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Clinical Consequences of Delayed Corneal Ulcer Treatment: A Systematic Review

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A B S T R A C T

Corneal ulcer is an ophthalmic emergency that can lead to irreversible blindness if not treated promptly. Multiple studies have linked delayed management to an increased risk of severe complications such as corneal perforation, reduced visual acuity, and the need for keratoplasty. This study aims to assess the impact of delayed management of corneal ulcers on clinical outcomes and to identify factors contributing to treatment delays. This study is a systematic review of publications from 2020 to 2025, retrieved from the PubMed, Scopus, and ScienceDirect databases, using the keywords "infectious corneal ulcer," "treatment delay," and "visual outcome." Eligible studies included observational designs (cohort, cross-sectional, retrospective) evaluating the association between delayed treatment (≥48-72 hours after symptom onset) and clinical outcomes. Three studies met the inclusion criteria following PRISMA 2020 screening guidelines. The analysis confirms that the interval between symptom onset and initiation of topical antibiotic therapy is a critical determinant of visual outcome. Early intervention guided by microbiological culture and resistance profiles markedly improves prognosis. Strengthening referral systems and adopting teleophthalmology services can effectively reduce diagnostic delays, particularly in resource-limited regions. Delayed management of corneal ulcers leads to severe clinical consequences affecting patients' visual function. Public education, improved primary care capacity, and the application of rapid, technology-assisted referral systems are essential strategies to ensure timely diagnosis and prevent blindness-related complications.

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INTRODUCTION

Corneal ulcer is one of the most serious ophthalmic conditions and has the potential to cause permanent blindness if not treated promptly and appropriately. This condition is characterized by a defect in the corneal epithelium involving the stroma, resulting from infectious or noninfectious processes, most commonly caused by bacteria, fungi, viruses, or protozoa such as Acanthamoeba (Kanski & Bowling, 2011). Globally, corneal ulcer remains a leading cause of corneal blindness, particularly in developing countries, with an estimated incidence of over 1.5 million new cases annually and a high disability burden due to vision loss (Ung et al., 2019). Despite significant advances in antimicrobial therapy and corneal surgical techniques, delays in initial management remain a major determinant factor that profoundly influences patients' visual prognosis (Ting et al., 2021).

Delayed management of corneal ulcers can be defined as a prolonged interval between the onset of initial symptoms and the initiation of appropriate therapy. Several studies have shown that the longer patients delay seeking medical care, the greater the likelihood of developing severe complications such as corneal perforation, permanent scar formation, and even total blindness (Kodali et al., 2024). In clinical practice, each day of delay may exacerbate stromal tissue destruction due to proteolytic and inflammatory activity, resulting in significant visual acuity reduction even after the infection has been resolved (Venugopal et al., 2024).

Several studies have reported that the factors contributing to delayed management include low public awareness of the warning signs of eye infections, limited access to ophthalmic services in rural areas, and the inappropriate use of eye drops, particularly unsupervised topical steroids (Hoffman et al., 2022). Furthermore, in middle-income countries such as Indonesia, socioeconomic barriers, long geographic distances from referral hospitals, and the shortage of ophthalmologists in primary healthcare facilities further exacerbate delays in diagnosis and treatment (Ung et al., 2019). This indicates that treatment delay is not merely a clinical issue but also a multidimensional health system problem.

Clinically, delayed management has several significant consequences. First, patients presenting late tend to have larger ulcer sizes and deeper stromal infiltrates at the time of initial diagnosis (Kodali et al., 2024). Second, delays increase the risk of corneal perforation, which may necessitate surgical procedures such as penetrating keratoplasty or even evisceration in severe cases (Woodward et al., 2023). Third, the final visual outcomes of patients who experience treatment delays exceeding seven days are substantially worse compared to those who receive therapy within 48 hours of symptom onset (Venugopal et al., 2024). In addition, the resulting social and economic impacts, such as loss of work productivity and increased long-term treatment costs, further aggravate the burden on patients and their families (Hoffman et al., 2022).

Although the relationship between delayed treatment and clinical outcomes has been frequently reported, inconsistencies remain regarding the

definition of "delay" across studies, variations in pathogen types, and differences in geographical and healthcare system contexts, all of which make synthesizing the findings complex (Ting et al., 2021). Therefore, a systematic review is needed to comprehensively compile, evaluate, and analyze the latest scientific evidence concerning the clinical impact of delayed management of corneal ulcers.

