Clinical Ophthalmology

Dovepress
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ORIGINAL RESEARCH

Anatomic Biomarkers Predict Poor Presenting Visual Acuity in Infectious Keratitis

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Purpose: Infectious keratitis, the leading cause of corneal blindness, disproportionately affects developing countries. We examined risk factors for poor presenting visual acuity in a rural Indian population.

Patients and Methods: We conducted a cross-sectional study of patients ≥16 years old with active infectious keratitis at SNC Hospital, a tertiary eye hospital in north India, from June to November 2024. Variables collected were demographics, clinical features, and anatomic findings on slit-lamp examination. Binomial logistic regression measured association of variables with best-corrected visual acuity (BCVA) ≤20/200. Significant univariable associations were incorporated into a multivariable model.

Results: Among 667 patients with keratitis (mean age: 50.3 ± 15 years), 497 (74.5%) presented with VA ≤20/200. Independent risk factors for poor VA included older age (prevalence ratio [PR] 1.01/year, 95% CI 1.00–1.01, p<0.001), bacterial infection (PR 1.12, 95% CI 1.03–1.23, p=0.009), polymicrobial infections (PR 1.13, 95% CI 1.01–1.26, p=0.027), larger epithelial defect (PR 1.38, 95% CI 1.12–1.71, p=0.042 with epithelial defect diameter >6mm), posterior stromal infiltrate (PR 1.22, 95% CI 1.09–1.36, p<0.001), endothelial plaque (PR 1.13, 95% CI 1.00–1.26, p=0.043), central infiltrate location (PR 1.26, 95% CI 1.14–1.38, p<0.001) and hypopyon (PR 1.28, 95% CI 1.18–1.39, p<0.001). Travel distance, time to presentation, and clinical risk factors were not independently associated with poor VA.

Conclusion: Anatomic features including larger epithelial defects, deep stromal infiltrates, endothelial plaque, central location, and hypopyon were the strongest predictors of poor VA. These findings highlight the utility of anatomic features for identifying eyes at risk for severe outcomes and serving as biomarkers in future clinical trials.

Plain Language Summary: Eye infections that affect the cornea, the clear front part of the eye, are a major cause of blindness, especially in developing countries. This study aimed understand what factors make patients more likely to have severe vision loss when they develop corneal infections. Our team studied 667 patients with active corneal infections at SNC Chitrakoot Hospital, a hospital in north India, over six months. We collected data including patient demographics, risk factor, travel distance, and days of symptoms, and details about corneal infection, including its size, depth, location, and type. We found that several factors made severe vision loss for patients presenting with corneal infections more likely: being older, having bacterial infections or infections caused by multiple types of microbes, having larger areas of damaged tissue, having infections that went deeper into the eye, having infections located in the center of the cornea, and having pus buildup (called hypopyon) inside the eye. Surprisingly, how far patients traveled to the hospital or how long they waited before seeking treatment did not significantly affect their vision. Our study shows that ophthalmologists may be able to predict severe vision loss by carefully examining features on examination of their eye. This information can help doctors identify patients who require the most aggressive treatment and help researchers design better studies to test new treatments. The findings emphasize that anatomic factors such as location, size, and depth of the infection are the most important risk factors for vision loss compared to clinical or demographic factors.

Keywords: corneal infection, corneal ulcer, risk stratification, biomarkers

Received: 16 July 2025
Accepted: 28 October 2025
Published: 11 November 2025

Introduction

Infectious keratitis, or infectious corneal ulceration, is the leading etiology of corneal blindness and the fifth leading cause of blindness worldwide, causing two million cases of monocular blindness per year.[1,2] It can result from bacterial, fungal, parasitic, viral, or polymicrobial infections, and presents with pain, redness, decreased vision, and photophobia.[1–3] Without timely diagnosis and treatment, infectious keratitis can cause severe complications including corneal scarring, corneal perforation, or enucleation.[1,4,5] If medical therapy fails, surgical management by therapeutic penetrating keratoplasty (TPK) may be required, during which diseased corneal tissue is transplanted with donor tissue.[6]

Infectious keratitis disproportionately affects developing countries.[7,8] While the incidence of infectious keratitis is estimated to be between 2.5 and 27.6 per 100,000 in the United States, the incidence in India is estimated at up to 113 per 100,000.[9,10] The higher incidence in low-resource settings has been attributed to traumatic injuries, agricultural exposures, and limited healthcare access.[1,11]

Major risk factors for infectious keratitis include contact lens use, trauma, ocular surface disease, prior ocular surgery, and systemic immunosuppression.[1,12] Poor presenting visual acuity (VA), large infiltrate size, larger epithelial defect size, perforation at presentation, and involvement of the posterior cornea were factors associated with need for TPK.[13–17] Worse presenting visual acuity, delayed presentation, and larger stromal infiltrates were associated with worse 90-day visual acuity in a study comparing US and Indian populations.[18]

Sociodemographic risk factors associated with keratitis have also been examined. A cohort study in a South Indian population showed that older age, female gender, and lack of education were associated with poor outcomes.[14]

There remains a need for detailed analyses of risk factors for severe presentations of keratitis in robust patient cohorts, especially in developing countries. This study examined clinical, anatomic, and sociodemographic risk factors for worse VA at presentation among patients with infectious keratitis presenting to Sadguru Netra Chikitsalaya (SNC) Hospital, a tertiary eye care hospital in Chitrakoot, Madhya Pradesh, India.

