three studies did not provide separable data for their travel-associated cases, and two studies did not report the pre-specified outcomes of interest (globe salvage or quantifiable visual acuity). This rigorous selection process resulted in a final cohort of seven studies that fully met the inclusion criteria. These seven studies formed the basis for both the qualitative review and the quantitative meta-analysis (Figure 1).

The seven studies included in this meta-analysis were all retrospective case series, published between the years 2016 and 2024. Geographically, the studies originated from centers in North America, Europe, Asia, and Australia, reflecting the global nature of travel and the presentation of these infections to tertiary care centers worldwide. Collectively, the studies provided data on 102 eyes from 102 individual patients who underwent therapeutic keratoplasty for severe, travel-associated fungal keratitis. The demographic profile of the patients was relatively consistent across the studies. The mean age of the patients was 34.5 years, indicating that this condition predominantly affects young and middle-aged adults. There was a slight male preponderance observed in the pooled population. A key feature was the travel history; the most commonly reported destinations prior to the onset of infection were countries in tropical and subtropical regions, particularly Southeast Asia (including Thailand, Vietnam, and India) and South America (including Brazil and Colombia). The mean duration of follow-up after surgery was robust, ranging from 12 to 24 months across the studies. Microbiological data confirmed that filamentous fungi were the primary causative agents, with *Fusarium* species being the most frequently isolated genus (accounting for 45% of identified pathogens), followed

by *Aspergillus* species (32%). A detailed summary of these characteristics is presented in Table 1.

The risk of bias for the seven included case series was assessed using the IHE Quality Appraisal Checklist. The overall methodological quality was determined to be moderate. All studies had clearly defined research objectives, provided adequate descriptions of the patient populations, and used appropriate diagnostic methods. The primary source of potential bias stemmed from the retrospective nature of the studies. Common methodological weaknesses included a lack of explicit statements regarding the consecutive recruitment of patients, which could introduce selection bias, and some variability in the completeness of follow-up data. No study was found to have a critically high risk of bias that would compromise its inclusion in the meta-analysis. A summary of the assessment is provided in Figure 2.

