ORIGINAL ARTICLE

Clinical characteristics and factors affecting visual outcomes in patients with herpes simplex keratitis: A tertiary hospital experience

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ABSTRACT

Introduction: Herpes Simplex Keratitis (HSK) is a leading cause of infectious corneal blindness globally. However, clinical data and visual outcomes specific to the Malaysian population are limited. This study aimed to identify common clinical features, visual outcome and its associated factors in patients treated at a Malaysian tertiary hospital.

Materials and Methods: A retrospective cohort study was conducted at Hospital Pakar Universiti Sains Malaysia (HPUSM) between June 2013 and June 2024. Medical records of patients diagnosed with HSK and followed for at least six months were reviewed. Sixty-seven patients were included. Data collected included demographics, presenting symptoms, best-corrected visual acuity (BCVA) at presentation and after treatment, ocular findings, subtype of HSK and complications. Statistical analyses were performed using SPSS version 28.0. Paired t-tests was used to analyse changes in BCVA and multiple linear regression was performed to identify factors associated with final visual outcome.

Results: The mean age at presentation was 50.42±17.19 years with a slight male predominance (52.2%). Most cases were unilateral (91.1%). Common presenting symptoms were reduced vision (89.6%) and eye redness (85.1%). Keratouveitis was the most frequent subtype (37.3%). Complications included corneal scarring (73.1%), recurrence (49.3%) and glaucoma (11.9%). BCVA significantly improved post-treatment (p<0.001). Older age, central corneal involvement, elevated intraocular pressure at presentation, and stromal vascularisation were significantly associated with poorer visual outcomes.

Conclusion: This study outlines the clinical spectrum and visual outcomes of HSK at a tertiary hospital in Malaysia and identifying several predictive factors for poor vision. These findings may aid clinicians in risk stratification and optimising management strategies.

KEYWORDS:
Herpes simplex virus, herpes simplex keratitis, risk factors, visual outcome

INTRODUCTION

Herpes Simplex Keratitis (HSK) is a major cause of infectious corneal blindness worldwide and is caused by the Herpes Simplex Virus (HSV).[1] The incidence of Herpes Simplex Keratitis (HSK) was 1.7 million in 2016 globally per year.[2]

In Malaysia, HSK remains a significant public health concern. However, detailed data on its clinical characteristics, visual outcomes and associated prognostic factors are still limited.[3] In addition, there are no published studies that specifically evaluate the factors associated with visual outcomes of HSK within the Malaysian population. Identifying these factors is essential for improving clinical decision-making and patient management in local settings.

Therefore, this study aimed to address this gap by analysing the clinical features and determining the factors associated with visual outcomes in patients with HSK treated at a tertiary hospital in Malaysia.

MATERIALS AND METHODS

This retrospective cohort study was conducted at the Ophthalmology Clinic, HPUSM from June 2013 to June 2024. Ethical approval was obtained from the Human Research Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/KK/25010124) and the study adhered to the ethical principles outlined in the Declaration of Helsinki.

All patients aged over 18 years who were diagnosed based on typical cornea signs of HSK such as a classical dendritic pattern on epithelium, stromal infiltrate/ opacification with or without ulceration, presence of fine keratic precipitates and presence of anterior chamber inflammation with decreased or absent corneal sensation, were selected. Patient who had a minimum follow-up of six months were included. Patients who presented with recurrent infection at their initial visit or those who were undergoing treatment were excluded. For bilateral cases, the eye with better visual acuity was excluded from analysis to avoid confounding, similar to the study done by Cabrera-Aguas et al.[10] Patients with other ocular conditions that may affect the visual outcome such as cataracts, iritis, glaucoma and other eye diseases were also excluded (Figure 1).

