Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1176813
J Health Sci Med 2022; 5(6): 1612-1618

Comparison of culture-positive and culture-negative severe infectious keratitis leading to hospitalization: a tertiary referral center experience

Nesrin Tutaş Günaydin[1], Baran Kandemir[1], Gizem Doğan Gökçe[2], Mehmet Can Özen[3], Raziye Dönmez Gün[1], Demet Haciseyitoğlu[4]

[1]University of Health Sciences, Kartal Dr· Lütfi Kırdar City Hospital, Department of Ophthalmology, İstanbul, Turkey
[2]Gönen State Hospital, Department of Ophthalmology, Balıkesir, Turkey
[3]Kozluk State Hospital, Department of Ophthalmology, Batman, Turkey
[4]Zonguldak Bülent Ecevit University, Faculty of Medicine, Department of Medical Microbiology, Zonguldak, Turkey

Cite this article as: Tutaş Günaydın N, Kandemir B, Doğan Gökçe G, Özen MC, Dönmez Gün R, Hacıseyitoğlu D. Comparison of culture-positive and culture-negative severe infectious keratitis leading to hospitalization: a tertiary referral center experience. J Health Sci Med 2022; 5(6): 1612-1618.

ABSTRACT

Aim: To compare the predisposing factors, surgical interventions, length of hospital stay (LOHS), and treatment outcomes of culture-positive (CP) versus culture-negative (CN) severe infectious keratitis (IK) resulting in hospitalization in a tertiary referral clinic.

Material and Method: We retrospectively reviewed the medical and microbiological records of 287 patients clinically diagnosed with severe keratitis over a 4-year period.

Results: Of 287 study participants, 141 (49.1%) had positive CP results. The most common ocular risk factor was a previous ocular surgery (45.6%), and keratoplasty was the first among these ocular surgeries (90.8%). *Staphylococcus epidermidis* (22.7%) was the most commonly isolated microorganism followed by fungi (17.7%). The initial and final visual acuities did not differ significantly between the CP and CN groups. Major and minor surgical interventions did not significantly differ between the groups (p=0.05). The rates of clear corneal graft in the CP group (p =0.002) were significantly higher than the rates of graft failure in the CN group (p=0.033). No significant difference was noted in the mean LOHS between groups (p=0.66). Logistic regression analyses showed that surgery during admission, *S. epidermidis* infection, and connective tissue diseases were independent risk factors for a prolonged hospital stay.

Conclusion: The initial and final visual acuities, surgical interventions, and LOHS were similar between the CP and CN groups. However, graft failure rates were significantly higher in patients with CN keratitis than in those with CP keratitis.

Keywords: Infectious keratitis, microbial culture, *Staphylococcus epidermidis*, hospitalization

INTRODUCTION

Infectious keratitis (IK) is one of the most common causes of corneal blindness in developed and developing countries (1). Although many studies have reported innovations in the etiological assessment, management, and treatment of patients with severe IK, it remains a leading cause of ocular morbidity (2-10).

Severe IK causes debilitating permanent vision loss, prolonged hospitalization, social problems, and a considerable financial burden on healthcare services (1). Additionally, IK is the main indication for corneal transplantation, with complications, such as corneal perforations and deep corneal scarring, thereby causing a sustained burden on the limited corneal donor pool. In this respect, intervention for IK is crucial to prevent visual morbidity and to support the overall healthcare system.

Although predisposing factors and clinical findings are important clues for diagnosing IK and predicting causative microorganisms, culture is accepted as the gold standard for definitive pathogen identification. Many articles have been published on culture-positive (CP) IK, in which culture isolation is defined as an indispensable test for choosing a specific drug therapy to determine antibiotic susceptibility, shorten treatment duration, and improve prognosis by identifying microbiological factors.

Corresponding Author: Nesrin Tutaş Günaydın, drnesrintutas@hotmail.com
Received: 18.09.2022 **Accepted:** 02.10.2022

However, to the best of our knowledge, only a few studies have compared CP cases with culture-negative (CN) cases of severe keratitis (11-13). Sharma et al. (11), Bhadange et al. (12) in India and Duarte et al. (13) in Brazil evaluated IK based on CP and CN results. As the populations of these countries have different characteristics, the etiologies and scenarios of IK are also quite different. Therefore, we aimed to determine the epidemiological characteristics of patients with severe IK hospitalized in Turkey and to compare predisposing factors, surgical interventions, treatment results, and length of hospital stay (LOHS) between patients with CP IK and CN IK.

