Outcomes of conjunctival flap in severe microbial keratitis

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ABSTRACT

Objectives: To describe the 3-month outcomes of conjunctival flap in managing severe Microbial Keratitis (MK).
Design: This was a prospective cohort study.
Setting: Patients were enrolled at two major eye hospitals in Mbarara, a major city in the Southwestern sub-region of Uganda, over a one year period.
Subjects: Individuals of any age that met the case definition of severe microbial keratitis, in which perforation occurred acutely or was impending.
Interventions: A complete Gunderson conjunctival flap was done in all suitable patients. Demographics, health access, clinical, and microbiological data were recorded.
Main outcome measures: Statistical significance testing was done to assess predictors of evisceration at the 3-month follow-up time point.
Results: Among 57 patients (57 affected eyes), median age was 44 years (IQR 38, 60) and 47.4% were women. Trauma was associated with 35.1% of cases. Median time to presentation was 23 days (IQR 12, 34). Etiology was 80.7% purely fungal pathogens, 10.5% mixed bacterial/fungal, and 8.8% undetermined. Mean infiltrate and epithelial defect sizes were 7.2mm (SD 2.3) and 6.0mm (SD 2.5), respectively. Presenting visual acuity was <3/60 in 78% of eyes. At 3-months, 19 eyes (34.5%, 95%CI 23.5-48.2) had improved best-corrected visual acuity, though 9 eyes required evisceration (15.8%, 95%CI 8.3-28.0). There were no clinically or statistically significant predictors for evisceration at 3 months.
Conclusions: Conjunctival flap is a reasonable rescue procedure, especially if therapeutic penetrating keratoplasty is an eventually feasible option. However, there are considerable risks of vision loss or lack of improvement and eventual need for evisceration.
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Key words: Conjunctival flap, Corneal ulcer, Microbial keratitis, Evisceration, Uganda

INTRODUCTION

Microbial Keratitis (MK) is a sight-threatening ocular emergency from infection of the cornea by microorganisms. This can present as ulceration of the cornea with stromal infiltration in severe cases[1]. MKis a significant cause of unilateral blindness globally with an estimated incidence of 1.5 to 2 million cases per year[2],which is an underrepresentation of the true burden due to under-reporting by population surveys in Low- and Middle-Income Countries (LMICs)[3], where the burden disproportionately falls on the rural poor. Nevertheless using these data sources, there were 4.2 million prevalent cases globally in 2015 including individuals who were visually impaired (<6/18 best-corrected visual acuity) or blind (<3/60) from corneal opacity[4]. Large-scale global efforts have been responsible for the sharp reduction in prevalence of trachoma from 4.4 million visually impaired or blind in 1990 to 2.0 million in 20154. This success should motivate similar policy and implementation mechanisms to control the "silent epidemic" of MK.

Unfortunately, the status quo is unacceptable and a considerable proportion of patients present to tertiary level healthcare facilities in Sub-Saharan Africa (SSA) with severe MK, which can be defined as;(i) Stromal infiltrate size >3mm by the longest diameter, (ii) Best-Corrected Visual Acuity (BCVA) of<6/60 at baseline, and/or (iii) Impending perforation or acute perforation. Severe MK is associated with poor visual prognosis in Tanzania[5,6] and southern India[7]. In High-Income Countries (HIC), corneal

tissue is readily available for therapeutic penetrating keratoplasty (PK), while 53% of the world has no access to corneal tissue[8]. Most of these individuals reside in SSA countries. Therefore, conjunctival flap has been the most reasonable alternative to prevent corneal perforation and preserve the globe[9],[10]. While the long-term goal must be to increase corneal tissue availability in SSA countries, the incident and backlog cases of severe MK warrant near-term measures to provide the best functional outcomes for patients. Losing an eye has detrimental psychological consequences to the patient. Stabilizing the ocular surface and preventing enucleation can be achieved successfully with conjunctival flap[11],[12]; complications such as flap retraction and button-holing can be managed with a revision operation and occur as much as 24% in all cases among all indications for conjunctival flap[12].

To the best of our knowledge, no prospective cohort study has been performed in SSA reporting outcomes of conjunctival flap in management of severe MK. In this large consecutive cohort study from Uganda, we describe outcomes at 3months and assess predictors for failure of conjunctival flap requiring evisceration.

MATERIALS AND METHODS

Setting and participants: From December 2016 to March 2018, patients were enrolled from two major eye hospitals in Mbarara, a major city in the Southwestern Sub-region of Uganda[13]. Patients' ocular history, self-reported onset of symptoms,alternative treatments prior to presentation, and indicators of socioeconomic status were collected. All patients were assessed by an attending ophthalmologist (S.A.).The MK case definition included: (i) Corneal epithelium defect(>1mm diameter) with underlying stromal infiltrate oralternatively a deep corneal abscess (>1mm) and(ii) Associated signs of inflammation, such as conjunctival hyperemia, anterior chamber reaction, with/withouthypopyon. Individuals meeting MK case definition were then asked for consent to enroll in this study; exclusion criteria were: emergent cases without time to triage, children under age 18 years, and inability to provide consent whether due to refusal or lack of capacity.

