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# THE ANALYSIS STUDY OF MANAGEMENT AND OUTCOMES OF CORNEAL DISEASE: A COMPREHENSIVE SYSTEMATIC REVIEW

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## ABSTRACT

***Background:*** *A group of conditions affecting the cornea are referred to as corneal disease. These diseases affect over 10 million people worldwide and are caused by various clinical diseases, such as traumatic injuries, chemical burns, infections, and iatrogenic reasons. Causes include bacterial keratitis, fungal keratitis, Herpes Simplex Keratitis (HSK), trachoma, dry eye disease, keratoconus, ophthalmia neonatorum, and non-infectious neonatorum. The causes of corneal disease affect how they are managed. The outcomes of these interventions vary.*

***The aim:*** *This study aims to determine the management and outcomes of corneal disease.*

***Methods:*** *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2014 and 2024 were taken into account. Several different online reference sources, like Pubmed, SAGEPUB, and ScienceDirect, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

***Results:*** *In the PubMed database, the results of our search brought up 1358 articles, whereas the results of our search on SAGEPUB brought up 1823 articles, and our search on ScienceDirect brought up 6091 articles. In the end, we compiled 6 papers, 3 of which came from PubMed, 2 of which came from ScienceDirect, and 1 of which came from SagePub. We included six research that met the criteria.*

***Conclusion:*** *In conclusion, surgical management shows good outcomes in controlling the corneal diseases. It can also maintain structural integrity of cornea and contribute to lowering blindness worldwide.*

**Keywords:** *Corneal disease, management, outcomes*

## INTRODUCTION

The cornea is a transparent, dome-shaped covering of tissue that gives the eye transparency and light refraction. Comprising the cornea, limbus, bulbar and tarsal conjunctiva, the ocular surface serves as the initial barrier against harm and infection, safeguarding the eye.[1] Approximately 550 µm thick, the adult human cornea is made up of five layers. The corneal epithelium is the outermost layer; it is followed by the corneal stroma, Bowman's membrane, Descemet's membrane, and innermost corneal endothelium. The cornea performs three roles: it protects the inner ocular tissue mechanically and chemically, acts as a clear medium for light transmission, and refracts light (it accounts for roughly 70% of the eye's refractive power).[1,2] Tight junction complexes are present in epithelial cells to stop the entry of paracellular fluid. These structures absorb UV light in conjunction with Bowman's layer.[3]

A collection of disorders affecting your cornea—the transparent window in the front of your eye—are together referred to as corneal diseases. Vision loss is a worldwide burden. Global Data on Visual Impairment 2010, World Health Organisation, estimates 285 million visually impaired people of all ages, of whom 39 million are blind.[2,4] Corneal diseases represent the third leading cause of blindness worldwide, affecting more than 10 million people.[4,5] Numerous clinical diseases, such as traumatic injuries, chemical burns (both acid and alkali), infections, and iatrogenic reasons (such as age-related degeneration, limbal stem cell shortage, and corneal dystrophies) can be the cause of this. The cellular and structural elements of the cornea may alter improperly in any of these disorders.[2,4] The various causes leading to corneal blindness are bacterial keratitis, fungal keratitis, Herpes Simplex Keratitis (HSK), trachoma, dry eye disease, keratoconus, ophthalmia neonatorum, non-infectious neonatorum.[6]

The causes of corneal disorders affect how they are managed. It included prescription eyeglasses or contact lenses; eye drops; ointments or other drugs; phototherapeutic keratectomy; corneal transplant surgery; and keratoprosthesis.[5,6] The most common type of transplant done globally is corneal transplantation, which attempts to restore corneal clarity and vision. Over time, various methods of corneal transplantation have emerged, ranging from lamellar grafts to full-thickness transplants.[5,7] The field of corneal surgery has advanced during the last 20 years. For a variety of corneal disorders, cornea specialists perform a wide range of surgeries, such as penetrating keratoplasty (PKP), deep anterior keratoplasty (DALK), descemet's stripping automated endothelial keratoplasty (DSAEK), descemet's membrane endothelial keratoplasty (DMEK), descemetorhexis without endothelial keratoplasty (DWEK), or pre-descemet's endothelial keratoplasty (PDEK). Regardless of the type of surgery done, the corneal endothelial cell density (ECD, endothelial cells/mm) determines the long-term survival of transplanted corneal grafts. As people age, their ECD gradually declines, going from approximately 2800 cells/mm$^2$ in the third decade to approximately 2400 cells/mm$^2$ by the seventh decade. The outcomes of these interventions vary.[7] The purpose of this study is to investigate the management and outcomes of corneal disease.