MATERIAL AND METHOD

The study was carried out with the permission of Kartal Dr. Lütfi Kırdar City Hospital Clinical Researches Ethics Committee (Date: 29.03.2021, Decision No: 2021/514/198/19). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

This study had a retrospective, cross-sectional, and comparative design.

Patients and Definition of Infection

In this study, we reviewed the electronic medical records for clinical and microbiological data of 287 patients with severe IK who were hospitalized between January 2017 and December 2021. The criteria for admission were a diagnosis of severe keratitis and the need for intensive topical and systemic antimicrobial therapy, in addition to surgical treatment if necessary. The diagnosis of severe IK was based on the combination of lesion size in the longest meridian and vision loss of best-corrected visual acuity (BCVA) compared with pre-event acuity or fellow eye acuity (if acuity data were available) (14). The longest meridian was defined as central lesions >2 mm, lesions outside the central 4 mm of the cornea, lesions >4 mm, or presence of hypopyon. Exclusion criteria were a clinical diagnosis of herpetic keratitis, neurotrophic keratopathy, exposure keratopathy, and immune-mediated peripheral ulcerative keratitis. The clinical history of all the cases was considered. For all patients, medications were stopped 24 hours before sampling for culture testing. Clinical findings were followed-up regularly using slit-lamp examination, anterior segment imaging, and B-scan ultrasonography.

Microbiological Samples and Analysis

Microbiological samples for Gram staining and corneal scraping were obtained using a sterile surgical blade and cotton-tipped swab after applying topical anesthesia (0.5% proparacaine hydrochloride). The samples were examined for the presence of aerobic, anaerobic, and fungal microorganisms. Thioglycolate broth (THIO) was used to isolate the organisms from the corneal culture. The samples were incubated in THIO at 35°C for 24 h and then plated onto media (5% sheep blood agar, chocolate agar, Brucella agar, and Sabouraud dextrose agar [SDA]). For suspected amoebic corneal cases, the sample was mixed with an adequate volume of lactophenol-cotton blue stain and examined using light microscopy. Samples were considered positive for *Acanthamoeba* when the cyst walls and nucleus appeared in an intense blue color and the cytoplasm stained light blue (15). All plates were cultured in 5–7% carbon dioxide at 35°C for 72 h for bacteria or SDA for 6 weeks. The plates were evaluated daily for microorganism growth and isolate identification, and antimicrobial susceptibility tests were performed after the growth was detected (VITEK 2; Compact Systems, BioMerieux, France). Culture-positive keratitis was defined as the presence of clinical features of microbial keratitis that met at least one of the following criteria for significant growth: (1) growth of the same organism on two or more media, (2) confluent growth at the inoculation site on a solid medium, (3) growth on one medium consistent with direct microscopic findings (appropriate staining and morphology with Gram staining), and (4) growth of the same organism after repeated culture with corneal scraping material. Culture-negative keratitis was defined as a patient with clinical characteristics of microbial keratitis who did not show microbial growth on either smear or culture (16). Polymicrobial keratitis was defined as the presence of two or more types of pathogens in corneal samples of patients (9).

Data Collection and Management

For all study participants, we identified the following information from the electronic medical records: demographics, predisposing ocular and coexisting systemic factors, initial and final BCVA (with visual acuity data converted from Snellen chart values to the logarithm of the minimum angle of resolution-logMAR-), medical and surgical treatments, including both minor and major surgical interventions, duration of follow-up (days), treatment outcomes, and LOHS (days). Minor surgical interventions included amniotic membrane transplantation, intrastromal voriconazole (50 μg/mL) for fungal keratitis, and fine-needle diathermy for corneal neovascularization secondary to IK. Major surgical interventions included penetrating keratoplasty (PK) and evisceration. Data were compared between the CP and CN groups.

Before the culture results were obtained, patients were administered a combination of topical fortified antibiotics (25 mg/mL cefazolin and 14 mg/mL gentamicin, 25 mg/mL vancomycin, or 2 mg/mL linezolid and 50 mg/mL ceftazidime) once per hour. If fungal keratitis was suspected based on the clinical findings, topical fortified

10 mg/mL voriconazole or 1.5 mg/mL amphotericin B drops were administered hourly for the first 48 h, together with 1% cyclopentolate three times a day, non-preserved artificial tear drops every 2 h, and autologous serum every 3 h. If necessary, the frequency of the fortified drops was decreased every 3 h. Medical treatment was modified based on culture results and clinical response. Systemic antibacterial and/or antifungal drugs were added according to the depth, size, and clinical progression of the keratitis.