Clinical data and microbiology: Slit lamp examination findings, including perforation status, were determined by an attending ophthalmologist (S.A.). Infiltrate size was determined using the greatest diameter of infiltrate (major axis) and widest perpendicular diameter (minor axis); the final infiltrate size is the geometric mean of these diameters14.Epithelial defect was determined using the same method with measurements taken under fluorescein staining. Corneal scrapings from the edges of the ulcer were used for microscopy (Gram, potassium hydroxide [KOH], calcofluor white [CFW] stains), culture agars (Sheep's Blood, Chocolate, Potato Dextrose), and Brain-Heart Infusion (BHI) broth. Corneal swabs were used for Polymerase Chain Reaction (PCR). Agar plates and broth were incubated at 35-37°C for up to 7 days for bacteria and at 25°C for 21 days for fungi.Organism identification and sensitivity testing were performed using standard microbiological techniques and reported using similar methods in Leck *et al*[15].

Surgical technique, medical management, and follow-up: If a patient was determined to have an acute perforation or the stromal infiltrate was deep enough such that perforation was impending, conjunctival flap surgical procedure was undertaken to prevent evisceration. Eyes already perforated with an overwhelming infection or extensive corneal necrosis with no healing potential underwent immediate evisceration (Figure 1).

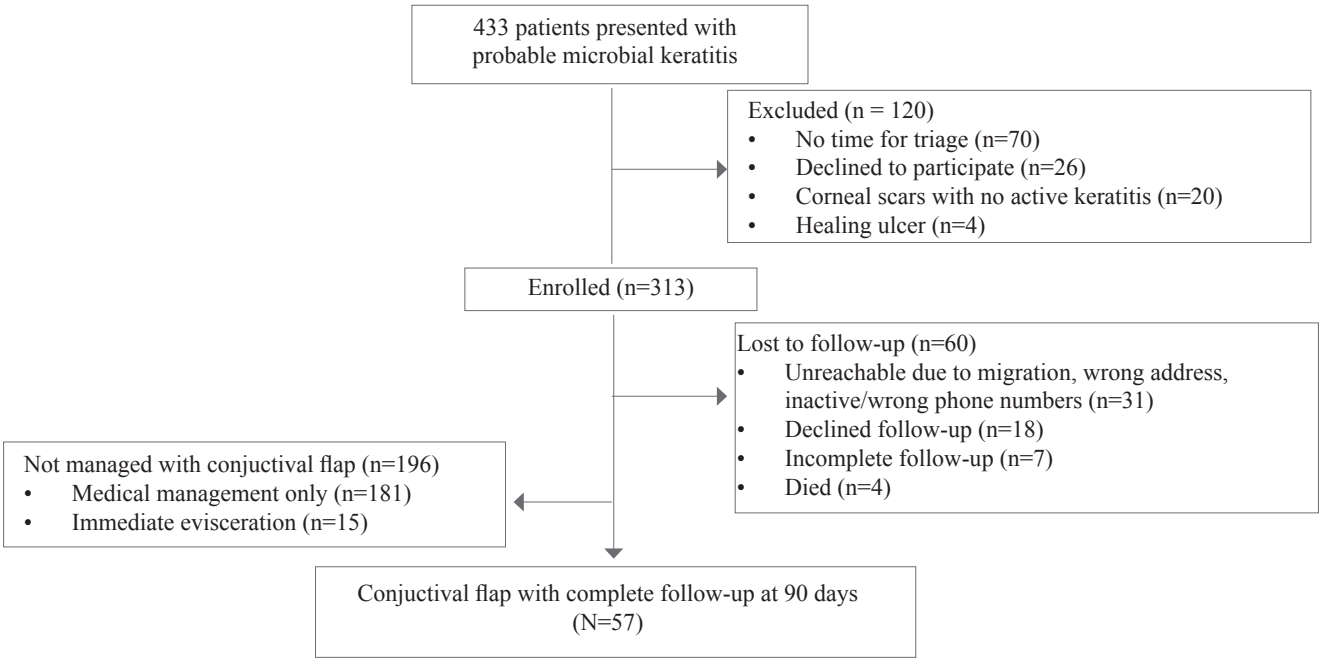

Figure 1: Study flow diagram

Conjunctival flap was carried out in a sterile operating theatre under an operating microscope by an attending ophthalmologist (S.A.) or a senior resident ophthalmologist (G.K.). All cases were performed under peribulbarblock with 3ml 2.0% lidocaine. A wide periorbital/hemifacial sterile field was established with 5.0% povidone iodine. The eye was draped, and a lid retractor was placed. A crescent blade was used to debride all necrotic tissue and denude corneal epitheliumto an area 1mm margin beyond the ulcer's extant. A complete Gunderson flap was then performed16. A traction suture (4-0 silk) was placed at the superior limbus to infraduct the globe, exposing superior conjunctiva. The conjunctiva was marked at the superior fornix, approximately 14mm superior to thelimbus. Admixture of 1% lidocaine and 1:100,000 epinephrine was injected into the subconjunctival space to facilitate mobilization. A 360° peritomy was performed, then a 20mm-length incision into conjunctiva was made at the superior fornix at the pre-marked location. The flap was created with sharp and blunt dissection with blunt-tipped scissors inferiorly toward the superior limbus. The flap was then mobilized inferiorly to completely cover the cornea. The flap was sutured in place at the superior and inferior limbus with simple, interrupted 10-0 monofilament nylon sutures. The flap remained tension-free. Empiric anti-microbial ophthalmic suspension wereapplied,and the eye was dressed.