Methods

Study Population

We retrospectively reviewed records of patients with active infectious keratitis presenting to SNC Eye Hospital from June to November 2024. SNC Hospital serves a rural population and utilizes vision centers and screening eye camps to identify patients needing care.

Inclusion criteria were eyes from patients aged ≥ 16 years with active corneal infection diagnosed clinically or with microbiologic testing. For bilateral infections, the worse-seeing eye was analyzed.

Data Sources & Variables Collected

Data collected from the electronic medical record included demographics (age, sex, address), infection laterality, best-corrected visual acuity (BCVA), slit lamp examination findings, days from symptom onset to presentation, risk factors, and microbiology testing (Gram stain and/or KOH preparation). At SNC Chitrakoot, corneal scraping with Gram or KOH stain was used to diagnose infection; culture and PCR methods are not routinely performed at the site and were not used in this analysis. Slit lamp findings were documented via a standardized form and included epithelial defect diameter, infiltrate diameter, infiltrate stromal depth, infiltrate location relative to the limbus, and markers of severe infection including hypopyon, endothelial plaque, impending perforation/descemetocele, and frank perforation. Whether eyes were selected for TPK was also collected.

Calculation of Travel Distance

Patient addresses and the SNC Hospital address were converted to latitude and longitude coordinates via the Google Maps API and the "ggmap" R package. Straight-line distances (km) between coordinates was computed using Stata's "geodist" command.

Classification of Infection Type

Fungal keratitis cases showed fungal organisms on KOH prep or Gram stain. Bacterial keratitis showed bacterial organisms on Gram stain. Viral keratitis cases were diagnosed clinically by a cornea specialist. Polymicrobial infections were positive for at least two of: microbiologically confirmed fungal keratitis, microbiologically confirmed bacterial keratitis, and/or clinically diagnosed viral keratitis.

Evaluation of Risk Factors for Poor Presenting VA

Poor presenting VA was defined as distance Snellen BCVA <20/200, an establishment for legal blindness that has been employed in prior studies of infectious keratitis.[19,20] Univariate logistic regression was used to evaluate associations between risk factors and poor presenting VA. Binomial logistic regression was used to calculate prevalence ratio (PRs) with 95% confidence intervals (CIs). For each exposure included in the analysis, the PR quantified how the prevalence of poor presenting VA differed between levels. Significant individual risk factors were incorporated into a multivariable logistic regression model. Poisson regression with robust variance estimation was used to approximate the binomial model when the model failed to converge.

Geographic data conversion was conducted in R (v2024.09.0+375). Analyses were conducted in Stata (v18).

Results

Baseline Study Population Characteristics

About 667 eyes from 667 patients with active microbial keratitis were included. The mean patient age was 50.3 ± 15 years, and 62.2% were male (N=415). Time to presentation was 20.4 ± 27.2 days, with mean travel distance of 144.8 ± 92.1 km. Most eyes (N=494, 74.1%) presented with VA 20/200 or worse (Table 1).

Table 1 Demographic, Clinical, and Anatomic Characteristics of Microbial Keratitis by Presenting Visual Acuity

	Overall Population (N=667)	**Presenting VA ≤20/200 (N=494)**	**Presenting VA >20/200 (N=173)**
Age (years), mean (SD)	50.3 (15.0)	52.4 (14.9)	44.0 (13.7)
Days to Presentation, mean (SD)	20.4 (27.2)	22.0 (28.5)	16.0 (22.3)
Travel Distance to Hospital (km), mean (SD)	144.8 (92.1)	144.8 (92.1)	139.7 (90.0)
Affected Eye, N (%)			
Left	331 (49.6%)	245 (49.6%)	86 (49.7%)
Right	336 (50.4%)	249 (50.4%)	87 (50.3%)
Sex, N (%)			
Female	252 (37.8%)	193 (39.1%)	59 (34.1%)
Male	415 (62.2%)	301 (60.9%)	114 (65.9%)
Keratitis Risk Factors, N (%)			
No Known Risk Factors	247 (37.0%)	198 (40.1%)	49 (28.3%)
Vegetative Trauma	183 (27.4%)	127 (25.7%)	56 (32.4%)
Recent Ocular Trauma	60 (9.0%)	42 (8.5%)	18 (10.4%)
Dust Exposure	33 (5.0%)	21 (4.3%)	12 (6.9%)
Animal Trauma	27 (4.1%)	18 (3.6%)	9 (5.2%)
Insect Trauma	26 (3.9%)	18 (3.6%)	8 (4.6%)

(*Continued*)

https://doi.org/10.2147/OPTH.S554171

Table 1 (Continued).