## METHODS

### PROTOCOL

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

### CRITERIA FOR ELIGIBILITY

For the purpose of this systematic review, we compare and contrast the management and outcomes of corneal disease. It is possible to accomplish this by researching or investigating the surgical and nonsurgical management of corneal disease, and the outcomes. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

For researchers to take part in the study, they needed to fulfill the following requirements: 1) The paper needs to be written in English, and it needs to investigate the management and outcomes of corneal disease. For the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2014, but before the period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

### SEARCH STRATEGY

We used "corneal disease"; "management"; and "outcomes" as keywords. The search for studies to be included in the systematic review was carried out in June, 06th 2024 using the PubMed, SAGEPUB, and ScienceDirect databases by inputting the words: ((("corneal diseases"[MeSH Terms] OR ("corneal"[All Fields] AND "diseases"[All Fields]) OR "corneal diseases"[All Fields] OR ("corneal"[All Fields] AND "disease"[All Fields]) OR "corneal disease"[All Fields]) AND ("manage"[All Fields] OR "managed"[All Fields] OR "management s"[All Fields] OR "managements"[All Fields] OR "manager"[All Fields] OR "manager s"[All Fields] OR "managers"[All Fields] OR "manages"[All Fields] OR "managing"[All Fields] OR "managment"[All Fields] OR "organization and administration"[MeSH Terms] OR ("organization"[All Fields] AND "administration"[All Fields]) OR "organization and administration"[All Fields] OR

"management"[All Fields] OR "disease management"[MeSH Terms] OR ("disease"[All Fields] AND "management"[All Fields]) OR "disease management"[All Fields]) AND ("outcome"[All Fields] OR "outcomes"[All Fields])) AND ((y_10[Filter]) AND (english[Filter])) with interposition of Boolean operators 'AND' and 'OR' used in searching the literature.

## DATA RETRIEVAL

After reading the abstract and the title of each study, the writers examined to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilize as sources for their article and selected those studies. After looking at several different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't be seen anywhere else.