Each patient was admitted and monitored post-operatively for one week. Dressing changes occurred every 24 hours. Pre-operative anti-microbial regimen was natamycin 5% and ofloxacin 0.3% every hour for first 3 days. When microscopy was available, the regimen was altered as follows. Fungal pathogens were treated with natamycin q1hour for 72 hours, then q1hour during waking hours for 2 weeks, q2hours during waking hours for 2 weeks, then four times per day until follow-up. Bacterial pathogens were treated with ofloxacin 0.3% ophthalmic solution q1hour for 3 days then 6 times per day for one week. Viralpathogens werepresumed herpetic andtreated with acyclovir 3% ophthalmic ointment 5 times per day for 3 weeks. Patients were evaluated at post-operative day 1 then 7, 21, and 90 days post initial presentation. Sutures were removed at day 21 visit. The primary outcome measures at 3months (90 days) were Best-Corrected Visual Acuity (BCVA), scar density, and need for evisceration. Independent variables were demographics, visual acuity at presentation, acuity of presentation, early operation, clinical characteristics of the ulcer, perforation status, microbiology, and medical comorbidities.

Data analysis: Summary statistics, error estimates, statistical significance testing of continuous and categorical variables, and regression modeling were performed in STATA 16 (Stata Corp, College Station, TX, USA). Data visualization was performed using STATA 16 and Microsoft Excel 2016 (Microsoft Corp, Redmond, WA, USA). Visual acuity was analyzed on the logMAR scale but converted to Snellen metric. Multivariable regression analysis was performed with the glmfunction to assess risk factors associated with evisceration at 3months (adjusted by age and gender). Forward selection stepwise regression analysis was used with variables tested for significance against a full adjusted model with likelihood ratio testing ($p< 0.05$) for retention. Univariable associations at $p < 0.3$ were considered for initial inclusion.Residual plots, AkaikeInformation Criterion (AIC) and Bayesian Information Criterion (BIC) were used to consider regression model fit.

Ethics statement: This study was approved by the London School of Hygiene and Tropical Medicine Ethics Committee (Ref 10647), Mbarara University Research Ethics Committee (Ref 10/04-16), and Uganda National Council for Science and Technology (Ref HS-2303). All patients provided written consent in their native language prior to participation in this study.

RESULTS

Demographics and clinical presentation: There were 57 patients for analysis, of whom none had previous ocular surgeries(Table 1). Median age was 44 years (interquartile range [IQR] 38, 60), and 47.4% were women. A majority (73.7%) were subsistence farmers, and 31.6% did not have a formal education. Per Uganda's criteria of health access as living within 5 km of a health facility, 75% of participants lived close to a primary care clinic or higher-level facility. However, the median distance to the definitive treating eye hospital was 118 km (IQR 76, 165).

In all cases of MK, median symptom duration prior to presentation was 23 days (IQR 12, 34). For those who eventually needed evisceration, median delay was 12 days versus 24 days among those who did not (p=0.209, Table 2). In terms of timeliness, only one participant presented within 3 days, and 14.4% presented within 7 days. The most frequently endorsed symptom at presentation was blurred vision (59.6%) followed by eye pain (35.1%). Trauma was sustained in 35.1% of cases with vegetation occurring in 30% of those traumatized. Nearly all patients (91.2%) sought other treatment, including Traditional Eye Medicines (TEM) (68.4%).TEM typically involve a plant-based extract from fresh leaves placed in the affected eye17. There was no association between patients who sought other treatment and delay in presentation. Regarding systemic diseases, diabetes mellitus and HIV infection was prevalent in 13.2% and 11.5%, respectively.