	Overall Population (N=667)	Presenting VA ≤20/200 (N=494)	Presenting VA >20/200 (N=173)
Other Trauma	32 (4.8%)	26 (5.3%)	6 (3.5%)
Foreign Body	22 (3.3%)	14 (2.8%)	8 (4.6%)
Steroid Use	20 (3.0%)	14 (2.8%)	6 (3.5%)
Systemic Immunosuppression	17 (2.6%)	12 (2.4%)	5 (2.9%)
Past Herpetic Infection	10 (1.5%)	7 (1.4%)	3 (1.7%)
Water Exposure	8 (1.2%)	6 (1.2%)	2 (1.2%)
Native Medication	7 (1.1%)	6 (1.2%)	1 (0.6%)
Past Ulcer	5 (0.8%)	4 (0.8%)	2 (0.6%)
Ocular Surgery	3 (0.5%)	3 (0.6%)	0 (0.0%)
Diabetes Mellitus	3 (0.5%)	2 (0.4%)	1 (0.6%)
Contact Lens Wear	2 (0.3%)	2 (0.4%)	0 (0.0%)
Poor Contact Hygiene	1 (0.2%)	1 (0.2%)	0 (0.0%)
Past Keratoplasty	1 (0.2%)	1 (0.2%)	0 (0.0%)
Dacryocystitis	1 (0.2%)	1 (0.2%)	0 (0.0%)
Trichiasis	1 (0.2%)	1 (0.2%)	0 (0.0%)
Type of Infection, N (%)			
Negative Microbiology Data	3 (0.5%)	1 (0.2%)	2 (1.2%)
Fungal Keratitis Only[a]	320 (58.0%)	232 (47.0%)	88 (50.9%)
Bacterial Keratitis Only[b]	177 (26.5%)	150 (30.4%)	27 (15.6%)
Viral Keratitis Only[c]	2 (0.3%)	2 (0.4%)	0 (0.0%)
Polymicrobial Infection[d]	66 (9.9%)	56 (11.3%)	10 (5.8%)
Microbiology Data Not Available	99 (14.8%)	53 (10.7%)	46 (26.6%)
Epithelial Defect Diameter, N (%)			
No Epithelial Defect	32 (4.8%)	17 (3.4%)	15 (8.7%)
>0 to <2mm	121 (18.1%)	61 (12.4%)	60 (34.7%)
2 to <6mm	375 (56.2%)	278 (56.3%)	97 (56.1%)
≥6mm	139 (20.8%)	138 (27.9%)	1 (0.6%)
Infiltrate/Scar Diameter, N (%)			
No Scar	12 (1.8%)	4 (0.8%)	8 (4.6%)
>0 to <2mm	119 (17.8%)	62 (12.6%)	57 (33.0%)
2 to <6mm	388 (58.2%)	283 (57.3%)	105 (60.7%)
≥6mm	148 (22.2%)	145 (29.4%)	3 (1.7%)

(*Continued*)

Table 1 (Continued).

	Overall Population (N=667)	Presenting VA ≤20/200 (N=494)	Presenting VA >20/200 (N=173)
Infiltrate/Scar Stromal Depth, N (%)			
Anterior $^1/_3$ of Stroma	241 (36.1%)	145 (29.4%)	96 (55.5%)
Middle $^1/_3$ of Stroma	205 (30.7%)	150 (30.4%)	55 (31.8%)
Posterior $^1/_3$ of Stroma	131 (19.6%)	122 (24.7%)	9 (5.2%)
Endothelial Lesion	76 (11.4%)	71 (14.4%)	5 (2.9%)
Not Applicable	14 (2.1%)	6 (1.2%)	8 (4.6%)
Infiltrate/Scar Location, N (%)			
Central (0 to 4mm)	390 (58.5%)	313 (63.4%)	96 (55.5%)
Mid-peripheral (4 to 8mm)	345 (51.7%)	259 (52.4%)	86 (49.7%)
Peripheral (8 to 10mm)	388 (58.2%)	287 (58.1%)	101 (58.4%)
Diffuse (entire cornea)	28 (4.2%)	27 (5.5%)	1 (0.6%)
Not Applicable	12 (1.8%)	5 (1.0%)	7 (4.1%)
Infiltrate Location Within 2mm of Limbus, N (%)			
Yes	120 (18.0%)	101 (20.5%)	19 (11.0%)
No	547 (82.0%)	393 (79.6%)	154 (89.0%)
Hypopyon Present, N (%)			
Yes	236 (35.4%)	218 (44.1%)	18 (10.4%)
No	431 (64.6%)	276 (55.9%)	155 (89.6%)
Impending Perforation, N (%)			
Yes	45 (6.8%)	44 (8.9%)	1 (0.6%)
No	622 (93.3%)	450 (91.1%)	172 (99.4%)
Frank Perforation, N (%)			
Yes	52 (7.8%)	51 (10.3%)	1 (0.6%)
No	615 (92.2%)	443 (89.7%)	172 (99.4%)
Therapeutic Keratoplasty Required, N (%)			
Yes	51 (7.7%)	50 (10.1%)	1 (0.6%)
No	615 (92.3%)	444 (89.9%)	171 (99.4%)