LITERATURE REVIEW

In this context, the present study is designed to address several key questions, which also serve as the research problems of this systematic review. First, to what extent is the delay in receiving definitive therapy associated with clinical outcomes in patients with corneal ulcers, particularly in terms of final visual acuity, incidence of perforation, the need for surgical intervention, and the duration of wound healing? Second, is there a specific time threshold, such as a delay exceeding 48 hours, seven days, or one month, that is consistently associated with an increased risk of poor clinical outcomes? Third, what factors moderate or exacerbate the clinical consequences of such delays, including the type of causative microorganism, prior medication use, patient age, or systemic comorbidities such as diabetes? Fourth, how do geographical and socioeconomic variations influence the relationship between delayed management and clinical outcomes? Finally, what is the methodological quality of the existing studies, and what are its implications for policy and clinical practice in corneal ulcer management across different levels of healthcare?

By summarizing and evaluating scientific evidence published between 2020 and 2025, this systematic review is expected to provide a comprehensive understanding of the clinical consequences of delayed management of corneal ulcers. Furthermore, the findings of this review are anticipated to serve as a foundation for developing preventive policies, strengthening rapid referral systems, and enhancing public and primary healthcare education to enable earlier detection and treatment of corneal ulcers, thereby reducing the incidence of blindness caused by preventable complications.

METHODOLOGY

This study employed a systematic review approach based on the PICO framework (Population, Intervention, Comparison, Outcome), designed to systematically identify, evaluate, and synthesize scientific evidence regarding the clinical consequences of delayed management of corneal ulcers. This approach was chosen because it provides a clear structure for identifying population factors, interventions, comparisons, and clinical outcomes under investigation, thereby minimizing bias and enhancing the validity of the review findings (Egger et al., 2022).

PICO Design

Table 1. PICO Framework

Patient/Problem	Patients diagnosed with corneal ulcers (infectious or non-infectious) of various ages and genders. The included studies involved patients from the onset of symptoms to the time of

	diagnosis and first medical intervention
Intervention	Medical or surgical treatments administered after a delay in diagnosis or initial therapy, including the use of topical antibiotics, antifungals, antivirals, or therapeutic keratoplasty procedures
Comparison	Patients who received prompt (early) management or timely interventions in accordance with standard ophthalmological guidelines
Outcome	Clinical consequences, including the degree of vision loss, corneal perforation, the need for keratoplasty, evisceration, or permanent blindness resulting from delayed management

This PICO framework helps focus the literature search and data analysis on the relationship between treatment delay and both short- and long-term clinical outcomes in patients with corneal ulcers (Rathi et al., 2022).

Literature Search

The literature search was conducted systematically across several major scientific databases, including PubMed, Scopus, ScienceDirect, and Google Scholar, using the following combination of keywords: ("corneal ulcer" OR "infectious keratitis") AND ("delayed treatment" OR "treatment delay" OR "late diagnosis") AND ("clinical outcomes" OR "visual prognosis" OR "corneal perforation").

The search was limited to publications from 2020 to 2025 to ensure the relevance of data to current clinical conditions and therapeutic guidelines. Only articles written in English and Indonesian were included. The search process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021).

The selection procedure consisted of four stages: identification of relevant articles based on titles and abstracts; screening to remove duplicates; eligibility assessment based on inclusion and exclusion criteria; and final inclusion for systematic analysis.

The inclusion criteria were: (1) observational or prospective cohort clinical studies on corneal ulcers; (2) clear reporting of treatment timing and clinical outcomes; and (3) studies involving human subjects. The exclusion criteria were: animal studies, single case reports, narrative reviews, and articles lacking quantitative clinical data.