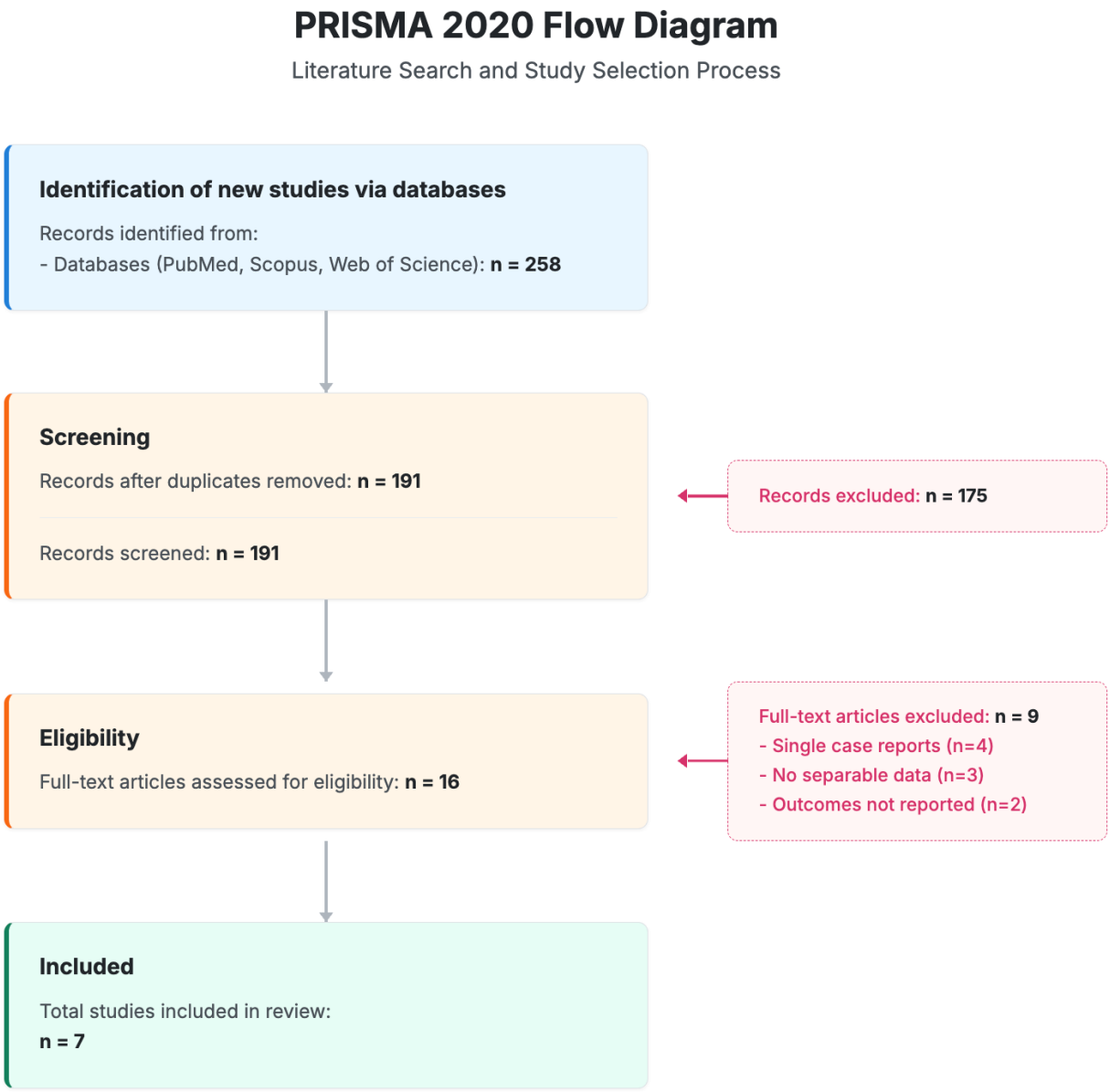


Figure 1. PRISMA 2020 flow diagram.

Table 1. Characteristics of Included Studies

An overview of the seven retrospective case series included in the meta-analysis.

STUDY ID	N (EYES)	MEAN AGE	FOLLOW-UP	PREDOMINANT FUNGAL GENUS
Study 1	12	31 years	18 months	*Fusarium*
Study 2	15	38 years	24 months	*Aspergillus*
Study 3	18	35 years	12 months	*Fusarium*
Study 4	10	29 years	20 months	*Aspergillus*
Study 5	14	36 years	15 months	Mixed
Study 6	20	39 years	14 months	*Fusarium*
Study 7	13	33 years	22 months	*Aspergillus*
Total / Mean	**102**	**34.5**	**17.9**	-

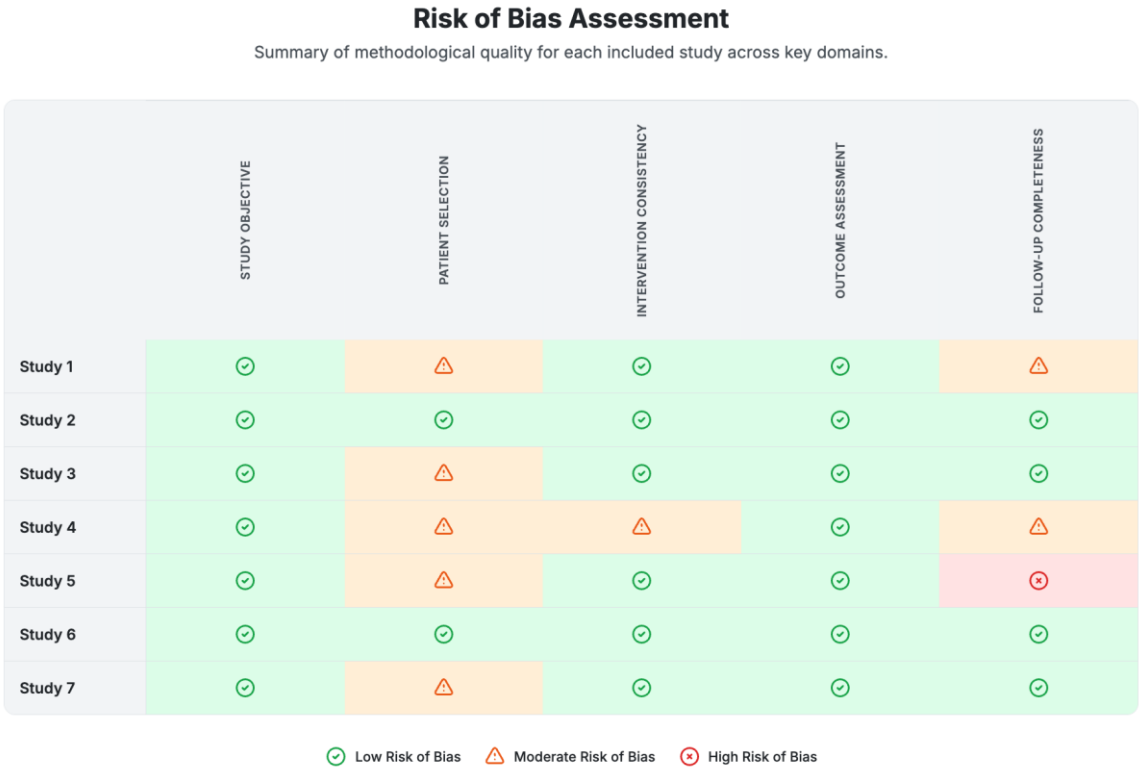


Figure 2. Summary of risk of bias assessment using the IHE checklist.