Best-Corrected Visual Acuity (BCVA) at presentation was worse than 3/60 in 87.7%. The BCVA at presentation was equally poor in non-eviscerated and eviscerated group (Table 2). The mean stromal infiltrate size, which is the geometric mean of longest diameter and largest perpendicular,was 7.2mm (SD 2.3) and the mean epithelial defect size was 6.0mm (SD 2.5). Both stromal and

Table 1: Participant demographics, socioeconomic indicators, health access

	Overall (n = 57)	Not eviscerated (n = 48)	Eviscerated (n = 9)	P value
Age (years)				
Mean (SD)	47.5 (14.8)	48.0 (14.9)	44.4 (14.5)	0.505
Median (IQR)	44 (38, 60)	45 (38, 61)	43 (36, 46)	
	20-85	20-85	25-70	
<30 years, n (col%)	6 (10.5)	5 (10.4)	1 (11.1)	
30-39 years, n (col%)	11 (19.3)	8 (16.7)	3 (33.3)	
40-49 years, n (col%)	18 (31.6)	15 (31.3)	3 (33.3)	
50-59 years, n (col%)	7 (12.3)	7 (14.6)	0 (0)	
>60 years, n (col%)	15 (26.3)	13 (27.0)	2 (22.2)	
Mean (SD)				
Women, n (col%)	27 (47.4)	22 (45.8)	5 (55.6)	0.722
Farmer, n (col%)	42 (73.7)	37 (77.1)	5 (55.6)	0.223
Education level				
None, n (col%)	18 (31.6)	16 (33.3)	2 (22.2)	0.774
Primary, n (col%)	27 (47.4)	21 (43.8)	6 (66.7)	
Secondary, n (col%)	9 (15.8)	8 (17.7)	1 (11.1)	
Tertiary, n (col%)	3 (5.2)	3 (6.2)	0 (0)	
Married, n (col%)	38 (66.7)	30 (62.5)	8 (88.9)	0.247
Distance to nearest health facility (km)				
Median (IQR), range	3 (1, 5), 1-45	3 (1, 5), 1-45	3 (2, 5), 1-5	0.435
Clinic, HC II, HC III, n (col%)	37 (63.2)	31 (64.6)	5 (55.6)	
HC IV and General hospital, n (col%)	16 (28.0)	12 (25.0)	4 (44.4)	
Don't know, n (col%)	5 (8.8)	5 (10.4)	0 (0)	
Distance to eye hospital (km)				
Median (IQR), range	118 (76, 165), 1.9-377.6	120 (76, 165), 1.9-377.6	112.4 (66, 265) 3-316.1	0.560

Acronyms: HC: health centre; IQR: interquartile range

infiltrate size was generally larger in the eviscerated group, but the difference was not statistically significant (p=0.525, 0.507). Common clinical signs were centrally-located ulcers (91.2%), raised slough (63.2%), serrated edges (88.9%), and white or cream-colored infiltrates (70.2%) (Table 2). Acute perforation was present among 40.4%; these individuals tended to present with longer delays than non-perforated given median of 24 days (IQR 14, 39) after symptom onset versus 17 days (IQR 12, 30) (p=0.173).The ulcer size was marginally smaller in individuals presenting with perforation: infiltrate size 7.01 (SD 1.96) versus 7.60 mm (SD 2.41) (p=0.339) and epithelial defect 5.58mm (SD 2.26) vs. 7.05mm (SD 2.60) (p=0.572).The proportion with perforation at presentation did not differ significantly between non-eviscerated and eviscerated group. The BCVA at presentation was also equally poor between perforated and non-perforated. Fungal pathogens were the main cause of severe MK in this cohort as they were isolated in 91.2% of cases with 80.7% of all cases growing only pathogenic fungus (Table 3).

Outcomes: At 3 months, 14 participants (24.6%) had good outcomes in which 2 healed, 4 had mild scar and 8 had moderate scarring, while 27 participants had dense scars and 7 had poor outcomes: 6 non-healing ulcers, 1 anterior staphyloma. The proportion of participants undergoing evisceration was 15.8% (95% CI, 8.3-28.0). The distribution of age, time from symptom onset to presentation, and perforation status are presented in Figure 2. The median presentation time was lowest in the eviscerated group, but the difference was not significant (p=0.684). The presenting BCVA was also not predictive of evisceration since the distribution of WHO category 3 (3/60 – 1/60) and category 4 (1/60 to light perception) were similar among all outcome groups (Figure 2D). For these patients with severe MK, changes in BCVA were not statistically significant, even when excluding the 9 individuals requiring evisceration. The proportion of patients with improved BCVA at 3 months was 34.5% (95%CI, 23.0-48.2). Overall visual outcome was poor with severe visual impairment (worse than 6/60) in 7.3% and blindness (worse than 3/60) in 72.7% (Figure 2E). There were no complications from the conjunctival flap procedure itself.

In assessing risk factors for evisceration, there were no significant predictors that could be delineated between the non-eviscerated and eviscerated group. The model provided no evidence for significant associations between the risk of evisceration and probable factors, such as demographics, delay to care, health access, clinical features on presentation, ulcer size, perforation, and baseline visual acuity (Table 3). Of note, surgeon level of experience (ophthalmologist or resident) did not impact outcome (p = 0.593) and was not included in the final model.