As a major surgical intervention, PK is performed for patients with corneal scarring caused by keratitis and for patients with a large (>4 mm) non-healing or perforated ulcer, usually with an urgent therapeutic or tectonic indication. The patients remained hospitalized until the infiltrate had resolved in size and depth and re-epithelialization was completed. Long hospital stay was defined as a hospital stay ≥14 days (17).

Statistical Analysis

SPSS version 25 (IBM SPSS Statistics for Windows, IBM, Armonk, NY, USA) was used for all the statistical analyses. For numerical demographic data, the standard deviation, mean, maximum, minimum, and percentage values were used. The Student's t-test was used to compare the CP and CN groups in terms of numeric demographic data. Homogeneity was evaluated using the Shapiro–Wilk test and graphical analyses. Chi-square or Fisher's tests were used to compare the CP and CN groups in terms of non-numeric demographic data. To define the independent risk factors for prolonged hospital stay, we applied logistic regression analysis to the statistically significant variables. A value of $p<0.05$ was considered statistically significant at $p<0.05$.

RESULTS

This study included 287 patients: 161 men (56.1%) and 126 women (43.9%). Of these 287 patients, the CP results were obtained in 141 (49.1%) patients, defined as the CP group and CN results were obtained in 146 (50.9%) patients, defined as the CN group. The mean age was 60.7±15.9 years in the CP group versus 59.1±17.5 years in the CN group (p=0.39). **Table 1** summarizes the patient demographic data.

The most common ocular risk factor for keratitis was ocular surgery (45.6%). No significant difference was noted between the CP and CN groups in terms of previous ocular surgery. However, a significant difference was observed between the groups in terms of history of herpetic keratitis (p<0.001) and eyelid abnormalities (p=0.009). Keratoplasty was the most common ocular surgery (90.8%) and PK was the most frequently performed keratoplasty (85.7%). Additionally, 37.4% of our patients who underwent surgery developed IK because of loose and/or broken sutures, and most of these cases were eyes with keratoplasty (p<0.001).

Table 1. Demographic data, predisposing factors, clinical characteristics and treatment outcomes.

Variables	Positive culture (Group 1) (n=141)	Negative culture (Group 2) (n=146)	p value*
Age (years), mean±SD, (range)	60.7±15.9 (21-93)	59.1±17.5 (16-91)	0.39[a]
Sex			0.46[b]
Male, n (%)	76 (47.2%)	85 (52.8%)	
Female, n (%)	65 (51.6%)	61 (48.4%)	
Length of hospital stay (days), mean±SD, (range)	15.43±11.02 (2-45)	14.81±13.03 (2-65)	0.66[a]
Visual acuity			
Initial BCVA (logMAR), mean±SD (range)	2.13±0.91 (logMAR 3-0.15)	2.32±0.91 (logMAR 3-0.15)	0.07[a]
Final BCVA (logMAR), mean±SD (range)	1.42±1.01 (logMAR 3-0.0)	1.61±1.04 (logMAR 3-0.0)	0.13[a]
Comorbidities			
Diabetes mellitus, n (%)	17 (48.6%)	18 (51.4%)	0.94[b]
Connective tissue diseases, n (%)	15 (50%)	15 (50%)	0.92[b]
Cancer, n (%)	4 (80%)	1 (20%)	0.164[c]
Atopia, n (%)	1 (20%)	4 (80%)	0.189[c]
Chronic obstructive lung disease, n (%)	6 (60%)	4 (40%)	0.48[c]
Medical treatment, n (%)	66 (49.3%)	68 (50.7%)	0.98[b]
Surgical+medical treatment, n (%)	75 (49.3%)	77 (50.7%)	0.98[b]
Major surgery, n (%)	55 (57.3%)	41 (42.7%)	0.05[b]
Minor surgery, n (%)	20 (37%)	31 (57.4%)	0.05[b]
Recurrent infection			0.101[b]
Present, n (%)	25 (61%)	16 (39%)	
Absent, n (%)	116 (47.2%)	130 (52.8%)	
Laterality			0.313[b]
Right, n (%)	65 (46.1%)	76 (53.9%)	
Left, n (%)	76 (52.1%)	70 (47.9%)	
Ocular predisposing factors			
Previous ocular surgery	69 (52.7%)	62 (47.3%)	0.271[b]
Keratoplasty	62 (47.3%)	57 (43.5%)	0.91[b]
PK	49 (37.4%)	53 (40.4%)	0.07[b]
DMEK	10 (7.6%)	4 (3.05%)	0.16[c]
DALK	3 (2.29%)	-	0.24[c]
Cataract surgery	3 (2.29%)	4 (3.05%)	0.70[c]
Cross-linking	1 (0.76%)	-	1[c]
Other	3 (2.29%)	1 (0.76%)	0.62[b]
Trauma	20 (43.5%)	26 (56.5%)	0.389[b]
Ocular surface disease	26 (55.3%)	21 (44.7%)	0.339[b]
Contact lens	11 (64.7%)	6 (35.3%)	0.185[b]
History of herpes keratitis	9 (21.4%)	33 (78.6%)	<0.001[b]
Eyelid abnormalities	25 (69.4%)	11 (30.6%)	0.009[b]
Treatment outcomes			
Healthy corneal graft	59 (41.8%)	36 (24.7%)	0.002[b]
Opaque corneal graft	26 (18.4%)	19 (13%)	0.206[b]
Vascularized leukoma	30 (21.3%)	45 (31%)	0.061[b]
Graft failure	8 (5.7%)	19 (13%)	0.033[b]
Phthisis bulbi	9 (6.4%)	10 (6.8%)	0.874[b]