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Demographic and clinical data were obtained from medical records, including age, sex, race, occupation and comorbidities. Presenting symptoms and BCVA at the first visit were recorded. Slit-lamp examination findings were documented for further subtypes classification. The clinical classification of HSV keratitis was based on the corneal site and anatomical localisation. Central involvement was considered if central 4-mm optical zone was involved. In this study, we used the following classification:[1] 1) Epithelial keratitis: a) dendritic epithelial ulcers (lesions with branching, linear pattern with terminal bulbs), and b) geographic epithelial ulcers (broad ulcers with swollen, scalloped, or geographic epithelial borders); 2) Stromal keratitis: a) stromal keratitis without ulceration (non-necrotizing, interstitial, or immune stromal), and b) stromal keratitis with ulceration (necrotizing); and 3) endothelial keratitis or endotheliitis (disciform).[1] Characteristic findings of herpetic keratouveitis included herpetic keratitis, elevated intraocular pressure (IOP) >21mmHg, keratic precipitates (KPs) and iris atrophy.[14] In addition, the location and associated features were also documented.

In this study, we followed the HSV keratitis treatment guidelines reviewed and accepted by the Hoskins Center for Quality Eye Care, American Academy of Ophthalmology, in the June 2014 Compendium of Evidence-Based Eye Care.[13] The antiviral agents used were topical acyclovir 3% and oral acyclovir 400mg or 800mg based on the clinical presentation, following the guideline. Topical prednisolone acetate 1% was used in cases requiring topical steroids. Oral acyclovir 400mg twice daily was given as prophylaxis for patients with stromal keratitis and for patients with multiple recurrences of any type of HSK. For patients who presented with high IOP, IOP-lowering agents like topical timolol 0.5%, topical dorzolamide 2% and topical brimonidine 0.15% were given. Patients were regularly re-examined after the initiation of treatment and assessed for treatment-related local or systemic adverse reactions. BCVA and the presence of corneal neovascularisation or haze were recorded after treatment completion. Any new symptomatic episode with typical findings of HSK following resolution of the previous episode was considered recurrence, regardless of duration from onset.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 28.0 (IBM Corp., Armonk, NY). A paired t-test was used to compare the mean BCVA at presentation and after treatment at the last follow-up. Simple linear regression analysis was done first, and the factors with a p-value <0.25 and factors that were found to be significant from the previous studies were used for multiple linear regression. Multiple linear regression was employed to identify factors associated with poor final visual outcomes. A p-value of < 0.05 was considered statistically significant. The significant factors were further analysed to report adjusted R^2 and to assess multicollinearity.

RESULTS

A total of 67 patients were included in the study. The mean follow-up duration was 24.49±22.72 months. The mean age at presentation was 50.42±17.19 years. There was a slight male predominance (52.2%), and most patients were of Malay ethnicity (91.0%). Comorbidities were observed in 41.8% of patients, with cardiovascular disease (20.9%) and combined diabetes and cardiovascular disease (14.9%) being the most common (Table I).

Unilateral involvement was seen in 91.1% of cases. The most frequently reported symptoms were reduced vision (89.6%) and eye redness (85.1%), followed by eye pain (50.7%) and eye discharge (41.8%). Keratouveitis was the most common clinical subtype (37.3%), followed by stromal keratitis (32.8%) (Table I).

Reduced corneal sensation was observed in 68.7% of eyes, while stromal vascularisation and Descemet striae were each noted in 25.4% of cases. Central and paracentral corneal involvement were nearly equally distributed. The most frequent complications were corneal scarring (73.1%), which was observed in all subtypes and recurrence (49.3%), while glaucoma was present in 11.9% of cases (Table I).

Comparison of BCVA before and after treatment revealed a statistically significant improvement. The mean BCVA at presentation was 0.81±0.75 logMAR, which improved to 0.44±0.70 logMAR at the final follow-up visit. The mean difference was 0.37 logMAR (95% CI: 0.18 to 0.55; p<0.001), indicating a significant gain in visual acuity following treatment (Table II).

Simple linear regression analysis was conducted to assess the association between various clinical variables and final visual acuity. Factors found to be significant were included in a multiple linear regression model. In the final model, four variables were significantly associated with poorer visual outcomes: increasing age (adjusted β=0.02; 95% CI: 0.01, 0.03; p<0.001), central corneal involvement (adjusted β=0.29; 95% CI: 0.02. 0.56; p=0.039), elevated intraocular pressure (IOP) at presentation (adjusted β=0.71; 95% CI: 0.31. 1.12; p<0.001) and presence of stromal vascularisation (adjusted β=0.45; 95% CI: 0.13, 0.76; p=0.006) (Table III).