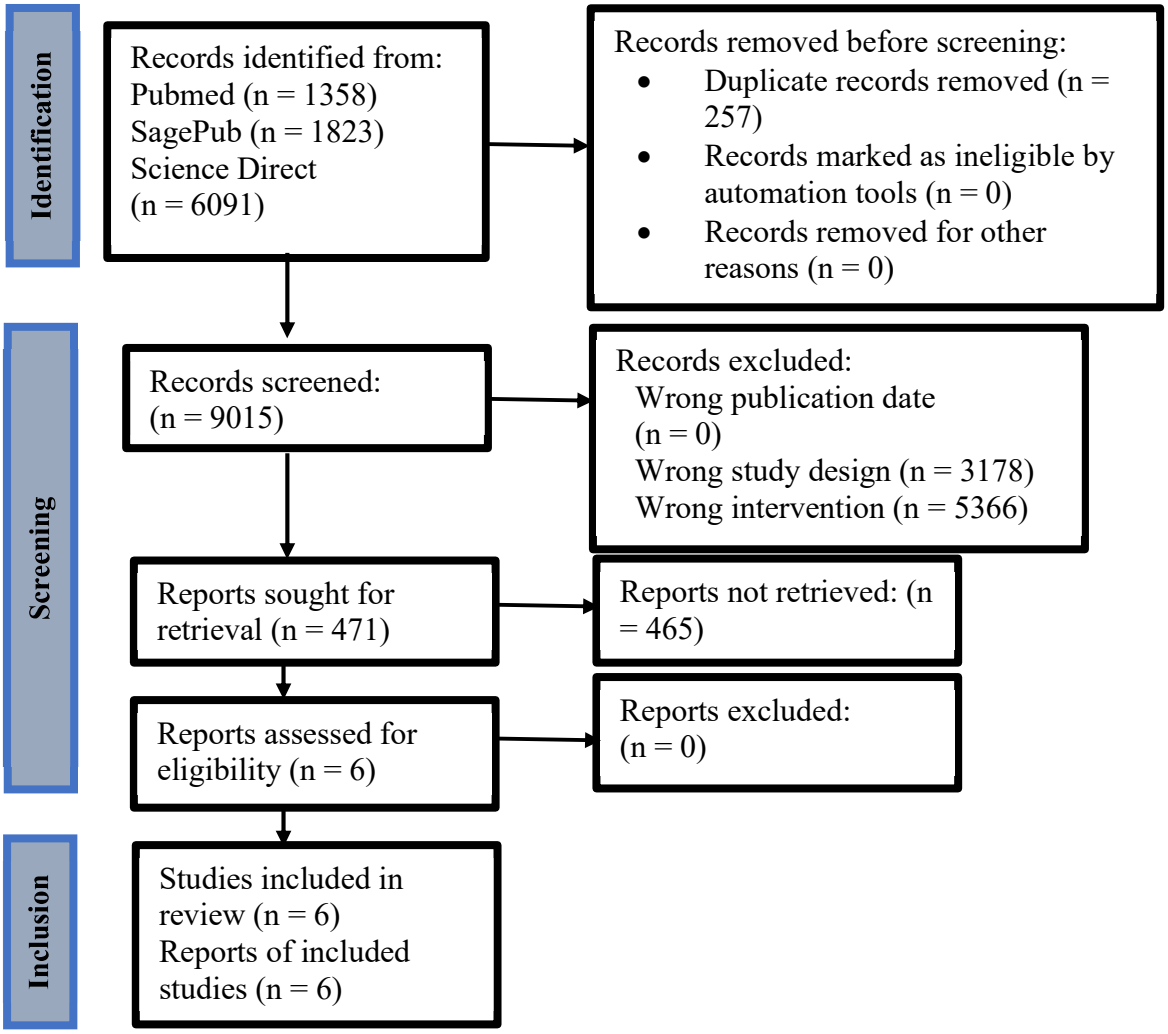


**Figure 1. Prisma Flow Diagram**

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

## QUALITY ASSESSMENT AND DATA SYNTHESIS

Each author did their own study on the research that was included in the publication's title and abstract before deciding on which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilized in the process of selecting papers for further assessment to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

## RESULT

In the PubMed database, the results of our search brought up 1358 articles, whereas the results of our search on SAGEPUB brought up 1823 articles, our search on ScienceDirect brought up 6091 articles. In the end, we compiled 6 papers, 3 of which came from PubMed, 2 of which came from ScienceDirect, and 1 of which came from SagePub. We included six research that met the criteria.

**Table 1. The literature included in this study**

| Author | Origin | Method | Sample Size | Result |
|---|---|---|---|---|
| Bouhout, 2017[8] | Canada | Retrospective study | 16 patients | This result showed that retroprosthetic membrane (RPM) formation and infectious keratitis enhance the likelihood of keratolysis after B-Kpro. Individuals who have had keratolysis are more likely to experience complications and need close observation. |
| Ferrini, 2023[9] | Italy | Prospective study | 38 patients | These findings imply that corneal cross-linking therapy is beneficial in stabilizing objective measures of disease progression as well as in enhancing the patient's subjective assessment of the condition. Values for keratometry, aberrometrics, and visual acuity significantly influenced self-reported VR-QoL. Corneal cross-linking may improve VR-QoL by stopping the deterioration of these parameters. |
| Li, 2020[10] | China | Retrospective study | 65 patients | In summary, an easy and safe surgical approach for treating eyes with infectious keratitis is accelerated corneal collagen cross-linking (CXL). It can help individuals who have recovered see better and lessen the duration of their illness. Our results show that accelerated CXL can be utilized as a useful adjunctive treatment for eyes with infectious keratitis, lowering the incidence of complications from the condition, increasing the likelihood that the condition would heal, and lessening the requirement for therapeutic keratoplasty. |

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| Qiao, 2020[11] | Canada | Retrospective case series | 40 cases | The findings of this study suggested that Candida keratitis is the most common cause of fungal keratitis cases that have been found. It seems required to be exposed to certain risk factors. For the majority of instances to be resolved, surgery is necessary. Similar clinical results were eventually observed across different subspecies of Candida. |
| Singhal, 2018[12] | India | Retrospective study | 8 cases | The results suggested that in cases of seemingly healed perforated corneal ulcers, corneal fistulas are frequently overlooked. The tenon patch graft is a useful procedure for treating corneal fistulas. |
| Trinh, 2021[13] | Canada | Retrospective study | 37 cases | Numerous factors contribute to neurotrophic keratopathy (NK), a chronic condition that often causes vision impairment and necessitates a variety of treatment approaches. A large percentage of NK is caused by neurosurgical, pars plana vitrectomy, and herpetic causes. Considering that corneal perforation is a dangerous consequence, persistent epithelial abnormalities need to be promptly addressed. Significant risk factors for corneal perforation include advanced age, herpetic origin, and Mackie Stage 3 at diagnosis. |