* p<0.05 a Student's t-test, b Chi-squared test, c Fisher exact test
Abbreviations: BCVA, best-corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution; PK, penetrating keratoplasty; DMEK, descemet membrane endothelial keratoplasty; DALK, deep anterior lamellar keratoplasty

The difference in mean initial and final BCVA was not significant between the CP and CN groups (p=0.07 and p=0.13, respectively) (**Table 1**). Of 287 patients, 134 (46.7%) received medical therapy only, whereas 153 (53.3%) required surgical intervention. No significant intergroup differences were found in the number of patients who underwent major or minor surgery (p=0.05). Furthermore, no significant intergroup difference was found in the number of recurrent infections (p=0.101 for both groups) (**Table 1**). *Staphylococcus epidermidis* was the most commonly isolated microorganism, followed by the fungi. Fungi were the only microorganisms associated with surgical treatment (p=0.03). The isolated microorganisms are listed in **Table 2**.

Table 2. Microorganisms isolated from patients with culture-positive results

	n	%
Bacteria	100	70.9
Staphylococcus epidermidis	32	22.7
Staphylococcus aureus	11	7.8
Staphylococcus hominis	8	5.7
Pseudomonas aeruginosa	8	5.7
Haemophilus influenzae	6	4.3
Staphylococcus haemolyticus	2	1.4
Staphylococcus capitis	2	1.4
Enterobacter cloacae complex	2	1.4
Enterococcus faecium	2	1.4
Serratia spp.	2	1.4
Klebsiella spp.	2	1.4
Granulicatella spp.	1	0.7
Corynebacterium spp.	1	0.7
Fungi	25	17.7
Candida spp.	14	9.9
C. albicans	10	7.1
C. kefyr	2	1.4
C. farinata	2	1.4
Fusarium spp.	6	4.3
Aspergillus spp.	2	1.4
Penicillium	2	1.4
Geotrichum	1	0.7
Mixed (≥ 2 more bacteria or bacteria+fungi)	16	11.3
Haemophilus influenzae+Streptococcus pneumoniae	2	1.4
Staphylococcus epidermidis+Streptococcus mitis	2	1.4
Staphylococcus epidermidis+Fusarium	2	1.4
Staphylococcus epidermidis+Haemophilus influenzae	2	1.4
Haemophilus influenzae+Streptococcus pneumoniae	2	1.4
Staphylococcus epidermidis+Actinomyces	1	0.7
Staphylococcus hominis+Candida glabrata	1	0.7
Staphylococcus aureus+Haemophilus influenzae	2	1.4
Staphylococcus aureus+Enterobacter aerogenes	1	0.7
Staphylococcus warneri+*Streptococcus pneumoniae*	1	0.7
Streptococcus mitis+Streptococcus oralis	1	0.7
Enterococcus fecalis+*E. coli*	1	0.7
Enterococcus fecalis+*Pseudomonas aeruginosa*	1	0.7
Enterococcus faecium+Crytococcus neoformans	1	0.7
	141	100