Table 2: Clinical history, signs at presentation and microbiology

	Overall (N = 57)	Not eviscerated (n = 48)	Eviscerated (n = 9)	P-value
Time from symptom onset to presentation (days)				
Early, 0-7 days, n (col%)	8 (14.0)	5 (10.4)	3 (33.3)	0.209
Intermediate, 8-14 days, n (col%)	12 (21.1)	10 (20.8)	2 (22.2)	
Late, 15-30 days, n (col%)	18 (31.6)	16 (33.3)	2 (22.2)	
Very late, >30 days, n (col%)	19 (33.3)	17 (35.4)	2 (22.2)	
Most important symptom (self-reported)				
Reduced vision, n (col%)	34 (59.6)	28 (58.3)	6 (66.7)	0.460
Pain, n (col%)	20 (35.1)	18 (37.5)	2 (22.2)	
Foreign body sensation, n (col%)	3 (5.3)	2 (4.2)	1 (11.1)	
Trauma, n (col%)	20 (35.1)	18 (37.5)	2 (22.2)	0.471
[1]Used traditional eye medicine, n (col%)	39 (68.4)	34 (70.8)	5 (55.6)	0.442
[2]Used other treatment, n (col%)	52 (91.2)	43 (89.6)	1 (100)	0.582
[3]Diabetes mellitus, n/N (col%)	7/53 (13.2)	7/44 (15.9)	0/9 (0)	0.334
[3]HIV infection, n/N (col%)	6/52 (11.5)	4/43 (9.3)	2/9 (22.2)	0.275
[4]Infiltrate size (mm) Mean (SD), range	7.2 (2.3), 0.9-11.5	7.1 (2.2), 0.9-10.9	7.6 (2.7), 1.7-11.5	0.525
[4]Epithelial defect size (mm) Mean (SD), range	6.0 (2.5), 0.5-10.8	5.9 (2.5), 0.5-10.8	6.6 (2.5), 1.7-10	0.507
[5]Ulcer located centrally, n (col%)	52 (91.2	44 (91.7)	8 (88.9)	0.787
Perforated, n (col%)	23 (40.4)	19 (39.6)	4 (44.4)	0.785
[6]Overall microbiological diagnosis, n (col%)				
Fungal species	46 (80.7)	38 (79.2)	8 (88.9)	0.822
Mixed fungal and bacterial species	6 (10.5)	5 (10.4)	1 (11.1)	
Undetermined	5 (8.8)	5 (10.4)	0 (0)	

Acronyms: BCVA: best-corrected visual acuity

[1]Traditional eye medicine involved any form of herbs the patient reported were placed in the affected eye.

[2]Other treatment includes traditional eye medicine and other treatments including eyedrops the patients could not report with specifics. Not all patients could describe what treatment was provided to them in detail.

[3]Not all patients consented to HIV and diabetes mellitus screening.

[4]These were calculated as the geometrical means using measurements per the Mycotic ulcer treatment trial (MUTT) protocol[14]. The upper limits exceeded normal 376 corneal diameter for some lesions, which extended up to the sclera.

[5]Non-central ulcers included 4 paracentral and 1 peripheral. Paracentral was when the ulcer was beyond 4 mm from the center of the cornea but was not a peripherally located either. The patient with the peripheral ulcer had an edge that reached within 2 mm from the cornea-limbus boundary.

[6]The order of material collection was 3 microscopy smears (gram, KOH, CFW), 3 agar inoculations (blood, chocolate, PDA) and 1 broth (BHI).

Table 3: Univariate and multivariate regression model of evisceration at 3 months on probable risk factors

	Univariable analysis			Multivariable analysis		
	Crude RR	95%CI	P-value	Adjusted RR	95%CI	P-value
Age (years)						
<50	Reference					
>50	0.45	0.10, 1.99	0.296			
Continuous variable (per 1 year increase)	0.98	0.94, 1.03	0.499	0.97	0.94, 1.01	0.190
Men	0.72	0.22, 2.41	0.594	0.56	0.19, 1.66	0.297
Education						
No formal education	Reference					
At least primary or beyond	1.62	0.37, 7.11	0.526			
Visual acuity at presentation (Snellen metric)						
6/10 – 3/60	Reference					
<3/60	1.12	0.16, 7.66	0.908			
Time from symptom onset to presentation						
Early, 0-7 days	Reference		0.305	Reference		
Intermediate, 8-14 days	0.44	0.09, 2.09	0.132	0.38	0.08, 1.78	0.222
Late, 15-30 days	0.29	0.06, 1.44	0.117	0.22	0.04, 1.30	0.095
Very late, >30 days	0.28	0.06, 1.37		0.27	0.05, 1.34	0.108