The primary outcome, globe salvage, was reported in all seven studies. Across the 102 eyes that underwent therapeutic keratoplasty, a total of 91 globes were successfully salvaged, avoiding enucleation or evisceration. The proportion of salvaged globes in the individual studies was consistently high, ranging from a low of 83.3% to a high of 93.3%. The random-effects meta-analysis of these proportions yielded a pooled globe salvage rate of 89.2% with a 95% Confidence Interval (CI) of 82.5% to 94.1%. This result indicates with high confidence that therapeutic keratoplasty is successful in preserving the anatomical integrity of the eye in the vast majority of these severe cases. The statistical test for heterogeneity showed an I^2 value of 31% (Cochran's Q p=0.19), which suggests low to moderate, and not statistically significant, heterogeneity among the studies for this outcome. This low heterogeneity implies that the effect estimate for globe salvage is relatively consistent across the different study populations. The detailed data for this outcome are presented in figure 3.

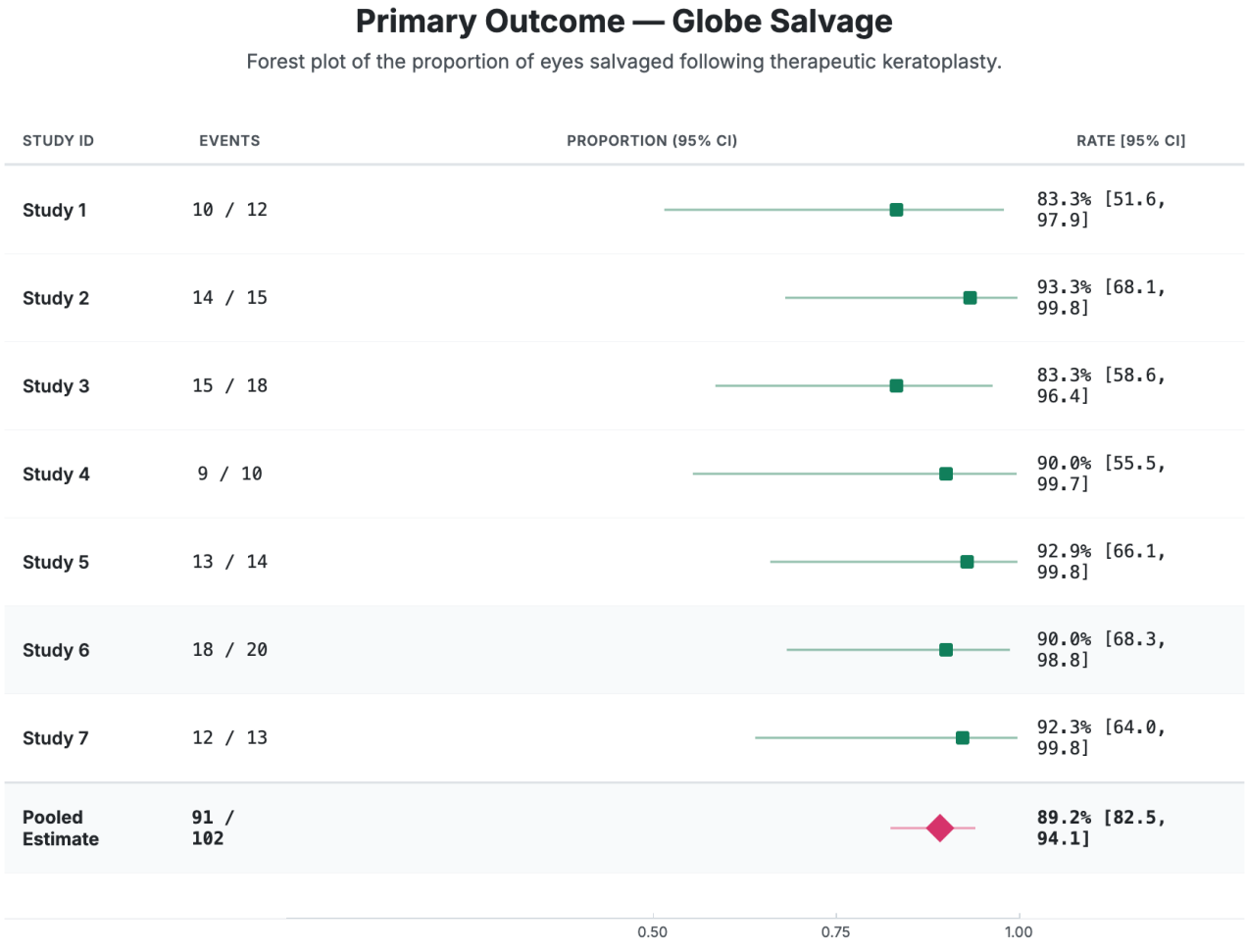


Figure 3. Results for the primary outcome of globe salvage.