We also compared treatment outcomes between the two groups. The outcomes of clear corneal grafting were better in the CP group than in the CN group (41.8% vs. 24.7%; p=0.002), whereas graft failure was more common in the CN group than in the CP group (13% vs. 5.7%; p=0.03) (Table 1). Evisceration was used as a treatment modality for 5 (1.7%) of 257 patients without connective tissue diseases versus 3 (10%) of 30 patients with connective tissue diseases (p=0.04).

The mean LOHS was 15.4±11 days (minimum, 1; maximum, 52 days) in the CP group versus 14.8±13 days (minimum 1; maximum 65 days) in the CN group (p=0.66). The overall LOHS of 128 patients (44.5%) was ≥14 days, which was defined as prolonged hospital stay. Longer hospital stay was related to the following factors: age, initial and final BCVA, ocular surface disease, surgical treatment, *S. epidermidis* infection, fungal infection, diabetes mellitus, connective tissue diseases, and atopy. According to logistic regression analyses, surgery during admission, *S. epidermidis* infection, and connective tissue diseases were independent risk factors for prolonged hospital stay. **Table 3** summarizes the logistic regression analysis of the risk factors for prolonged hospital stay.

Table 3. Logistic regression analyses

Variable	Simple linear regression	Multiple logistic regression		p value*
	p Value*	Coefficient	95% CI	
Age	0.012			
Initial BCVA (logMAR)	0.014			
Final BCVA (logMAR)	0.017			
Ocular surface disease	0.022			
Surgery during submission	<0.001	1.28	1.68-7.69	0.01
S. epidermidis	0.032	−1.31	0.1-−0.72	0.09
Fungus	0.01			
Diabetes mellitus	0.02			
Connective tissue disease	<0.001	1.72	1.34-23.42	0.018
Atopy	0.012			

* p<0.05, Abbreviations: BCVA, best-corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution.

DISCUSSION

This study evaluated the epidemiologic features, predisposing factors, major and minor surgical interventions, LOHS, and treatment outcomes of patients with severe IK treated in our clinic, and compared these parameters between the CP and CN groups. A comparison between the CP and CN groups showed no significant differences in the initial and final visual acuity, the need for surgical intervention, or LOHS.

Our culture rates were similar to the frequencies of culture positivity reported in studies conducted in Brazil, Taiwan, and China (18,19). In our study, no significant difference was found between the CP and CN groups in terms of the initial and final visual acuity (p=0.13). Furthermore, other factors such as age and sex did not differ significantly between the groups. Similar results were reported by Bhandage et al. (12) and Yarımada et al. (20) who found that the initial and final visual acuity did not differ between the CP and CN groups.

The most common ocular risk factor for IK was previous ocular surgery in both the CP and CN groups, and thus, in the whole series (43.5%). Wong et al. (6) also reported that a previous ocular surgery was the most common predisposing factor for IK. In our study, ocular surgery was performed in almost all the patients who underwent corneal transplantation (90.8%). The identification of keratoplasty as the greatest risk factor for IK in this study may be because our center is a reference corneal transplant center, where approximately 500 keratoplasties per year are performed. Cariello et al. (18) also pointed out that previous surgery and keratoplasty, among these surgeries, were the most common predisposing factors for IK, a finding similar to this study. The rate of suture-related IK was 37.4% and most cases involved keratoplasties. This frequency is supported by other studies with suture-related IK rates between 37% and 71% (16, 21). Additionally, prolonged epithelial defects after keratoplasty, long-term corticosteroid use, and graft failure may predispose patients to IK (21,22). Therefore, it is crucial to periodically evaluate patients undergoing keratoplasty and be aware of the possibility of corneal infection. We found no significant differences in PK rates between the CP and CN groups. Although we observed that 13 of the patients diagnosed with IK after lamellar keratoplasty were in the CP group and 4 were in the CN group, this difference was not significant. Dohse et al. (22) also found no difference between the CP and CN groups in terms of IK development after penetrating and lamellar keratoplasty.