The final regression model, including IOP, age, stromal vascularisation and central corneal involvement, explained 40.5% of variability in the outcome. Each variable added improved the model, indicating these factors are independently associated with the dependent variable. The strongest additional predictor was age, followed by IOP, then stromal vascularisation and lastly central corneal involvement. There was no multicollinearity (VIF<5), confirming that each predictor contributed uniquely to the final model.

Gender, keratitis subtype, comorbidities (diabetes and cardiovascular disease), reduced corneal sensation, corneal scarring, and recurrence were not significantly associated with post-treatment visual outcomes in this cohort (Table III).

DISCUSSION

HSK is a significant cause of corneal blindness and is a considerable public health challenge worldwide, including Malaysia.[2,3] Detailed epidemiological data and clinical outcomes specific to the Malaysian population remain

Table I: Demographic and Clinical Characteristics of Patients with HSK

Variables	n (%)
Age in years, mean±SD	50.42±17.19
Gender	
Male	35 (52.2)
Female	32 (47.8)
Race	
Malay	61 (91.0)
Chinese	5 (7.5)
Siamese1 (1.5)	
Co-morbidities	
Diabetes Mellitus	14 (20.9)
Cardiovascular Disease	10 (14.9)
Both DM and CVD	39 (58.2)
Others	2 (3.0)
Laterality	
Right	28 (41.8)
Left	33 (49.3)
Bilateral	6 (9.0)
Presenting symptoms	
Eye redness	57 (85.1)
Eye discharge	28 (41.8)
Eye pain	34 (50.7)
Eye discomfort	30 (44.8)
Foreign body sensation	28 (41.8)
Photophobia	25 (37.3)
Reduced vision	60 (89.6)
HSK subtype	
Epithelial keratitis	9 (13.4)
Stromal keratitis	22 (32.8)
Endotheliitis	11 (16.4)
Keratouveitis	25 (37.3)
Associated features	
Corneal oedema	33 (49.3)
Immune Weisley ring	0 (0.0)
Reduced corneal sensation	46 (68.7)
Stromal vascularisation	17 (25.4)
Descemet striae	17 (25.4)
Hypopyon	1 (1.5)
Site of keratitis	
Central	31 (46.3)
Paracentral	32 (47.8)
Peripheral	4 (6.0)
Complications	
Recurrence	33 (49.3)
Corneal scarring	49 (73.1)
Glaucoma	8 (11.9)
Endophthalmitis	1 (1.5)
Corneal perforation	1 (1.5)

Abbreviations: SD: Standard deviation

Table II: Comparison of mean BCVA at presentation and post-treatment

Variables	At presentation (Mean ± SD)	After treatment (Mean ± SD)	MD (95%CI)	p-value
BCVA (logMAR)	0.81±0.75	0.44±0.70	0.37 (0.18, 0.55)	<0.001

Abbreviations: SD: Standard deviation, MD: Mean difference, CI: Confidence interval, BCVA: Best corrected visual acuity, logMAR: Logarithm of the Minimum Angle of Resolution

limited, and, to the best of our knowledge, the factors associated with the visual outcome of HSV among the Malaysian population remain unexplored. In our study, we analysed 67 patients with HSK over an 11-year period, aiming to explore the clinical spectrum, complications and prognostic factors associated with visual outcomes in a Malaysian tertiary hospital setting.