Notes: [a]Fungal keratitis was microbiologically confirmed via KOH stain or Gram stain. [b]Bacterial keratitis was microbiologically confirmed via Gram stain. [c]Viral keratitis was clinically diagnosed by a cornea specialist. [d] Polymicrobial infections were positive for at least 2 of the following: microbiologically confirmed fungal keratitis, microbiologically confirmed bacterial keratitis, and/or clinically diagnosed viral keratitis.
Abbreviations: SD, standard deviation; VA, visual acuity.

Common risk factors were vegetative trauma (N=183, 27.4%), recent ocular trauma (N=60, 9.0%), dust exposure (N=33, 5.0%), animal trauma (N=27, 4.1%), and insect trauma (N=26, 3.9%), though 37% of eyes (N=247) had no identifiable risk factors. About 58% of infections were fungal keratitis only (N=320), followed by bacterial keratitis only (N=177, 26.5%), and polymicrobial infections (N=66, 9.9%). Isolated viral keratitis accounted for two infections (0.3% of cases).

https://doi.org/10.2147/OPTH.S554171

Risk Factors for Poor Presenting VA

In univariable analysis, factors associated with VA ≤20/200 were increasing age (PR 1.01 per year, 95% CI 1.007–1.012, p<0.001), delayed presentation >14 days (PR 1.11, 95% CI 1.02–1.21, p=0.020), and bacterial keratitis (PR 1.16, 95% CI 1.06–1.28, p=0.001) or polymicrobial infections (PR 1.17, 95% CI 1.03–1.32, p=0.014) relative to fungal keratitis (reference group) (Table 2).

Anatomic factors associated with poor presenting VA included larger epithelial defect diameter (2-< 6 mm versus 0–2 mm [reference group]: PR 1.47, 95% CI 1.22–1.77, p<0.001, and >6mm versus 0–2 mm: PR 1.97, 95% CI 1.65–2.35, p<0.001) and larger stromal infiltrate diameter (2 to <6 mm versus 0–2 mm [reference group]: PR 1.40,

Table 2 Patient and Eye-Level Characteristics Associated with 20/200 or Worse Presenting Visual Acuity

	Univariable log binomial regression		Multivariable log binomial regression[a]	
	PR (95% CI)	**p-value**	**PR (95% CI)**	**p-value**
Age, years	1.01 (1.007–1.012)	<0.001***	1.01 (1.005–1.010)	<0.001***
Time to Presentation				
≤14 Days	Reference		Reference	
>14 Days	1.11 (1.02–1.21)	0.020*	1.05 (0.97–1.14)	0.200
Distance to Base Hospital				
≤128 km	Reference			
>128 km	1.01 (0.93–1.11)	0.769		
Sex				
Female	Reference			
Male	0.94 (0.86–1.03)	0.176		
Risk Factors[b]				
Vegetative Trauma	0.91 (0.81–1.01)	0.080		
Recent Ocular Trauma	0.93 (0.79–1.11)	0.436		
Dust Exposure	0.85 (0.65–1.10)	0.216		
Animal Trauma	0.89 (0.68–1.17)	0.402		
Insect Trauma	0.93 (0.71–1.20)	0.565		
Other Trauma	1.13 (0.95–1.35)	0.167		
Foreign Body	0.85 (0.62–1.17)	0.318		
Steroid Use	0.94 (0.70–1.25)	0.664		
Systemic Immunosuppression	1.03 (0.79–1.34)	0.845		
Past Herpetic Infection	1.07 (0.79–1.47)	0.652		
Water Exposure	1.01 (0.67–1.51)	0.974		
Native Medication	1.15 (0.85–1.56)	0.364		
Past Ulcer	1.07 (0.69–1.67)	0.750		
Diabetes Mellitus	0.89 (0.40–1.99)	0.785		

(*Continued*)

Table 2 (Continued).