	Univariable analysis			Multivariable analysis		
	Crude RR	95%CI	P-value	Adjusted RR	95%CI	P-value
Reference operation (per 1 day increase)	0.98	0.93, 1.03	0.467			
Infiltrate size at presentation (per 1 mm increase)	1.11	0.82, 1.50	0.500			
Epithelial defect size at presentation (per 1 mm increase)	1.09	0.85, 1.40	0.500			
Hypopyon at presentation	0.94	0.28, 3.12	0.916			
Presence of satellite lesions at presentation	0.42	0.11, 1.50	0.180	0.44	0.11, 1.68	0.230
Perforated at presentation	1.18	0.35, 3.94	0.785			
Monomicrobial (fungus only)	1.91	0.26, 13.74	0.519			
HIV infection	2.19	0.58, 8.21	0.245			

Acronym: CI: confidence interval, RR: risk ratio

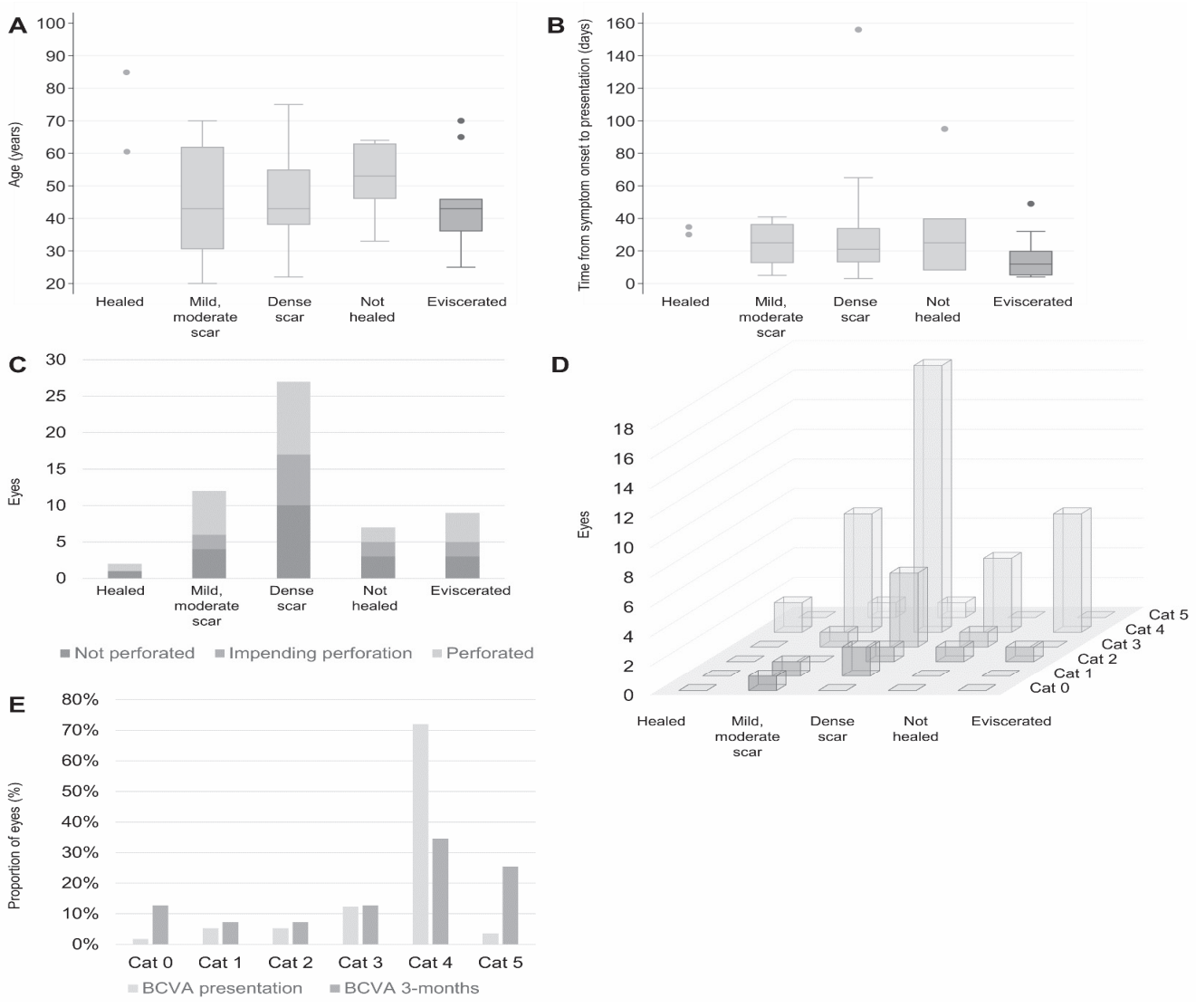

Figure 2: Outcome at 3 months grouped by status of the cornea.