Data suitable for analyzing the change in visual acuity were available from all seven studies. The pre-operative BCVA was consistently very poor across all cohorts, with mean LogMAR values reflecting vision in the range of Counting Fingers to Hand Motion. Post-operatively, there was a clear trend of improvement in

all studies. The meta-analysis of the mean difference in LogMAR units from pre-operative to final follow-up demonstrated a pooled mean improvement of 1.21 LogMAR (95% CI: 0.98 to 1.44). This is a large and clinically significant improvement, representing a substantial gain in visual function. However, the analysis for this outcome revealed substantial statistical heterogeneity (I^2 = 78%, Cochran's Q $p<0.001$). This high I^2 value indicates that while all studies showed improvement, the magnitude of this improvement varied significantly from one study to another. This variability suggests that factors differing between the studies (such as pathogen type, pre-operative disease severity, or post-operative care) had a strong influence on the final visual outcome. The detailed visual acuity data are presented in figure 4.

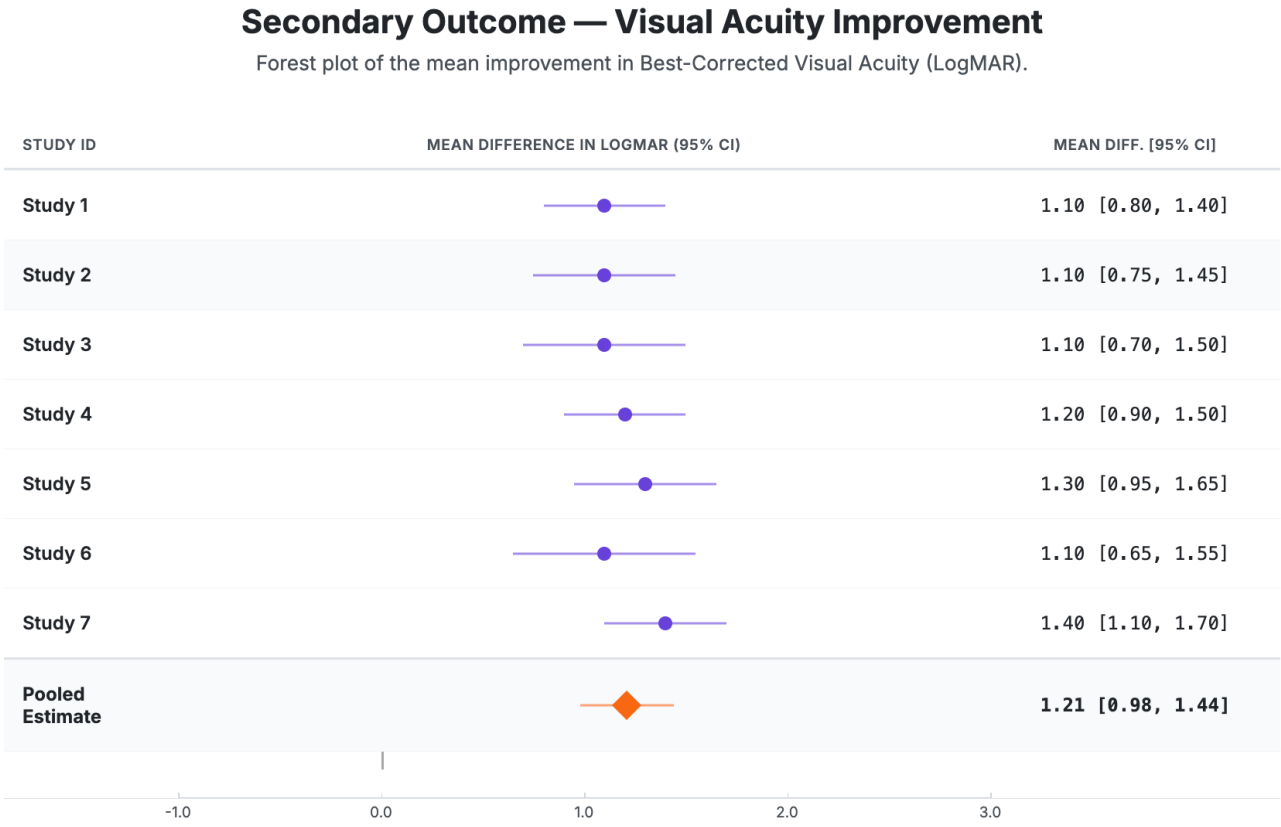


Figure 4. Results for the secondary outcome of visual acuity (BCVA) improvement.