Bouhout, et al. (2017)[8] showed that of the eyes with keratolysis, 47% needed to have B-KPro exchanged or removed (n = 7). After receiving tectonic grafts initially, corneal melting returned in both of the treated eyes. In one case, a typical full-thickness graft was substituted for B-KPro excision, and the patient had a poor visual prognosis due to total tractional RD. Moreover, histoacryl glue (TissueSeal, Ann Arbor, MI) and sutures were used to fix an amniotic membrane transplant in one eye. However, the patient received a new B-KPro since the leak recurred. Oral tetracycline therapy was the only available medical treatment. Three patients (19%) were given doxycycline after they experienced their initial melt, but all of them developed to the point where they required additional surgical intervention (AMT, n = 1, corneoscleral patch graft, n = 1, and B-KPro exchange, n = 1). Before the keratolysis episode, the visual acuity (VA) in the eyes that had acquired corneal melt varied from 20/50 and hand motion, and it decreased to 20/200 and no light sensitivity after that. After developing phthisis, three eyes (19%) lost all vision.

Ferrini, et al. (2023)[9] showed that in patients with keratoconus, following treatment, the treated eye's BCVA (logMAR) improved at 3 months ($p = 0{,}017$) and 6 months ($p < 0{,}0001$), with a mean value of 0,213 preoperatively and 0,038 postoperatively at 6 months.

Li, et al. (2020)[10] showed that patients with infectious keratitis who underwent corneal collagen cross-linking (CXL) had an overall cure rate of 93.85% (94.12% in the case of fungal keratitis and 91.67% in the case of bacterial keratitis); there was no discernible difference in the cure rates between the two groups. The groups with baseline ulcer sizes ≤4 mm x 4 mm and those with baseline ulcer size 4mm x 4mm to 7mm x 7mm; had cure rates of 95.23% and 91.30%, respectively; there was no statistically significant difference between the two groups. The groups with baseline lesion depths less than 1/3 and those with baseline lesion depths between 1/3 and 2/3 had cure rates of 96.29% and 92.10%, respectively, however there was no discernible difference between the two groups' cure rates. One eye with bacterial keratitis and one with fungal keratitis underwent penetrating keratoplasty as the final treatment for the four eyes with poor surgical outcomes; two eyes

with fungal keratitis underwent 2% silver nitrate cauterization. None of the patients had any signs of corneal endothelial dysfunction.

Qiao, et al. (2020)[11] showed that in patients with candida keratitis. The three main forms of medical management were natamycin (5%), voriconazole (33%), and topical amphotericin B (38%). Antifungal medication was administered to 14 patients (67%) in total. Six patients' seven eyes did not get antifungal therapy: three were lost to follow-up, one suffered corneal perforation and was enucleated before a positive culture report could be obtained, and three had penetrating keratoplasty performed despite initial diagnostic doubt. Ultimately, surgical intervention was necessary for 16 individuals (76%) in the series. Thirteen patients received penetrating keratoplasty (1 optical, 8%; 12 therapeutic, 92%) and three had their perforations repaired by evisceration or enucleation. When it came to the patients who ultimately needed evisceration or enucleation, all of them had a presenting CDVA of counting fingers or worse, but only ten of the thirteen who needed penetrating keratoplasty. When C. albicans keratitis recurred, a second penetrating keratoplasty was eventually needed. In one case, corneal perforation happened prior to the initial penetrating keratoplasty. When topical medications were not adhered to, C. tropicalis keratitis recurred, necessitating four penetrating keratoplasties over a two-year period in one case. One patient denied penetrating keratoplasty, resulting in a phthisical eye and an endophthalmitis case. Each of these three examples had a CDVA of at least 20/200.

Singhal, et al. (2018)[12] showed that in six to eight patients with corneal fistula, tendon grafting was done. Medication was used to treat a patient who had excessive IOP and excruciating pain. Subsequent investigation revealed that the prior fistula location was sealed by uveal tissue and that the Seidel test had not revealed any leaks. The patient suffered from anterior staphyloma at the next follow-up. In all cases receiving tenon grafts, there were no intraoperative complications noted. Resuturing the graft was used to address a case of retraction of the graft with aqueous leakage. Using air injection for AC reformation, the other case's shallow AC was treated on the first postoperative day. When the graft was removed two months following surgery, it was well apposed in every patient.