(A) Age (years): median (IQR) are 43 (30.5, 62) among mild/moderate scar, 43 (38, 55) among dense scar, 53 (46, 63) among not healed, 43 (36, 46) among eviscerated (p=0.298). **(B)** Time from symptom onset to presentation (days): median (IQR) are 25 (13, 37) among mild/moderate scar, 21 (13, 34) among dense scar, 25 (8, 40) among not healed, 12 (5, 20) among eviscerated (p=0.684). **(C)** Perforation at presentation: bars show the number of individuals in each outcome category. Proportion of those presented with perforated ulcer are 50% among healed, 50% among mild/moderate scar, 37% among dense scar, 28.6% among not healed, and 44.4% among eviscerated (p=0.987). **(D)** Proportion of individuals at presentation and 3 months grouped by World Health Organization (WHO) best-corrected visual acuity; at 3 months, 7.3% were category 2, 12.7% were category 3, 34.6% were category 4, 25.5% were category 5 (p=0.181). Category 0 (> 6/18), Category 1 (6/18 – 6/60), Category 2 (6/60 – 3/60), Category 3 (3/60 – 1/60), Category 4 (1/60 – Light perception), Category 5 (No light perception). **(E)** BCVA at 3 months.

DISCUSSION

In this prospective cohort study, we have described clinical features and outcomes of conjunctival flap in patients with severe MK. In these cases, the visual prognosis is already poor and intervention is considered with the main goal of preserving the eye, which we achieved in 84% of patients. Based on our study results, we recommend an attempt to save the eye in all cases of severe MK unless there is extensive corneal necrosis or endophthalmitis. Without access to corneal tissue or amniotic membranes, the conjunctival flap procedure resulted in acceptable outcomes. Clinicians seek presenting factors that predict outcome to adjust treatment approach; however, there were no specific baseline clinical presentation or signs predictive of eventual evisceration. Therefore, clinical judgment on case-by-case basis is of utmost importance.

Outcomes: At 3 months,47.3% of patients had dense scars, a modest proportion of the cohort with improvement in BCVA (34.5%). However, the proportion of blindness worse than 3/60 was 72.7%. In Nigeria, the proportion of corneal scarring among a milder case mix of MK was 49.6%[18]. In a retrospective cohort from Tanzania with a preponderance of milder MK cases, the proportion<3/60 was 66.9% at 3 months[6]. In an Egyptian cohort of 20 MK patients (12 fungal), Abdulhalim *et al*[19] achieved 55% improvement in VA at 6 months with 80% globe preservation rate, and the ulcers were smaller (mean 4.98 mm vs 7.2 mm in our cohort). In a cohort of severe MK patients based out of Tamil Nadu, India, the proportion of worse than 3/60 went from 10% at presentation to 16% at 3-month follow-up[7], whereas our cohort with significantly worse baseline VA actually decreased from 87.7% to 72.7%. Investigators based in China have seemingly produced the most evidence on conjunctival flap in MK. In a cohort of 10 with fungal keratitis, VA improved in 60% of patients at 3 months though none of these patients had infiltrates reaching beyond the posterior half of the cornea20.A study from Changsha, China reported globe preservation of 80.6% (n = 29/36 MK patients)[21]. In Nizeyimana *et al.*'s[22] cohort of 16 fungal keratitis patients, globe preservation was achieved in 93.7% (n = 15/16), though 0% had improved VA at follow-up evaluations. Within this context, our cohort of severe MK with an approximate 60/40 split between impending and acute perforation, the outcomes are within expected range.

Without eye bank infrastructure and established corneal tissue imports, the conjunctival flap will be needed in the foreseeable future. Efforts must be made to improve outcomes. However, a paucity of modern conjunctival flap literature means the global data is very heterogenous across different continents with varying patient selection. Ultimately, the experiences in our setting suggest conjunctival flap is an appropriate treatment modality when no other options exist. A couple disadvantages of conjunctival flap should be noted. None of our participants had previous glaucoma filtering or posterior segment surgeries. Secondly, limbal stem cell loss may adversely affect further operations19, which is an important consideration as a temporary bridge to PK. From a visual outcomes standpoint, surgically managing severe MK is challenging as even penetrating keratoplasty results in 61.4% with <6/60 in Uttarakhand, India[23]. The same measure in our cohort was 80.1% even though conjunctival flap is not intended to improve VA. Since surgical options generally yield poor visual prognosis, prevention of MK incidence and progression is of the utmost importance.