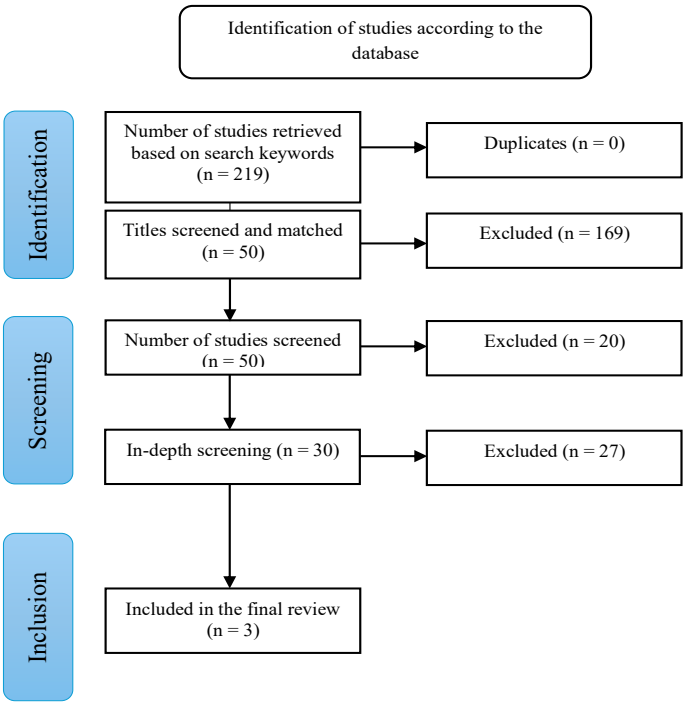

Figure 1. Literature Search Flowchart

The research identification process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow (Bagan 1), resulting in a total of three studies that met the inclusion criteria.

Data Extraction and Analysis

Data from each article that met the inclusion criteria were extracted using a standardized worksheet, which included the following variables: authors, year of publication, study location, sample size, patient characteristics, type of intervention, delay duration, and key clinical outcomes.

The analysis was conducted using a descriptive and comparative approach, comparing clinical outcomes between groups that received delayed versus timely management. The results were categorized based on the main clinical consequences, such as loss of visual acuity, corneal perforation, and the need for further surgical intervention (Atta et al., 2022).

Table 2. Characteristics of Included Studies

Authors & Year	Study Design	Population and Sample Size (n)	Definition or Context of Delayed Management	Intervention / Main Variables	Measured Outcomes	Main Findings
Indian Journal of Ophthalmology (2023) "Long-Term	Retrospective cohort	86 patients with severe corneal infections who underwent	Delay in presentation to a referral hospital (≥7 days	Therapeutic Penetrating Keratoplasty (TPK) performed on patients	Anatomical graft success, improvement in visual	Patients with delayed presentation showed

Outcomes of Therapeutic Corneal Transplantation in Patients with Delayed Presentation"		Therapeutic Penetrating Keratoplasty (TPK)	after symptom onset)	with advanced corneal ulcers (often already perforated)	acuity, and postoperative complications	a higher rate of corneal perforation (48%) and poorer visual outcomes ($p < 0.01$) compared to those who presented earlier
Outcome of Therapeutic Penetrating Keratoplasty in Advanced Infectious Keratitis (2020)	Retrospective non-comparative	57 eyes with advanced corneal ulcers (bacterial/fungal)	No specific time cutoff mentioned, but all patients were categorized as having "advanced keratitis" due to delayed medical therapy	TPK procedure for perforated or impending perforation corneal ulcers	Post-TPK anatomical integrity, graft clarity, and complications (rejection, reinfection)	TPK successfully maintained anatomical integrity in 82.4% of cases; however, only 29.8% achieved a visual acuity of ≥3/60. Delayed initiation of therapy was identified as a factor contribut

						ing to poorer prognosis
A Case Series of Overnight Orthokeratology-Related Acanthamoeba Keratitis in Northwest China (2025)	Retrospective case series	10 patients (15 eyes) who were orthokeratology lens users with Acanthamoeba keratitis	Median delay in diagnosis: 5 days (range 2–150 days) from symptom onset	Combination therapy with topical antimicrobials, debridement, and keratoplasty in selected cases	Final visual acuity, length of hospital stays, and need for surgical intervention	The longer the diagnostic delay, the greater the risk of corneal perforation and the need for therapeutic keratoplasty ($r = 0.61$, $p < 0.05$). The mean final visual acuity was worse in patients with delays exceeding seven days

RESULT AND DISCUSSION

This systematic review found consistent evidence that delayed diagnosis or management of corneal ulcers is strongly associated with poorer clinical outcomes, including reduced final visual acuity, increased frequency of corneal perforation, and a higher likelihood of requiring therapeutic surgical interventions such as therapeutic penetrating keratoplasty (TPK) or other reconstructive procedures. These findings are reflected in large-scale studies highlighting the high proportion of patients who presented with corneal perforation and subsequently required TPK (Christy et al., 2023), as well as in case series on Acanthamoeba keratitis, which reported a median diagnostic delay of five days and a correlation between delay and the need for surgical procedures (Zhao et al., 2025). Conceptually, these results align with the broader literature on the microbiology and disease progression of infectious keratitis, in which the time to diagnosis and initiation of therapy are identified as key determinants of prognosis (Ting, 2021).