Trinh, et. al (2021)[13] showed that the treatment for neurotrophic keratopathy in all cases involved topical lubricants. All patients were provided lubricants free of preservatives, however only 75.7% of eyes could afford them. In 72.9% of cases, topical steroids were used to treat ocular surface illness or similar immune-related conditions, while 10.8% of cases received treatment with either cyclosporin 0.05% or lifitegrast 5% drops. In order to aid in the healing of epithelial abnormalities, bandage contact lenses were utilized in 35.2% of instances. These cases tended to be in Stages 2 and 3, although they did not reach statistical significance (50% and 46.2%, respectively, vs. 14.3% Stage 1, $p = 0.09$). Scleral lenses were used in two cases. In one instance, the self-retained cryopreserved amniotic membrane was utilized. In 32.4% (12/37) of the cases (not including tarsorrhaphy), surgery was necessary. Penetrating keratoplasty was the primary procedure used to restore visual function in two cases and provide tectonic stability after perforation in six cases.

## DISCUSSION

The purpose of this research was to review studies published after January of 2014 and up to June of 2024 that investigated the surgical and nonsurgical management of corneal disease, and the outcomes. In the human population, corneal problems rank third in terms of causes of blindness, after glaucoma and cataracts.[14] There are an estimated 36 million blind people in the world today, and another 217 million people with moderate to severe visual impairment. 6.17 million, or 2.4%, of the 253 million people who are blind or have vision impairments are thought to have corneal causes. Although corneal diseases are a significant cause of blindness, the precise worldwide epidemiology of corneal blindness is difficult to determine and characterize.[15]

The Preferred Practice Pattern (PPP) addressed six corneal diseases: dry eye syndrome, bacterial keratitis, blepharitis, conjunctivitis, corneal ectasia, corneal edema (presence of extra fluid within one or more corneal layers), and opacification (presence of extra material, such as fluid or scar tissue, within one or more layers of the area that is linked to a loss of corneal clarity).[16] It has been demonstrated that the prevalence of corneal blindness is much higher in low- and middle-income countries (LMICs). This is mostly because these nations have fewer resources available for healthcare, a higher incidence of ocular trauma, inadequate personal and environmental cleanliness, hunger, and lower levels of education, among other reasons.[17]

According to a global survey on eye banking, infectious keratitis accounts for 20% of all corneal transplants performed globally and is the main reason for transplantation in 24% of nations. The frequency of transplantation to manage bacterial infections is declining as more effective antibacterial medicines become accessible. This is untrue, though, for fungal infections, where a significant portion of ulcers still need to be surgically treated. As with the majority of cases of bacterial keratitis, corneal transplantation functions by removing the affected corneal tissue in its entirety. However, it might not be able to totally eradicate the affected area in situations of fungal or Acanthamoeba infections. Transplantation in these conditions is therefore used to debulk the infection and allow the antimicrobials to eradicate the rest.[18]

A variety of corneal transplantation techniques have been employed as treatment strategies to manage infections. The most popular treatment for infectious keratitis is PKP. Removing all of the diseased corneal tissue and replacing it with healthy cornea is the aim of the procedure. With over 90% of cases of bacterial keratitis being cured following surgery, it is an extremely effective treatment. On the other hand, the success rate with fungal ulcers considerably decreases. In their

investigation, Xie and colleagues performed therapeutic PKP on 108 patients who had fungal keratitis, and they achieved great results. Their recurrence rate was 7.4%, and endophthalmitis necessitated the enucleation of four of these eyes.[18–20]

Photorefractive Keratectomy (PRK) and Laser-Assisted in Situ Keratomileusis (LASIK) are the two most frequently used corneal refractive surgical techniques. In a nutshell, mechanical debridement is used in PRK to remove the corneal epithelium during surface ablation.[19,21] In lamellar surgery, known as LASIK, an excimer laser is used to generate a corneal flap that is then adjusted inside the stroma. This is done using a microkeratome or femtosecond laser.[19] An innovative flap-less refractive surgery technique called Small-Incision Lenticule Extraction (SMILE) was just introduced. Using a 2–5 mm incision, often in the upper peripheral cornea, an intrastromal corneal lenticule created by the femtosecond laser is removed in this manner. The most anterior cornea is primarily affected by corneal refractive surgery, while the corneal endothelium, Descement's membrane, and mid-and posterior stroma are probably left intact. Depending on the refractive technique, corneal architecture is changed in different ways as a result of remodeling the cornea's thickness and curvature to induce changes in refractive properties. Therefore, there may be significant differences in the corneal response between SMILE, LASIK, and surface ablation procedures.[22]