Risk factors among severe microbial keratitis patients: Risk factors necessitating surgical treatment for MK have been previously studied and include: older age, low education, delayed presentation, outdoor manual labour (especially agriculture), prior treatment with topical steroids, poor visual acuity at presentation, central ulcer, large size ulcer, presence of perforation, and hypopyon[24]. Usual demographic factors appear blunted in our multivariable regression model as they are evenly distributed between the non-eviscerated and eviscerated group. This may be an effect of our cohort characteristics and does not necessarily invalidate significance of known risk factors. For example, our cohort had relatively low number of cases associated with trauma (35.1%), which is similar to 25% in a cohort from Tanzania6 but lower than the 48-64% from cohorts in India[14,24]. The proportion of male agriculture workers was high, suggesting a tendency for MK to affect adult males who work outdoors with higher occupational hazard exposure. Unlike Chidambaram *et al*'s[7] severe MK cohort, we did not find a significant association between female gender, older age, lack of education, ulcer size, and symptom duration. In fact, it appeared individuals with shorter presentation time were more likely to be in the eviscerated group. This is likely a surrogate for disease severity with symptoms more bothersome driving the individuals to seek attention sooner.

HIV infection did not appear to increase risk of evisceration in our cohort, though CD4 levels were not acquired. HIV infection has been implicated in increasing risk of herpes keratitis and keratouveitis since cell-mediated immunity is important in controlling corneal infections, though no direct evidence exist for control of corneal infections by extracellular pathogens, such as fungi. The HIV prevalence in our cohort is nearly double the prevalence in Ugandan adults; this cannot be merely coincidental, but perhaps the effects of immune suppression on evisceration is mediated by the similar level of MK severity. The severity was rather uniform between non-eviscerated and eviscerated groups. There were similar distributions between the groups in demographics, delays to care, 91% seeking alternative treatments prior including traditional eye medicines, presenting BCVA, infiltrate and epithelial defect sizes, central location of the ulcer, and perforation status. It is likely that once the

severity of MK has reached a certain level sharing all these clinical features, the visual prognosis will be poor and the risk for eventual evisceration is rather unpredictable. This was also observed in Nizeyimana *et al.*'s[22] cohort in which there was no difference in risk factors (age, gender, surgical duration, combined surgery) on complication rate and evisceration[22].

Fungal keratitis, referral system, and traditional eye medicines: Taking all cases of MK in our southwestern Uganda cohort (n = 313), fungal keratitis is responsible for 62%[13]. In this present study, fungal keratitis accounts for 80.7% of severe MK. This is not surprising given in sub-Saharan Africa, fungal species are the predominant if not one of the leading causative pathogens in MK[5,6,15,18,25]. Yet fungal keratitisis difficult to treat medically due to poor drug bioavailability, diminished corneal penetration, and the length of regimens. Fungal keratitis is associated with worse visual prognosis and higher rate of surgical intervention than bacterial keratitis[26,27]. Fungal keratitis can be worsened by use of combined steroid/antibacterial ophthalmic solutions commonly dispensed by lower level health facilities in Uganda. Diagnosis and treatment of MK should occur as soon as possible. This requires expedited referral to facilities that can perform a slit lamp examination and have access to topical natamycin. As in other SSA countries, there was a high rate of TEM use, potentially introducing pathogenic fungal spores into the eye and likely worsen progression of MK[28]. Traditional healers are well-integrated into their communities and are trusted; therefore, engaging with traditional healers to change their practice may be a practical approach rather than outright outlawing their work.

TEM and alternative treatments further delay care seeking as evidence by the high median time to presentation in our cohort. Clear and widely-adapted referral protocols are needed. Lower level health facilities should refer to facilities that can perform corneal scrapings to determine aetiology. Microscopy is useful in southwestern Uganda given such a high prevalence of fungal keratitis; sensitivity and specificity are approximately 90% and 95%, respectively for Gram, KOH, and CFW stains[27]. Ophthalmic clinical officers (OCOs – mid level ophthalmic care providers) are well positioned to implement this diagnostic workup and initial management. If a patient is likely to be lost to follow-up, we strongly encourage immediate referral to the tertiary level eye hospital despite the long travel distances. Microbiology lab and rapid diagnostics at these facilities enable more accurate diagnosis, and the OCO closest to the patient may manage follow-up and monitoring as the primary eye care provider.

Our study has three limitations. Despite our sample size being the largest to date in the literature, it is not adequately powered to fully assess specific clinical risk factors for evisceration, such as infiltrate and epithelial defect size. We believe a larger, multi-country collaborative clinical trial similar to the Asia Cornea Society Infectious Keratitis Study is needed in SSA. Another limitation is the data were collected from two eye hospitals within the same town, though these hospitals serve a catchment area of 5 million inhabitants and are the only tertiary eye hospitals in the Southwestern sub-region of Uganda. Finally, we did not have access to anterior segment Optical Coherence Tomography (OCT) at the time of this study. Anterior segment OCT could have improved precision in measurements of infiltrate and epithelial defect size pre- and post-operatively.

In conclusion, our results show conjunctival flap is an effective procedure in severe MK, restoring surface integrity and providing structural, immunologic, and metabolic support to promote corneal healing. This is important if the patient's goal is to avoid evisceration. Patients should be counseled that the visual prognosis is poor, but the flap may serve as bridge to PK.

Conflicts of interest: None to declare.

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