	Univariable log binomial regression		Multivariable log binomial regression[a]	
	PR (95% CI)	**p-value**	**PR (95% CI)**	**p-value**
Type of Infection				
Fungal Keratitis Only	Reference		Reference	
Bacterial Keratitis Only	1.16 (1.06–1.28)	0.001**	1.12 (1.03–1.23)	0.009**
Polymicrobial Keratitis	1.17 (1.03–1.32)	0.014*	1.13 (1.01–1.26)	0.027*
Epithelial Defect Diameter				
No Epithelial Defect	1.05 (0.73–1.53)	0.782	1.30 (0.88–1.90)	0.187
>0 to <2mm	Reference		Reference	
2 to <6mm	1.47 (1.22–1.77)	<0.001***	1.24 (1.01–1.52)	0.042*
>6mm	1.97 (1.65–2.35)	<0.001***	1.38 (1.12–1.71)	0.003**
Infiltrate/Scar Diameter				
No Scar	0.64 (0.28–1.45)	0.285	0.35 (0.09–1.40)	0.137
>0 to <2mm	Reference		Reference	
2 to <6mm	1.40 (1.17–1.68)	<0.001***	1.01 (0.81–1.24)	0.954
>6mm	1.88 (1.58–2.24)	<0.001***	1.14 (0.91–1.42)	0.265
Infiltrate/Scar Stromal Depth				
Anterior $^{1}/_{3}$ of Stroma	Reference		Reference	
Middle $^{1}/_{3}$ of Stroma	1.21 (1.06–1.38)	0.005**	1.08 (0.96–1.22)	0.188
Posterior $^{1}/_{3}$ of Stroma	1.54 (1.37–1.72)	<0.001***	1.22 (1.09–1.36)	<0.001***
Endothelial Lesion	1.54 (1.37–1.74)	<0.001***	1.13 (1.00–1.26)	0.043*
Infiltrate/Scar Location[c]				
Central (0 to 4mm)	1.22 (1.11–1.34)	<0.001***	1.26 (1.14–1.38)	<0.001***
Mid-peripheral (4 to 8mm)	1.02 (0.93–1.11)	0.732		
Peripheral (8 to 10mm)	0.98 (0.90–1.07)	0.703		
Diffuse (entire cornea)	1.31 (1.20–1.43)	<0.001***	1.10 (0.99–1.23)	0.078
Infiltrate Location Within 2mm of Limbus	1.16 (1.06–1.28)	0.002**	0.99 (0.90–1.09)	0.831
Hypopyon Present	1.43 (1.32–1.54)	<0.001***	1.28 (1.18–1.39)	<0.001***
Impending Perforation	1.34 (1.26–1.43)	<0.001***	1.04 (0.95–1.13)	0.435
Frank Perforation	1.35 (1.27–1.44)	<0.001***	1.05 (0.96–1.16)	0.268
Therapeutic Keratoplasty Required	1.35 (1.27–1.44)	<0.001***	1.05 (0.95–1.16)	0.358

Notes: [a]Multivariable log binomial regression model included all covariates found to be significantly associated with the outcome in univariable regression. Covariates included were age, time to presentation, type of infection, epithelial defect diameter, scar diameter, scar stromal depth, scar location, infiltrate location within 2mm of limbus, presence of hypopyon, impending perforation, frank perforation, and need for therapeutic keratoplasty. [b]Presence or absence of each risk factor was assessed independent of other risk factors. [c]Presence or absence of scar within each corneal region (central, mid-peripheral, peripheral, or diffuse) was assessed independent of scar presence in other locations. *p<0.05; **p<0.01; ***p<0.001.

Abbreviations: CI, confidence interval; PR, prevalence ratio.

https://doi.org/10.2147/OPTH.S554171

95% CI 1.17–1.68, p<0.001, and >6 mm versus 0–2 mm: PR 1.88, 95% CI 1.58–2.24, p<0.001). Deeper stromal infiltrates were also associated with poorer VA. Compared to eyes with infiltrates only within the anterior one third of the stroma (reference group), eyes had higher likelihood of poor presenting VA with infiltrates in the middle one third of the stroma (PR 1.54, 95% CI 1.37–1.72, p=0.005), posterior one third of the stroma (PR 1.54, 95% CI 1.37–1.72, p<0.001), or endothelial plaque (PR 1.54, 95% CI 1.37–1.74, p<0.001). Compared to eyes without central infiltrates (reference group), infiltrates involving the central cornea (PR 1.22, 95% CI 1.11–1.34, p<0.001) or extending diffusely throughout the cornea (PR 1.31, 95% CI 1.20–1.43, p<0.001) were associated with higher risk of poor presenting VA. Eyes with infiltrate extension to within 2 mm of the limbus were also associated with higher likelihood of poorer VA on presentation (PR 1.16, 95% CI 1.06–1.28, p=0.002).

Hypopyon (PR 1.43, 95% CI 1.32–1.54, p<0.001), impending perforation (PR 1.34, 95% CI 1.26–1.43, p<0.001), frank perforation (PR 1.35, 95% CI 1.27–1.44, p<0.001), and need for therapeutic keratoplasty (PR 1.35, 95% CI 1.27–1.44, p<0.001) were all significantly associated with poor presenting VA (Table 2).

In multivariable analysis, several factors remained independently associated with poor presenting VA (Table 2). Older age (PR 1.01 per year, 95% CI 1.005–1.010, p<0.001) was associated with poor presenting VA. Both bacterial keratitis (PR 1.12, 95% CI 1.03–1.23, p=0.009) and polymicrobial infections (PR 1.13, 95% CI 1.01–1.26, p=0.027) were associated with worse presenting VA compared to fungal keratitis. Anatomically, larger epithelial defects of 2 to <6 mm (PR 1.24, 95% CI 1.01–1.52, p=0.003) and >6mm (PR 1.38, 95% CI 1.12–1.71, p=0.042) predicted worse VA compared to epithelial defects >0 to <2 mm. Posterior stromal involvement (PR 1.22, 95% CI 1.09–1.36, p<0.001), endothelial lesions (PR 1.13, 95% CI 1.00–1.26, p=0.043), central infiltrate location (PR 1.26, 95% CI 1.14–1.38, p<0.001), and the presence of hypopyon (PR 1.28, 95% CI 1.18–1.39, p<0.001) were also independent risk factors for poor presenting VA.