The mean age of presentation was 50.4 years, notably higher than that reported in earlier Malaysian studies (36.2 years)[3] This may reflect changing demographics and improved access to healthcare for older populations. A slight male predominance was observed, aligning with global patterns,[4] though differing from local data where equal gender distribution was previously reported.[3]

Table III: Factors Associated with Visual Outcome in HSK

Factors	Simple linear regression		Multiple linear regression	
	Crude b (95% CI)	p-value	Adjusted b (95% CI)	p-value
Age	0.02 (0.01, 0.03)	<0.001	0.02 (0.01, 0.03)	<0.001
Female	-0.28 (-0.61, 0.07)	0.111	-	-
Cardiovascular and DM	0.36 (-0.11, 0.84)	0.132	-	-
Keratitis subtype				
Stromal	0.02 (-0.35, 0.39)	0.909	-	-
Endothelial	-0.09 (-0.56, 0.38)	0.696	-	-
Keratouveitis	0.13 (-0.22, 0.49)	0.457	-	-
Corneal involvement				
Central	0.31 (-0.03, 0.65)	0.073	0.29 (0.02, 0.56)	0.039
Paracentral	-0.22 (-0.56, 0.12)	0.202	-	-
Ocular co-morbid	0.27 (-0.10, 0.64)	0.151	-	-
Associated ocular features				
Corneal oedema	0.27 (-0.07, 0.61)	0.113	-	-
High IOP	0.97 (0.52, 1.42)	<0.001	0.71 (0.31, 1.12)	<0.001
Reduced corneal sensation	-0.22 (-0.59, 0.15)	0.241	-	-
Stromal vascularisation	0.47 (0.09, 0.85)	0.017	0.45 (0.13, 0.76)	0.006
Descemet striae	0.16 (-0.24, 0.55)	0.426	-	-
Complications:				
Glaucoma	0.62 (0.11, 1.13)	0.018	-	-
Recurrence	-0.08 (-0.43, 0.27)	0.648	-	-
Corneal scarring	0.18 (-0.21, 0.56)	0.366	-	-
Antiviral prophylaxis	0.12 (-0.33, 0.57)	0.596	-	-

Abbreviations: CI: Confidence interval, IOP: Intraocular pressure, DM: Diabetes mellitus

Table IV: Comparison of factors associated with visual outcomes in previously published studies

Authors	Country	Year published	Sample size	Factors associated with visual outcome
Rosenberg et al.[9]	USA	2020	104	Older age, DM, surgeries, scarring, glaucoma, recurrence
Cabrera-Aguas et al.[10]	Australia	2021	296	Recurrence, keratouveitis, scarring
Lotfi et al.[11]	Kuwait	2023	72	Corneal haze
Zhang et al.[12]	China	2024	198	Age ≥ 65, prolonged disease, epithelial/stromal type

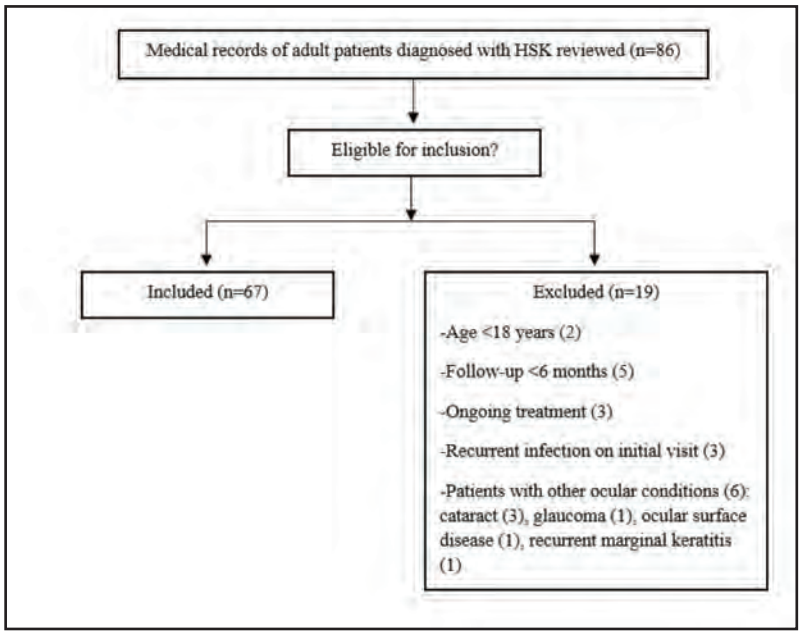

Fig. 1: Sample derivation

The most common presenting symptoms were reduced vision and eye redness, followed by pain, discomfort, photophobia, and foreign body sensation. Similar symptoms were reported in studies from Malaysia and Korea.[3,4] Reduced corneal sensation was present in 68.7% of cases, a well-recognised clinical sign of herpetic keratitis, corroborating the findings of Danileviciene et al.[5] A previous study done in Malaysia found 75.0% cases with reduced corneal sensation. It is important to note that corneal sensation was assessed with the cotton wisp test, and quantitative assessment was not done in our study, and this may introduce bias. Other associated findings of stromal vascularisation observed by Rodriguez-Garcia et al.,[6] was also present in our patients.