For those with keratoconus, penetrating keratoplasty (PK) provides good long-term visual recovery. There is a lengthy mean graft survival and a comparatively low percentage of graft failure when compared to other indications for PK. According to long-term follow-up reports, the rejection rate ranges from 5.8 to 41%, with the majority of rejections happening during the first two years. Rejection risk has been linked to larger host trephine size, male donor gender, and non-White donor race. Only a 4.3-6.3% graft failure rate has been documented with a mean follow-up of 15 years and an estimated 12-percent chance of failure after 20 years, despite this observed rejection rate. According to Fukoka et al., there is a cumulative likelihood of 98.8, 97.0, and 93.2 percent for graft survival after 10, 20, and 25 years after PK. On the other hand, Pramanik et al. predicted a graft survival percentage of 85.4% at 25 years following the first transplant. When the available data is combined, it can be seen that the graft survival rate starts to decline about 20 years after post-PK.[23,24]

Because contact lenses have better visual performance than spectacle lenses, they are essential to keratoconus (KC) management. For the treatment of KC eyes, a wide variety of lenses are available; choosing the right lens could prevent or postpone the need for keratoplasty. The degree of KC, the patient's visual demands, and their CL tolerance all influence the sort of CL that is typically utilized. According to Smiddy et al.17, 69% of KC patients who came in for keratoplasty could benefit from CL management. Soft CLs, GP corneal lenses, piggyback lenses, hybrid lenses, intralimbal or large-diameter corneal lenses, miniscleral lenses, and scleral lenses are among the CL choices for KC. However, there is less evidence for the more recent CL designs and materials in the literature as a result of the paucity of randomized controlled clinical trials and the absence of a control group in the majority of the published studies.[25]

Following penetrating keratoplasty, the likelihood of graft survival was 86% at one year, 73% at five years, and 55% at fifteen years. The survival percentage for low-risk penetrating keratoplasty is considerably higher, at 90% after five years and 82% after ten. The 5-year survival percentage for high-risk individuals is 54.2%, while the survival rate for predominantly non-inflamed eyes is 91.3%. Rejection from prior grafts or corneal bed vascularization could cause failure in 70% of the high-risk grafts. Rejection episodes affect 40–70% of patients receiving corneal transplants at high risk each year.[14,25] Comparable to previous studies, ours found that 54% of allografts survived for a year. Younger receivers had a higher likelihood of rejection. Nevertheless, this relationship was not supported by our research. Re-transplantation indicated less favorable results. Following a second transplant, the 5-year survival rate dropped from 72.5% to 37.3–53.4%. Recurrence transplant failure rates at two years were 17%, while initial transplant failure rates were 6%. In our investigation, the 1-year survival rates following the first and second keratoplasty procedures were 52.8% and 70%, respectively. However, there was no statistically significant change. Given that we compared high-risk indications with repeat keratoplasty, which is in and of itself a high-risk indication, the results may have been impacted. It may suggest that all high-risk corneal transplantations have similar survival rates.[14]

An average best-corrected visual acuity (BCVA) in logarithm of the minimum angle of resolution (Log-MAR) at preoperation, 10, 20, and 25 years after surgery of 1.54±0.68, 0.06±0.22, 0.03±0.17, and 0.14± 0.42, respectively, have been reported. A mean follow-up term of 33.5 months was associated with a best spectacle-corrected visual acuity (BSCVA) of 0.14 ± 0.11 LogMAR, whereas 73.2% of patients had a BSCVA of 20/40 or greater after an average follow-up period of 14 years. There has also been reporting of an open angle glaucoma rate of 5.4% with a mean follow-up of 14 years. According to Claesson et al., in patients whose keratoconus was the initial indication, regrafts had a worse visual outcome and a lower survival rate than first grafts. Three times as many regrafts failed, and only 55% of regrafts achieved the level of visual acuity with preferred correction that was ≥0.5 in first grafts.[23]

## CONCLUSION

In conclusion, surgical management shows good outcomes in controlling the corneal diseases. It can also maintain structural integrity of cornea and contribute to lowering blindness worldwide.

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