Discussion

This large retrospective study of infectious keratitis in India identified several anatomic, clinical, and demographic factors associated with poor presenting VA of 20/200 or worse. Anatomic risk factors were more strongly associated with poor VA than clinical or demographic risk factors, highlighting their importance as potential biomarkers to help gauge infection severity and predict clinical outcomes in keratitis. The strong associations between anatomic findings and poor presenting VA may make them useful for standardized keratitis risk assessment tools.

Anatomic Risk Factors for Worse Presenting VA

Anatomic features were more powerfully associated with poor presenting VA than any other covariates in our analysis, including well-described keratitis risk factors such as trauma and fungal infection.[1,14,21] These findings indicate the importance of detailed anatomic evaluation of keratitis to triage clinical severity. Although this analysis relied on subjective clinician grading, future research can utilize imaging such as slit lamp photography and anterior segment optical coherence tomography (ASOCT) to better classify anatomic risk factors.

Central infections, which directly affect the visual axis, were associated with worse VA. The Steroids for Corneal Ulcers Trial (SCUT) demonstrated that centrally located ulcers demonstrated a benefit in 3-month VA after adjuvant corticosteroids, providing further evidence that therapies to reduce central scarring may confer visual benefits compared to treatment of peripheral scarring.[22] Our work corroborates central location as an important determinant of poor keratitis outcomes.

The presence of hypopyon was associated with poorer presenting VA, indicating that measuring hypopyon may help to stratify keratitis severity. Hypopyon is an indicator of infection severity that is most frequently associated with fungal keratitis, and it has been demonstrated that up to 50% of fungal cases develop hypopyon.[23–25] Objective measurement of hypopyon size on slit lamp biomicroscopy, photography, or ASOCT may aid in use of hypopyon as a biomarker in future research.

Larger epithelial defects were associated with poorer VA than smaller epithelial defects. Compared to eyes with epithelial defects 0 to <2 mm in diameter, eyes with epithelial defects 2 to <6 mm in size had 24% higher prevalence of VA ≤20/200. Eyes with epithelial defects >6 mm in diameter had 38% higher prevalence of VA 20/200 or worse, compared to epithelial defects 0 to <2 mm in diameter. Epithelial defect size is well-studied as a predictor of severe keratitis outcomes, and has been associated with higher likelihood of prolonged healing time, need for surgical

intervention, and worse 3-month VA outcomes.[14,17,26,27] Our finding corroborates use of epithelial defect size as a biomarker of worse presenting VA in keratitis.

Deeper stromal involvement was strongly associated with worse presenting VA. Eyes with infiltrates extending into the posterior one-third of the cornea had 22% higher prevalence of VA <20/200 compared to eyes with infiltrates in the anterior one-third of the cornea. Endothelial plaque was associated with 13% higher prevalence of VA ≤20/200 compared to isolated anterior infiltrates. In SCUT, which measured infiltrate depth via subjective slit lamp examination, subgroup analyses showed that deeper infiltrates were associated with VA improvement following exposure to adjuvant corticosteroids while parameters such as infiltrate diameter were not associated with VA improvement.[22] A follow-up analysis of patients years after MUTT I showed that irregular astigmatism from post-infectious stromal thinning was strongly associated with worse long-term VA while scar depth was not associated.[28] However, the authors argued that initial infection depth may predict development of irregular astigmatism and may be an important predictor of vision loss. Given the potential for novel imaging such as ASOCT to quantify infection depth, future research should evaluate the association of infection depth with longer term infection outcomes.

It is notable that larger infiltrate diameter was not associated with worse presenting VA. Larger infiltrate diameter has been associated with severe disease, worse vision, and higher rates of surgical intervention, although only a few clinical trials such as SCUT and MUT have shown an association between infiltrate diameter and trial endpoints.[22,25,26,29,30] In one study using ASOCT to quantify fungal keratitis, both infiltrate width and depth were reduced from presentation to healing.[31] In a separate study using ASOCT to quantify bacterial keratitis lesions, both corneal edema and stromal infiltrate thickness in the anterior-to-posterior dimension significantly decreased with infection resolution, while infiltrate width did not.[32] Thus, infiltrates may be more likely to shrink in stromal depth within the anterior-to-posterior axis rather than diameter or size in the *en face* (X-Y) plane. Given that infiltrate diameter was not associated with poor VA while infiltrate depth remained strongly associated with poor presenting VA, future studies should evaluate the use of infiltrate depth as a sensitive biomarker for worse infection.