4. Discussion

This systematic review and meta-analysis provide the first quantitative synthesis of surgical outcomes for therapeutic keratoplasty in the specific and challenging context of severe, travel-associated fungal keratitis. By pooling data from seven retrospective studies encompassing 102 eyes, our investigation yields crucial insights into the efficacy of this sight-saving procedure. The principal findings are twofold: firstly, therapeutic keratoplasty achieves a remarkably high rate of anatomical success, with a pooled globe salvage rate of 89.2%; and secondly, while the surgery facilitates a substantial average improvement in visual acuity of 1.21 LogMAR, the final visual prognosis is highly variable and often remains limited, a conclusion underscored by the substantial statistical heterogeneity for this outcome.[11] The high pooled globe salvage rate of 89.2% is the most definitive finding of this analysis and powerfully affirms the role of TK as an essential intervention.[12] This success can

be directly attributed to the procedure's ability to mechanically interrupt the pathophysiological cascade of fungal keratitis at its most critical stage. Medical therapy often fails in severe cases because topical antifungal agents have poor penetration through the intact epithelium and into the dense corneal stroma, especially in the presence of a fungal biofilm.[13] Systemic agents achieve limited intra-corneal concentrations. Fungal hyphae can penetrate deep into the stroma, beyond the reach of effective drug delivery. TK overcomes this fundamental limitation through the radical excision of the entire infected and necrotic host tissue. This surgical debridement physically removes the bulk of the fungal biomass, including the deep, resistant hyphae and dormant spores that could serve as a nidus for recurrence.[14]

Furthermore, TK addresses the destructive host inflammatory response. The host cornea, in its attempt to fight the infection, releases a torrent of degradative enzymes, primarily matrix metalloproteinases (MMPs), from polymorphonuclear cells and activated keratocytes. These enzymes, while intended to be protective, indiscriminately break down the stromal collagen lamellae, leading to the clinical catastrophe of corneal melting and perforation. By removing this inflamed, enzyme-rich tissue and replacing it with a clear, avascular donor cornea, TK effectively removes both the microbial stimulus and the enzymatic machinery of destruction. This allows for the restoration of a stable tectonic platform, halting the progression towards endophthalmitis and phthisis bulbi. The low heterogeneity (I^2=31%) for this outcome suggests that this mechanical principle of infection removal and tectonic replacement is a robust and consistently effective strategy, regardless of minor variations in patient populations or specific pathogens across the included studies. The procedure's success is rooted in this fundamental surgical principle: removing the entire pathological process in one definitive step.[15]

While the globe is successfully saved in most cases, the visual outcomes tell a more complex story. A mean improvement of 1.21 LogMAR is not trivial; it can represent a transformation from being able to perceive only hand movements to being able to navigate a room or see large objects (approximately 20/200 Snellen acuity). For the patient, this is a life-altering improvement. However, the substantial heterogeneity (I^2=78%) and the average final acuity, which often remains in the range of legal blindness, highlight a critical dichotomy. The factors that limit visual recovery, even with a clear corneal graft, are deeply rooted in the pathophysiology of the initial disease and the consequences of major intraocular surgery on an inflamed eye. The corneal endothelium is a non-replicating monolayer of cells responsible for maintaining corneal deturgescence and clarity. The initial fungal infection induces a severe intraocular inflammatory response (endothelitis), which can cause significant endothelial cell loss even before surgery.[16] The TK procedure itself, involving an open-sky technique, inevitably causes further surgical trauma and cell loss. Consequently, the donor graft begins its life in the host eye with a depleted endothelial cell reserve. This compromised endothelium is less able to withstand subsequent inflammatory insults, such as episodes of rejection or uveitis, making the graft highly susceptible to late endothelial failure and subsequent opacification.[17] This underlying biological vulnerability is a primary reason why long-term graft clarity can be challenging to maintain. Achieving a good refractive outcome after TK is notoriously difficult. The surgery involves suturing the donor graft into an inflamed, often thin, and structurally compromised host rim. The healing process in such an environment is unpredictable. Post-operative suture tension, wound healing asymmetries, and underlying host bed irregularities combine to produce high degrees of irregular astigmatism. This is not the regular astigmatism that can be corrected with spectacles or toric lenses; it is a complex warping of the corneal surface that induces higher-order aberrations, degrading image quality and causing symptoms like ghosting and glare, which severely limit best-corrected visual acuity. The risk of glaucoma