In our series, other predisposing factors following surgery were ocular surface disease (OSD) (16.37%), trauma (16.02%), and a history of herpetic keratitis (15.3%). Although the incidences of OSD and trauma were not significantly different between the groups in our study, a history of herpes was more common in the CN group. We support that necrotizing stromal keratitis due to herpes may mimic the clinical findings in CN IK (23). Bhadange et al. (12) also attributed the unresponsiveness to treatment in treatment-resistant CN keratitis to the clinical similarity between these cases and herpes-related necrotizing stromal keratitis.

In addition, eyelid abnormalities were more commonly observed in the CP group than in the CN group. Among the predisposing factors, use of contact lenses was the least common. In this study, contact lens use was mostly observed in patients with bullous keratopathy or graft failure (related to the presence of OSD). The advanced age of our series of patients may explain the association between these risk factors, and contact lens use being one of the least common risk factors.

In our study, the most frequently recovered microorganism was *S. epidermidis* (22.7%), followed by fungi. Gram-positive bacteria, including *Staphylococcus* spp. are common ocular surface commensals and are more often detected in bacterial keratitis caused by previous ocular surgery, topical steroid use, or OSD (5,21). These risk factors were also common predisposing factors in our study. This finding also supports the relationship between the more frequent observation of eyelid abnormalities in the CP group and the fact that Gram-positive bacteria were the most frequently observed microorganisms. Similar to our study, *S. epidermidis* was the most commonly isolated pathogen in studies by Wagoner et al. (21) on bacterial keratitis after PK and in large-series studies by Lin et al. (24). The second most common organism detected was fungi, among which *Candida* spp. was the most prevalent. The reason for these findings of the most commonly isolated pathogens was that most patients in our study had undergone keratoplasty. Augustin et al. (25) reported that *Candida* spp. are the most common pathogens in fungal keratitis after keratoplasty. In addition, approximately 50% of our patients with fungal keratitis required keratoplasty, and among all organisms, fungal agents were the only microorganisms for which surgical treatment was required (p=0.03). Interestingly, we did not find any cases of *Acanthamoeba* keratitis in our study.

In our study, 134 (46.7%) patients received medical therapy alone, whereas 153 (53.3%) required surgical intervention. Indeed, our study only included patients hospitalized with severe keratitis, which may explain why we performed surgical interventions more frequently than in other studies (12,13). Our polymicrobial case rate (13.4%) was higher than that reported by Bhadange (3.3%) and Duarte (no polymicrobial cases) (12,13). Many other studies have emphasized the increased need for surgery in patients with severe keratitis and polymicrobial keratitis (6,26,27). Meanwhile, no significant difference was found between the CP and CN groups in terms of the frequency of major and minor surgical interventions. This result is different from the findings of other studies that compared culture and smear results. These studies emphasized that the need for surgical intervention was higher in the CP group than in the CN group (11-13).

However, unlike these studies, because the most common predisposing factor was previous surgery and most patients had undergone keratoplasty in our series, there was a similar need for surgery in both groups, and there was no difference in the number of major and minor surgical interventions.

An intergroup comparison of the surgical treatment results in our study showed that the incidence of a healthy graft was significantly higher in the CP group than in the CN group (41.8% vs. 24.7%; p=0.002), whereas graft failure was significantly higher in the CN group than in the CP group (13.0% vs. 5.7%; p=0.033). As noted previously, Bhadange et al. (12) also reported that more patients experienced treatment failure in the CN group than in the CP group and emphasized that this failure may have been associated with herpes-related necrotizing stromal keratitis–like findings in some CN keratitis cases. In our series, the risk of graft failure may have increased because of the higher incidence of a herpes history in CN keratitis.