Biological Mechanism

Pathophysiologically, infectious corneal ulcers can develop very rapidly. Pathogenic microorganisms (aggressive bacteria, filamentous fungi, Acanthamoeba) trigger an acute inflammatory response and the release of proteolytic enzymes (e.g., collagenase) as well as microbial toxins that destroy the stromal matrix. If antimicrobial therapy is administered promptly, pathogen replication is inhibited, the inflammatory response is modulated, and tissue loss can be minimized. If a delay occurs, the destructive process lasts longer, the infiltrate enlarges and penetrates the corneal layers, thereby increasing the risk of perforation and leaving significant scarring, factors that explain the decrease in final visual acuity even after the infection is controlled (Ting, 2021). The analyzed studies showed that patients who presented late tended to have larger infiltrates and greater stromal depth, conditions that forced therapeutic choices to become more invasive (TPK) and reduced the chances of functional visual improvement.

Differences by Microbial Etiology

The etiology of infection moderates the effect of delay. Fungal (filamentous fungi) and Acanthamoeba infections tend to show different clinical courses compared to most bacterial cases: in some fungal infections, lesions may progress more slowly but penetrate deeper and are more resistant to initial empirical therapy. Therefore, delays in diagnosis or empirical treatment that do not include antifungal coverage will worsen the prognosis (Ting, 2021). The Acanthamoeba case series (Zhao et al., 2025) confirmed that delayed diagnosis (median 5 days in their sample) was strongly associated with the need for surgical intervention in a substantial proportion of cases. Hence, the local microorganism pattern should guide the clinical threshold of suspicion and early empirical therapy in endemic areas.

Observed Clinical Impacts: Perforation, TPK, and Final Visual Acuity

Evidence from the analyzed studies and published literature indicates several outcomes most affected by treatment delay:

1. Corneal perforation: Patients presenting late have a higher risk of corneal perforation. Perforation not only worsens visual prognosis but also shifts

management from conservative therapy to emergency surgery, which in many settings is associated with poorer anatomical and functional outcomes (Christy et al., 2023).

2. Need for surgical intervention (TPK/reconstruction): Delay increases the frequency of TPK. Large-scale studies in India and clinical experience have shown that nearly half of TPK patients present with perforation or non-healing ulcers, confirming a direct relationship between delayed presentation and surgical requirement (Christy et al., 2023). Graft survival and postoperative visual outcomes after TPK are influenced by preoperative conditions (such as perforation, active infection, and graft size), so patients presenting late tend to have worse prognoses.
3. Final visual acuity: Although some patients experience visual improvement after medical or surgical therapy, those who receive early intervention and avoid perforation have a higher likelihood of achieving functional vision. A preliminary multicenter prospective study reported a negative correlation between time-to-treatment and best-corrected visual acuity (BCVA) at day 90. Therefore, time-to-treatment serves as a practical and meaningful prognostic parameter.

Systemic, Socioeconomic, and Behavioral Factors Contributing to Delay

Qualitative studies and surveys have described several non-medical factors contributing to treatment delay, including patients' lack of awareness regarding the urgency of ocular symptoms, limited geographic access to ophthalmologic services, financial constraints, inappropriate use of topical medications (including unsupervised steroid use), and weak referral pathways between primary and tertiary care facilities. In developing countries, the combination of these factors often results in patients presenting at an advanced stage of the disease. Interventions limited to the specialist level are insufficient; instead, a systemic approach is required, encompassing community education, screening training for primary healthcare providers, and the establishment of rapid referral mechanisms (Das et al., 2022).

The Role of Rapid Diagnosis and Laboratory Capability

Rapid etiological diagnosis (scraping and culture, PCR, and confocal imaging for Acanthamoeba or fungi) influences the selection of appropriate therapy and clinical outcomes. Most major referral centers possess microbiological facilities that shorten the time to targeted therapy; however, in regions lacking such facilities, empirical therapy alone is often used. When this empirical treatment does not cover the correct etiologic agent (for example, antifungal coverage for fungal keratitis), the likelihood of treatment failure increases, further exacerbating the negative impact of delay (Ting, 2021; Cabrera-Aguas & Watson, 2023). Improving access to rapid diagnostic tools (e.g., point-of-care PCR, confocal microscopy) could mitigate poor outcomes associated with delayed management.