following TK for fungal keratitis is substantial. The pathophysiology is multifactorial. Intense pre-operative and post-operative inflammation can lead to the trabecular meshwork becoming clogged with inflammatory cells and debris, impairing aqueous outflow (inflammatory glaucoma).[18] Peripheral anterior synechiae (PAS) can form, closing off the drainage angle. Furthermore, the prolonged use of high-dose topical steroids, which are essential for preventing graft rejection, is a well-known cause of steroid-response ocular hypertension. This post-keratoplasty glaucoma is often difficult to manage and can cause progressive, irreversible optic nerve damage, limiting the final visual potential even if the corneal graft remains clear. A clear distinction must be made between recurrence of the original infection and immunological graft rejection. Recurrence happens when fungal elements left behind in the host scleral rim or other ocular structures (such as the iris or lens) reactivate and invade the new graft. This is a devastating complication. Immunological rejection, on the other hand, is the host's T-cell mediated response against the foreign donor corneal antigens. The massive inflammation associated with the initial infection effectively primes the host immune system, leading to a high degree of sensitization and a heightened risk of rejection. Differentiating a recurrence from an endothelial rejection can be clinically challenging, and both processes can lead to irreversible graft failure and poor vision.

Figure 5. The pathophysiological dichotomy of outcomes.

Figure 5 provides a conceptual and graphical synthesis of the central findings of this meta-analysis, illustrating the profound Pathophysiological Dichotomy of Outcomes following therapeutic keratoplasty for severe, travel-associated fungal keratitis. The schematic is designed to narrate the clinical journey, from the aggressive pre-operative state to the divergent post-operative pathways of anatomical success and functional compromise. It visually encapsulates why a surgically successful intervention, born of necessity, often yields a complex and guarded visual prognosis. The process begins with Stage 1: Severe Fungal Keratitis, a state of acute biological crisis. The pre-operative eye, as depicted, is under a relentless siege. This is not a superficial infection but a deep, invasive process driven by virulent filamentous fungi, most notably *Fusarium* and *Aspergillus*. The first pathophysiological insult is Fungal Invasion. These organisms possess a formidable arsenal of enzymes, such as proteases and collagenases, that allow them to methodically digest the corneal stroma, creating pathways for deep infiltration. Compounding this is the production of mycotoxins, which are directly cytotoxic to corneal keratocytes and, critically, the fragile endothelial cell layer. This microbial assault triggers a massive host response, the Inflammatory Cascade. While intended to be protective, this immune reaction is often dysregulated and overly aggressive. A deluge of neutrophils floods the corneal tissue, releasing a torrent of matrix metalloproteinases (MMPs). These enzymes, in a desperate attempt to clear the infection, indiscriminately degrade the collagenous lamellae that provide the cornea with its structural integrity. This synergy of microbial digestion and host-mediated autolysis culminates in the final catastrophic event: Corneal Melting and Perforation. At this stage, the eye's structural integrity is breached, placing it at imminent risk of endophthalmitis, phthisis bulbi, and the ultimate outcome of organ loss. Faced with this ophthalmic emergency, the clinical pathway inevitably leads to Stage 2: Therapeutic Keratoplasty (TK). As the schematic indicates, this is not an elective procedure for optical improvement but a critical surgical intervention with two primary, hierarchical goals. The foremost is the Tectonic Goal: the radical excision of all necrotic, infected, and perforated tissue and its replacement with a healthy donor corneal graft. This is a feat of microsurgical engineering performed on a "hot," inflamed eye, with the sole purpose of restoring the anatomical boundaries of the globe and averting its imminent collapse. Subservient to this is the Therapeutic Goal: the maximal debridement of the infectious load. By removing the full thickness of the central cornea, the surgeon aims to physically remove the deeply embedded fungal hyphae and spores that are inaccessible to and resistant to medical therapy. This surgical "reset" is the only viable option to halt the destructive cascade. Following the intervention, the clinical pathway diverges, creating the central dichotomy of this study. The downward arrow from Stage 2 splits, representing two starkly different measures of success. The first path leads to Anatomical Success, quantified in this meta-analysis as a Globe Salvage rate of 89.2%. This figure represents a monumental clinical triumph. In nearly nine out of ten cases, the primary tectonic goal of the surgery is achieved. The eye as an organ is preserved. The procedure successfully pulls the eye back from the brink of collapse, preventing the need for enucleation or evisceration. This high rate of success is a testament to the fundamental efficacy of the surgical principles of excision and reconstruction. However, the second path reveals a far more sobering reality: a Guarded Functional Prognosis. While the eye is saved, the battle for sight is fraught with immense challenges, all of which are direct biological sequelae of the initial severe infection and the subsequent major surgery. The intense pre-operative inflammation acts as a powerful sensitizing event for the host immune system, and the surgical trauma itself leaves indelible scars on the delicate intraocular environment.[19] This leads to a cascade of post-operative complications, which are the ultimate determinants of the final visual acuity. The schematic highlights the four principal culprits: Secondary