The distribution of HSK subtypes revealed keratouveitis as the most frequent, followed by stromal keratitis, endotheliitis and epithelial keratitis. These findings contrast with reports from Korea, Australia and China where epithelial keratitis was more common.[4,10,12] This discrepancy could be due to our centre being a tertiary referral hospital, hence likely to manage more severe cases. Milder epithelial cases might be treated at primary care level and not referred. Ethnic and genetic variations could also contribute to these differences.

Complications were common, with corneal scarring affecting the majority of patients (73.2%), followed by recurrence and glaucoma. Other studies reported recurrence of HSK as the main complication.[2,7,9] Recurrence was noted in 49.3% in our study, whereas it was 36.4% in the previous study done in Malaysia.[3] This difference in recurrent rates may be attributed to longer duration of study and a greater number of patients included in the current study compared to the previous study. Additionally, demographic changes like an older mean age may have contributed to the higher recurrent rates. Rare cases of endophthalmitis and corneal perforation were also observed. These findings are consistent with previous studies reporting high recurrence and complication rates in HSK.[2,7-9] Furthermore, corneal scarring and recurrence remain the primary causes of long-term visual impairment. This underscores the need for improved training and awareness among healthcare providers regarding the clinical signs of HSK, enabling early diagnosis and timely management.

There was significant improvement in the visual acuity from initial presentation and post- treatment, highlighting the effectiveness of medical and supportive interventions. However, the extent of visual recovery varied depending on disease severity and complications. This suggests that current treatment protocols should be reinforced and possibly expanded to include more aggressive management approaches for patients presenting with severe symptoms, high IOP or complications.

Age of the patient, central corneal involvement, presence of stromal vascularization and high IOP at presentation are the statistically significant factors associated with the final visual acuity. Our findings are in line with Rosenberg et al., who found older age, scarring, glaucoma, and recurrent disease as predictors of poor outcomes.[9] Cabrera-Aguas et al.,[10] also highlighted keratouveitis, recurrence, and scarring as significant prognostic factors. The differences and similarities across studies underscore the multifactorial nature of HSK outcomes and the importance of localised data to guide clinical decisions. Increasing age has been consistently associated with worse visual prognosis, possibly due to delayed healing and pre-existing ocular comorbidities.[9,12] Central corneal involvement directly affects the visual axis, thus compromising visual recovery. Elevated IOP, likely due to herpetic trabeculitis or steroid-induced glaucoma, can also impair visual outcomes. Stromal vascularisation reflects chronic inflammation and scarring, leading to corneal opacity.[6,10] Hence, monitoring and control of IOP needs to be prioritised, and close monitoring is critical in patients presenting with the risk factors.

Interestingly, factors such as gender, coexisting diabetes or cardiovascular disease and keratitis subtype were not statistically significant predictors in our model. A summary of previously published studies and their associated visual outcome predictors is provided in Table IV.[9-12] While other studies found recurrence, scarring, and diabetes mellitus to be significant factors,[9-11] these were not statistically significant in our cohort. This could be due to variability in our presentation, with keratouveitis being the most common presentation compared to other studies.

This retrospective study from a single centre relied on clinical diagnosis without standardised laboratory confirmation, which may introduce bias. These factors limit internal validity and highlight the need for prospective multicentre studies with standardised diagnostic investigations.

CONCLUSION

Recognition of clinical patterns is crucial for early diagnosis and management of HSK. Visual outcomes were influenced by patient age, site of corneal involvement, IOP and stromal vascularisation. These findings provide a basis for improved local management strategies and may inform national clinical guidelines.

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