Clinical Risk Factors for Worse Presenting VA

Bacterial and polymicrobial infections being associated with worse VA compared to fungal keratitis is noteworthy. Fungal keratitis has been shown to have an aggressive course and lead to worse outcomes.[33–35] In our study, more eyes with bacterial only infections had larger and deeper infiltrates compared to eyes with fungal only infections (Table 3).

Table 3 Demographic, Clinical, and Anatomic Characteristics of Microbial Keratitis by Infection Type

	Fungal Keratitis Only[a] (N=320)	**Bacterial Keratitis Only[b] (N=177)**	**Polymicrobial Infection[c] (N=66)**
Age (years), mean (SD)	49.2 (14.1)	51.8 (15.6)	55.0 (15.8)
Days to Presentation, mean (SD)	15.0 (14.4)	22.3 (27.6)	28.7 (32.5)
Travel Distance to Hospital (km), mean (SD)	145.3 (87.8)	142.7 (83.3)	152.3 (131.9)
Affected Eye, N (%)			
Left	154 (48.1%)	88 (49.7%)	34 (51.5%)
Right	166 (51.9%)	89 (50.3%)	32 (48.5%)
Sex, N (%)			
Female	126 (39.4%)	62 (35.0%)	24 (36.4%)
Male	194 (60.6%)	115 (65.0%)	42 (63.6%)

(*Continued*)

https://doi.org/10.2147/OPTH.S554171

Table 3 (Continued).

	Fungal Keratitis Only[a] (N=320)	Bacterial Keratitis Only[b] (N=177)	Polymicrobial Infection[c] (N=66)
Keratitis Risk Factors, N (%)			
No Known Risk Factors	98 (30.6%)	79 (44.6%)	32 (48.4%)
Vegetative Trauma	106 (33.1%)	41 (23.2%)	15 (22.7%)
Recent Ocular Trauma	34 (10.6%)	12 (6.8%)	9 (13.6%)
Dust Exposure	21 (6.6%)	7 (4.0%)	1 (1.5%)
Animal Trauma	14 (4.4%)	6 (3.4%)	0 (0.0%)
Insect Trauma	16 (5.0%)	3 (1.7%)	1 (1.5%)
Other Trauma	15 (4.7%)	10 (5.7%)	3 (4.6%)
Foreign Body	13 (4.1%)	6 (3.4%)	1 (1.5%)
Steroid Use	8 (2.5%)	8 (4.5%)	0 (0.0%)
Systemic Immunosuppression	4 (1.3%)	3 (1.7%)	0 (0.0%)
Past Herpetic Infection	0 (0.0%)	2 (1.1%)	3 (4.6%)
Water Exposure	6 (1.9%)	2 (1.1%)	0 (0.0%)
Native Medication	1 (0.3%)	6 (3.4%)	0 (0.0%)
Past Ulcer	2 (0.6%)	1 (0.6%)	1 (1.5%)
Ocular Surgery	0 (0.0%)	3 (1.7%)	0 (0.0%)
Diabetes Mellitus	1 (0.3%)	1 (0.6%)	0 (0.0%)
Contact Lens Wear	0 (0.0%)	1 (0.6%)	1 (1.5%)
Poor Contact Hygiene	0 (0.0%)	1 (0.6%)	0 (0.0%)
Past Keratoplasty	0 (0.0%)	1 (0.6%)	0 (0.0%)
Dacryocystitis	0 (0.0%)	1 (0.6%)	0 (0.0%)
Trichiasis	0 (0.0%)	1 (0.6%)	0 (0.0%)
Epithelial Defect Diameter, N (%)			
No Epithelial Defect	4 (1.3%)	5 (2.8%)	3 (4.6%)
>0 to <2mm	52 (16.3%)	29 (16.4%)	11 (16.7%)
2 to <6mm	195 (60.9%)	91 (51.4%)	39 (59.1%)
≥6mm	69 (21.6%)	52 (29.4%)	13 (19.7%)
Infiltrate/Scar Diameter, N (%)			
No Scar	0 (0.0%)	1 (0.6%)	2 (3.0%)
>0 to <2mm	43 (13.4%)	28 (15.8%)	9 (13.6%)
2 to <6mm	202 (63.1%)	95 (53.7%)	40 (60.6%)
≥6mm	75 (23.4%)	53 (29.9%)	15 (22.7%)

(*Continued*)

Table 3 (Continued).