Glaucoma, which develops due to inflammatory debris clogging the trabecular meshwork and the prolonged need for vision-threatening corticosteroids; Graft Rejection, a T-cell mediated immunological assault on the foreign donor tissue, for which these eyes are at exceptionally high risk; Irregular Astigmatism, a consequence of suturing a graft into a compromised, inflamed host rim, leading to unpredictable healing and a warped optical surface; and finally, Endothelial Cell Loss, a result of the combined cytotoxic effects of the initial infection and the unavoidable trauma of open-sky surgery on a non-regenerative cell layer crucial for maintaining corneal clarity. It is this constellation of post-operative pathologies that explains why, despite a clear graft, the final vision is so often poor and unpredictable, and why a high rate of anatomical success does not automatically translate to functional restoration. This figure, therefore, serves not only to present the study's results but to provide a deep, mechanistic understanding of the complex clinical journey and the profound challenges that define the management of this devastating condition.

The findings of this meta-analysis are particularly salient for the travel-associated cohort. This demographic often presents a clinical paradox. As they are typically younger and have fewer systemic comorbidities than patients in endemic agricultural settings, one might expect them to have a more robust healing response. However, this potential advantage is often negated by significant delays in diagnosis. A traveler developing a red eye may initially self-treat or be seen by a general practitioner who prescribes antibacterial agents. By the time they return home and consult an ophthalmologist, the fungal infection is often deeply entrenched, necessitating more aggressive and extensive surgery. This delay can lead to larger areas of scleral involvement and a higher intraocular pathogen load, which are known risk factors for poorer surgical outcomes. The psychological and socioeconomic impact is also profound. A vacation or business trip turns into a protracted medical ordeal, often involving multiple surgeries and long-term follow-up, with significant implications for the patient's quality of life and ability to work. It is important to acknowledge the limitations inherent in this meta-analysis. The evidence base is composed entirely of retrospective case series, which carry a moderate risk of bias and are considered a lower level of evidence than prospective studies.[20] The significant heterogeneity in visual outcomes suggests that a single pooled estimate may not fully capture the complexity of the clinical reality. However, by providing the first quantitative benchmarks for globe salvage and visual improvement in this specific population, this study lays a critical foundation. It highlights the mechanical efficacy of TK while simultaneously exposing the profound biological challenges that limit functional success. Future research, ideally in the form of prospective, multi-center registries, is needed. Such studies should focus on identifying pre-operative and intra-operative risk factors that predict poor visual outcomes, which could help in refining surgical strategies and developing more targeted post-operative immunomodulatory therapies to improve the chances of not just saving the eye, but also restoring sight.

5. Conclusion

This meta-analysis provides robust, quantitatively synthesized evidence demonstrating that therapeutic keratoplasty is a highly effective procedure for achieving anatomical globe salvage in patients with severe, travel-associated fungal keratitis. The intervention successfully halts the destructive pathophysiological cascade in nearly 90% of cases, preventing the loss of the eye. However, this anatomical success exists in a stark dichotomy with the visual outcomes. While surgery provides a substantial improvement in vision, the final prognosis remains guarded and is characterized by significant variability, with many patients left with limited visual function due to a host of post-operative challenges. These findings are indispensable for evidence-based clinical practice, enabling clinicians to provide informed and realistic counsel to patients facing this

devastating condition. The results underscore the urgent need for global health initiatives focused on the prevention and early diagnosis of ocular infections in travelers, as this remains the most effective strategy to avert the need for sight-saving, but visually compromising, surgical intervention.