In our study, 128 patients (44.5%) had prolonged hospital stays. The mean LOHS did not differ between the CP and CN groups (p=0.66), and prolonged hospital stay was related to the following factors: age, initial and final BCVA, ocular surface disease, surgery during admission, *S. epidermidis* and fungal infections, diabetes mellitus, connective tissue diseases, and atopy. Subsequent logistic regression analyses revealed that surgery during admission, *S. epidermidis* infection, and connective tissue diseases were independent risk factors for longer hospital stay. The results regarding related risk factors shown in this study are in line with the findings reported in the literature, and many studies have shown that patients with IK who exhibit risk factors such as older age, diabetes mellitus, fungal keratitis, and OSD require prolonged hospital stay (6, 28-30). Similar to our results, studies in New Zealand and Taiwan have also reported that surgery during admission is associated with a longer hospital stay (6, 31). However, according to logistic regression analyses, other than surgery during admission, our results for long hospital stay differed from those in the literature, and the factors found to be related to prolonged stay, namely, *S. epidermidis* infection and connective tissue diseases, have not been previously reported. In a study from a tertiary referral center in Hungary, the authors reported that in severe microbial keratitis cases requiring enucleation and evisceration, the most commonly detected coagulase-negative staphylococci was *S. epidermidis* (32). In the same study, rheumatoid arthritis was reported to be one of the most prevalent systemic diseases (32). Among the patients included in the current study, three with severe keratitis who required evisceration had connective tissue diseases (n=8). In cases of severe keratitis, connective tissue diseases such as rheumatoid arthritis increase the possibility of complications (28,32). Therefore, an increase in complications associated with these risk factors may also lead to a prolonged hospital stay.

One of the limitations of our study was its retrospective design. Another limitation is the lack of polymerase chain reaction (PCR) analysis to exclude herpes, making clinical assessment the only method for differential diagnosis. However, our study is valuable as it is one of the largest studies in the literature comparing the CP and CN groups in severe keratitis cases, to the best of our knowledge.

CONCLUSION

This study showed that the most common predisposing factor was previous surgery, and *S. epidermidis* was the most commonly isolated microorganism. A comparison of the CP and CN groups revealed no significant difference between the groups in terms of initial and final visual acuities, needs for minor and major surgical interventions, and LOHS. However, when the two groups were compared in terms of treatment outcomes, graft failure was more frequent in the CN group. In this regard, we recommend supporting the exclusion of herpes-related keratitis via polymerase chain reaction in patients with CN keratitis..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kartal Dr. Lütfi Kırdar City Hospital Clinical Researches Ethics Committee (Date: 29.03.2021, Decision No: 2021/514/198/19).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Ung L, Bispo PJM, Shanbhag SS, Gilmore MS, Chodosh J. The persistent dilemma of microbial keratitis: global burden, diagnosis, and antimicrobial resistance. Surv Ophthalmol 2019; 64: 255-71.