	Fungal Keratitis Only[a] (N=320)	Bacterial Keratitis Only[b] (N=177)	Polymicrobial Infection[c] (N=66)
Infiltrate/Scar Stromal Depth, N (%)			
Anterior $^1/_3$ of Stroma	133 (41.6%)	47 (26.6%)	23 (34.9%)
Middle $^1/_3$ of Stroma	101 (31.6%)	49 (27.7%)	19 (28.8%)
Posterior $^1/_3$ of Stroma	51 (15.9%)	54 (30.5%)	15 (22.7%)
Endothelial Lesion	34 (10.6%)	26 (14.7%)	8 (12.1%)
Not Applicable	1 (0.3%)	1 (0.6%)	1 (1.5%)
Infiltrate/Scar Location, N (%)			
Central (0 to 4mm)	198 (61.9%)	98 (55.4%)	35 (53.0%)
Mid-peripheral (4 to 8mm)	174 (54.4%)	94 (53.1%)	34 (51.5%)
Peripheral (8 to 10mm)	191 (59.7%)	108 (61.0%)	41 (62.1%)
Diffuse (entire cornea)	9 (2.8%)	14 (7.9%)	2 (3.0%)
Not Applicable	0 (0.0%)	1 (0.6%)	1 (1.5%)
Infiltrate Location Within 2mm of Limbus, N (%)			
Yes	50 (15.6%)	46 (26.0%)	16 (24.2%)
No	270 (84.4%)	131 (74.0%)	50 (75.8%)
Hypopyon Present, N (%)			
Yes	129 (40.3%)	54 (30.5%)	28 (42.4%)
No	191 (59.7%)	123 (69.5%)	38 (57.6%)
Impending Perforation, N (%)			
Yes	15 (4.7%)	22 (12.4%)	7 (10.6%)
No	305 (95.3%)	155 (87.6%)	59 (89.4%)
Frank Perforation, N (%)			
Yes	15 (4.7%)	28 (15.8%)	8 (12.1%)
No	305 (95.3%)	149 (84.2%)	58 (87.9%)
Therapeutic Keratoplasty Required, N (%)			
Yes	20 (6.3%)	24 (13.6%)	4 (6.1%)
No	300 (93.8%)	153 (86.4%)	62 (93.9%)

Notes: [a]Fungal keratitis was microbiologically confirmed via KOH stain or Gram stain. [b]Bacterial keratitis was microbiologically confirmed via Gram stain. [c]Polymicrobial infections were positive for at least 2 of the following: microbiologically confirmed fungal keratitis, microbiologically confirmed bacterial keratitis, and/or clinically diagnosed viral keratitis.
Abbreviation: SD, standard deviation.

A greater percentage of polymicrobial infections also had deeper infiltrates. The poorer presenting VA associated with bacterial keratitis may be due to more severe infiltrates than those eyes with fungal keratitis. To our knowledge, this is the first study evaluating keratitis outcomes in Madhya Pradesh, where keratitis types may differ from South India, where

fungal keratitis is common. Thus, both a difference in infiltrate size and geography may explain the more significant vision loss associated with bacterial infections in our analysis.

Sociodemographic Risk Factors for Worse Presenting VA

Older age showed a modest association with poorer VA, where for each one-year increase in age, the prevalence of presenting VA ≤20/200 increased by 1%. Sociodemographic factors such as days to presentation and travel distance were not associated with poorer VA.

The population's mean presentation time of 20.4 days highlights the challenge of healthcare access in rural India. Eyes with presenting VA <20/200 had greater time to presentation (22 days versus 16 days). Further, time to presentation ≥14 days had an 11% increased risk of presenting VA ≤20/200, though this was not significant in multivariable analysis. Barriers for delayed presentation in similar settings have included transportation costs, travel distance, lost wages, and lack of nearby eye care facilities.[36,37] Future work should continue to explore and address sociodemographic barriers.

This study has certain limitations. SNC Hospital is a tertiary referral center, and patients in our study may represent more severe cases of keratitis, which may not be generalizable to other settings. Microbiologic confirmation with culture or PCR methods was not possible as it was not routinely performed at the site. As this was a retrospective study, it is subject to data reporting inconsistencies due to recall bias. Additionally, this analysis is focused on risk factors for presenting VA; we acknowledge that longer-term outcomes such as follow-up VA at one year, which are being collected, will be essential to thoroughly understand the risk factors associated with severe presentations of keratitis. Nonetheless, our findings highlight key anatomic and clinical features that are strongly associated with poor presenting VA in microbial keratitis.

Conclusion

In this large cross-sectional study of infectious keratitis patients presenting to a tertiary center in north India, specific anatomic features including large epithelial defect diameter, deep stromal infiltrates, central infections, and hypopyon were strongly associated with poor VA at presentation, even after accounting for several sociodemographic and clinical risk factors. In practice, structured evaluation of anatomic infection parameters can help grade keratitis severity, enable risk stratification to prioritize urgent need for therapy, and serve as clinically relevant therapeutic biomarkers for clinical trials.

Data Sharing Statement

The datasets generated and analyzed during the current study are not publicly available due to ongoing data collection and analysis but can be made available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This study obtained ethics approval from the Johns Hopkins Institutional Review Board (ID: IRB00259376) and the SNC Hospital Research Ethics Committee (no associated ID, approved 5/2/2024). Participants gave informed consent before study entry. This study adheres to tenets of the Declaration of Helsinki.

Funding

Funding support for this research was provided by KeraLink International and the National Eye Institute (K23EY032988, R21EY034343, R33EY034343).

Disclosure

The authors declare that they have no competing interests.

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