Clinical and Policy Implications

Based on the collected evidence, several recommendations can be formulated:

1. Public education and early detection campaigns. Outreach programs emphasizing that symptoms such as severe eye pain, reduced vision, and ocular discharge require immediate medical attention can help reduce the average delay in presentation.
2. Training of primary healthcare providers. Implementing corneal symptom triage screening in primary care centers or community clinics can prevent unnecessary topical steroid use and ensure timely referral.
3. Strengthening referral networks and tele-ophthalmology. Standardized referral pathways and the use of teleconsultation can accelerate triage and early management, especially in remote areas.
4. Availability of regional microbiological diagnostics and development of empirical therapy algorithms that account for local pathogen prevalence (e.g., fungal dominance in agricultural regions).
5. Preparation of surgical services (TPK) as an emergency care option at referral centers, including graft stock readiness and trained surgical teams to handle perforation cases promptly.

Implementing these recommendations requires synergy between health policymakers, healthcare facility management, and clinical practitioners to minimize delays and improve patient outcomes.

Limitations of Evidence and Review

Several limitations were identified:

1. Heterogeneity in the definition of delay: The available studies used varying definitions (e.g., >48 hours, >72 hours, ≥5 days, or simply "delayed presentation"), making it difficult to establish a universal time cut-off. This heterogeneity hinders quantitative meta-analysis.
2. Observational study design: Much of the evidence originates from retrospective studies that are susceptible to selection bias and confounding (for example, more severe patients tend to present later). Only multinational prospective studies can adequately minimize these biases.
3. Geographical representativeness: Most large-scale studies come from referral centers in countries with a high disease burden (such as India and China). While this is valuable for the local context, generalization of findings should be done cautiously.
4. Variability in microbial etiology: Because etiology influences prognosis and treatment response, pathogen heterogeneity adds complexity to interpreting the specific effects of delay.

CONCLUSIONS AND RECOMMENDATIONS

To strengthen the evidence and generate more prescriptive recommendations, researchers should:

1. Conduct multicenter prospective studies that measure time-to-treatment continuously and adjust for confounding factors such as initial infiltrate size, prior steroid use, and comorbidities.
2. Develop a core outcome set for corneal ulcers (including standardized definitions of delay, final visual outcomes, perforation criteria, and

healing time) to enable meaningful comparison and data pooling across studies.

3. Implement implementation studies (such as cluster randomized controlled trials or quasi-experimental designs) to evaluate system-level interventions aimed at reducing delays and improving outcomes, for example, fast-track referral pathways, community education programs, and tele-ophthalmology.

Assess the economic aspects (cost-effectiveness) of interventions that prevent delays, as early preventive measures are likely to reduce long-term costs associated with surgery and prolonged care

Delay in the management of corneal ulcers has been proven to have a significant clinical impact on visual prognosis and ocular integrity. Based on a systematic review of studies published between 2020 and 2025, delayed diagnosis and treatment, whether caused by limited access to healthcare, inadequate diagnostic facilities, low public awareness, or initial mismanagement, are consistently associated with increased infection severity, higher risk of corneal perforation, and greater need for emergency keratoplasty. Moreover, treatment delays heighten the likelihood of long-term complications such as iatrogenic astigmatism, endothelial damage, and even permanent blindness.

These findings emphasize that time is a critical factor in the management of corneal ulcers. Interventions initiated within the first 24-48 hours after symptom onset play a pivotal role in limiting disease progression and preserving visual acuity. Therefore, a more efficient referral system, continuous training for primary healthcare providers, and public education regarding the early signs of corneal ulceration are essential to prevent treatment delays.

In addition, a standardized national protocol for the diagnosis and early management of corneal ulcers should be implemented, including the use of rapid microbiological cultures, evidence-based empirical therapy, and continuous monitoring through tele-ophthalmology. A multidisciplinary approach involving general practitioners, ophthalmologists, and public health professionals is expected to reduce the incidence of severe complications resulting from delayed treatment.

In conclusion, delayed management of corneal ulcers is not merely a clinical concern but also a systemic issue within eye healthcare services. Prevention and early detection must become top priorities to significantly reduce visual morbidity caused by corneal ulcers in the coming decade.

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