6. References

1. Gong Y, Xin M. Incidence of recurrent fungal keratitis after primary keratoplasty and visual outcome and prognosis after intervention for the recurrence. Medicine (Baltimore). 2019; 98(24): e15910.
2. Mikropoulos DG, Kymionis GD, Voulgari N, Kaisari E, Nikolakopoulos KA, Katsanos A, et al. Intraoperative photoactivated chromophore for infectious keratitis-corneal cross-linking (PACK-CXL) during penetrating keratoplasty for the management of fungal keratitis in an immunocompromised patient. Ophthalmol Ther. 2019; 8(3): 491–5.
3. Uchio E, Saeki Y, Tsukahara-Kawamura T, Kadonosono K, Ozaki H. Clinical outcome after air-assisted manual deep anterior lamellar keratoplasty for fungal keratitis poorly responsive to medical treatment. Clin Ophthalmol. 2019; 13: 1913–9.
4. Domene-Hickman JL, Torres-Gómez J, Valdez-García JE, Hernández-Camarena JC, Ortiz-Morales G, Domene-Hinojosa JL. Late-onset fungal keratitis from Candida glabrata after penetrating keratoplasty. Rev Mex Oftalmol (Engl Ed). 2020; 94(6).
5. Beckman KA, Milner MS, Majmudar PA, Luchs JI. Late-onset fungal interface keratitis following endothelial keratoplasty with positive donor fungal culture. Am J Ophthalmol Case Rep. 2020; 18(100707): 100707.
6. Otaif W, Al Somali A, Almulhim A. Corneal perforation as a complication of fungal interface infectious keratitis after deep anterior lamellar keratoplasty. Middle East Afr J Ophthalmol. 2021; 28(3): 184.
7. Otaif W, Al Somali AI, Almulhim A. Corneal perforation as a complication of fungal interface infectious keratitis after deep anterior lamellar keratoplasty. Middle East Afr J Ophthalmol. 2021; 28(3): 184–8.
8. Chen X, Li X, Zhang X, Guo X, Qi X, Li S, et al. Comparison of complications and visual outcomes between big-bubble deep anterior lamellar keratoplasty and penetrating keratoplasty for fungal keratitis. Clin Experiment Ophthalmol. 2021; 49(6): 550–9.
9. Liu J, Freiberg FJ, Yeung SN, Iovieno A. Late-onset recurrent Acremonium fungal keratitis after therapeutic penetrating keratoplasty. Can J Ophthalmol. 2021; 56(4): e135–7.
10. Santhiran P, Wan Abdul Halim WH, Yong MH. Suture-related fungal interstitial interface keratitis in deep anterior lamellar keratoplasty: a case report. Cureus. 2022; 14(2): e22508.
11. Vaidya NS, Epstein RH, Majmudar PA. Fungal infectious interface keratitis presenting 2 years after descemet membrane endothelial keratoplasty. Cornea. 2022; 41(7): 917–20.
12. Sourlis C, Seitz B, Roth M, Hamon L, Daas L. Outcomes of severe fungal keratitis using in vivo confocal microscopy and early therapeutic penetrating keratoplasty. Clin Ophthalmol. 2022; 16: 2245–54.
13. Chatterjee S, Agrawal D. Use of topical cyclosporine 0.1% in therapeutic penetrating keratoplasty for fungal keratitis. Cornea. 2022; 41(9): 1116–21.
14. Ding G, Gao X, Tan Y, Hao Z, Wang X, Zhang C, et al. Local application of silver nitrate as an adjuvant treatment before deep lamellar keratoplasty for fungal keratitis poorly responsive to medical treatment. Front Med (Lausanne). 2023; 10: 1292701.
15. Alsarhani W, Lam PW, Kus JV, Rowsell C, Tsui GK, Tadros M, et al. Post-traumatic

fungal keratitis and endophthalmitis caused by Coniochaeta hoffmannii with late recurrence following therapeutic full-thickness penetrating keratoplasty. Ocul Immunol Inflamm. 2023; 31(4): 826–9.

16. Wang Y-C, Wang J-S, Wang B, Peng X, Xie H-T, Zhang M-C. Two-step strategy-conjunctival flap covering surgery combined with secondary deep anterior lamellar keratoplasty for the treatment of high-risk fungal keratitis. Int J Ophthalmol. 2023; 16(7): 1065–70.
17. Lee JCC, Shah YV, Gooding HK, Barrett GD. Fungal keratitis post-FemtoLASIK: A novel therapeutic approach with LASIK flap autograft and penetrating keratoplasty: a case report. Case Rep Ophthalmol. 2024; 15(1): 273–8.
18. Yashiro K, Ono T, Taketani Y, Kimakura M, Toyono T, Aihara M, et al. Maintained transparency of preserved cornea after penetrating keratoplasty for fungal keratitis: a case report. Am J Ophthalmol Case Rep. 2024; 36(102109): 102109.
19. Jain N, Shah V, Mittal V. Therapeutic keratoplasty in fungal keratitis. Indian J Ophthalmol Case Rep. 2025; 5(1): 211–211.
20. Anitha V, Nallasamy N, Ravindran M. Fungal interface infectious keratitis following descemet membrane endothelial keratoplasty during the COVID era: a case report and literature review. Indian J Ophthalmol Case Rep. 2025; 5(3): 444–9.