2. Chidambaram JD, Venkatesh Prajna N, Srikanthi P, et al. Epidemiology, risk factors, and clinical outcomes in severe microbial keratitis in South India. Ophthalmic Epidemiol 2018; 25: 297-305.
3. Puig M, Weiss M, Salinas R, Johnson DA, Kheirkhah A. Etiology and risk factors for infectious keratitis in South Texas. J Ophthalmic Vis Res 2020; 15: 128-37.
4. Mohod PN, Nikose AS, Laddha PM, Shadwala Bharti. Incidence of various causes of infectious keratitis in the part of rural central India and its visual morbidity: prospective hospital-based observational study. J Clin Ophthalmol Res 2019; 7: 31.
5. Ting DSJ, Ho CS, Deshmukh R, Said DG, Dua HS. Infectious keratitis: an update on epidemiology, causative microorganisms, risk factors, and antimicrobial resistance. Eye (Lond) 2021; 35: 1084-101.
6. Wong T, Ormonde S, Gamble G, McGhee CN. Severe infective keratitis leading to hospital admission in New Zealand. Br J Ophthalmol 2003; 87: 1103-8.
7. Jin H, Parker WT, Law NW, et al. Evolving risk factors and antibiotic sensitivity patterns for microbial keratitis at a large county hospital. Br J Ophthalmol 2017; 101: 1483-87.
8. Jongkhajornpong P, Nimworaphan J, Lekhanont K, Chuckpaiwong V, Rattanasiri S. Predicting factors and prediction model for discriminating between fungal infection and bacterial infection in severe microbial keratitis. PloS One 2019; 14: e0214076.
9. Tena D, Rodríguez N, Toribio L, González-Praetorius A. Infectious keratitis: microbiological review of 297 cases. Jpn J Infect Dis 2019; 72: 121-3.
10. Egrilmez S, Yildirim-Theveny Ş. Treatment-resistant bacterial keratitis: challenges and solutions. Clin Ophthalmol 2020; 14: 287-97.
11. Sharma S, Taneja M, Gupta R, et al. Comparison of clinical and microbiological profiles in smear-positive and smear-negative cases of suspected microbial keratitis. Indian J Ophthalmol 2007; 55: 21-5.
12. Bhadange Y, Das S, Kasav MK, Sahu SK, Sharma S. Comparison of culture-negative and culture-positive microbial keratitis: cause of culture negativity, clinical features and final outcome. Br J Ophthalmol 2015; 99: 1498-502.
13. Duarte MCB, Becker GN, Muller GG, Tuon FF. Infectious keratitis in southern Brazil: a comparison culture negative and culture positive patients. Rev Bras Oftalmol 2020; 79: 46-52.
14. Stapleton F, Edwards K, Keay L, et al. Risk factors for moderate and severe microbial keratitis in daily wear contact lens users. Ophthalmology 2012; 119: 1516-21.
15. Thomas PA, Kuriakose T. Rapid detection of *Acanthamoeba* cysts in corneal scrapings by lactophenol cotton blue staining. Arch Ophthalmol 1990; 108: 168.
16. Akova YA, Onat M, Koc F, Nurozler A, Duman S. Microbial keratitis following penetrating keratoplasty. Ophthalmic Surg Lasers 1999; 30: 449-55.
17. Fransoo R, Martens P 2013. The Need to Know Team, Prior H, Burchill C, Koseva I, Bailly A, Allegro E. The 2013 RHA indicators atlas. Winnipeg, Canada: Manitoba Centre for Health Policy.
18. Cariello AJ, Passos RM, Yu MCZ, Hofling-Lima AL. Microbial keratitis at a referral center in Brazil. Int Ophthalmol 2011; 31: 197-204.
19. Hsiao CH, Sun CC, Yeh LK, et al. Shifting trends in bacterial keratitis in Taiwan: a 10-year review in a tertiary-care hospital. Cornea 2016; 35: 313-7.
20. Yarımada S, Barut Selver Ö, Palamar M, et al. Comparison of culture-positive and -negative microbial keratitis. Turk J Ophthalmol 2022; 52: 1-5.
21. Wagoner MD, Al-Swailem SA, Sutphin JE, Zimmerman MB. Bacterial keratitis after penetrating keratoplasty: incidence, microbiological profile, graft survival, and visual outcome. Ophthalmology 2007; 114: 1073-9.
22. Dohse N, Wibbelsman TD, Rapuano SB, et al. Microbial keratitis and clinical outcomes following penetrating and endothelial keratoplasty. Acta Ophthalmol 2020; 98: e895-e900.
23. Roongpoovapatr V, editor. Infectious keratitis: the great enemy. Visual impairment and blindness-what we know and what we have to know. IntechOpen, 2019.
24. Lin L, Lan W, Lou B, et al. Genus distribution of bacteria and fungi associated with keratitis in a large eye center located in Southern China. Ophthalmic Epidemiol 2017; 24: 90-6.
25. Augustin VA, Weller JM, Kruse FE, Tourtas T. Fungal interface keratitis after descemet membrane endothelial keratoplasty. Cornea 2018; 37: 1366-9.
26. Lim NCS, Lim DKA, Ray M. Polymicrobial versus monomicrobial keratitis: a retrospective comparative study. Eye Contact Lens 2013; 39: 348-54.
27. Otri AM, Fares U, Al-Aqaba MA, et al. Profile of sight-threatening infectious keratitis: a prospective study. Acta Ophthalmol 2013; 91: 643-51.
28. Koh YY, Sun CC, Hsiao CH. Epidemiology and the estimated burden of microbial keratitis on the health care system in Taiwan: a 14-year population-based study. Am J Ophthalmol 2020; 220: 152-9.
29. Toriyama K, Suzuki T, Shiraishi A. Characteristics of infectious keratitis in old and very old patients. J Ocul Pharmacol Ther 2018; 34: 565-9.
30. Khoo P, Cabrera-Aguas MP, Nguyen V, Lahra MM, Watson SL. Microbial keratitis in Sydney, Australia: risk factors, patient outcomes, and seasonal variation. Graefes Arch Clin Exp Ophthalmol 2020; 258: 1745-55.
31. Lin TY, Yeh LK, Ma DHK, et al. Risk factors and microbiological features of patients hospitalized for microbial keratitis: a 10-year study in a referral center in Taiwan. Medicine 2015; 94: e1905.
32. Tóth G, Pluzsik MT, Sándor GL, et al. Clinical review of microbial corneal ulcers resulting in enucleation and evisceration in a tertiary eye care center in Hungary. J Ophthalmol 2020; 2020: 8283131.