Clinical Profile and Treatment Outcomes of Herpes Simplex Virus Keratitis at the Philippine General Hospital

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ABSTRACT

Background. Herpes simplex virus (HSV) keratitis is a significant cause of infectious corneal disease and visual impairment, with clinical manifestations ranging from epithelial to stromal and endothelial involvement. Despite its reported burden in the Philippines, updated local data on its clinical presentation, treatment outcomes, recurrence, and visual outcomes are limited.

Objective. The study aimed to describe the demographic profile, clinical manifestations, treatment outcomes, visual outcomes, and recurrence rates of locally diagnosed Herpes simplex virus (HSV) keratitis cases.

Methods. This cross-sectional, retrospective review examined medical records of clinically diagnosed HSV keratitis patients at the Philippine General Hospital from 2013 to 2023. Data on demographics, clinical presentation, initial and latest uncorrected distance visual acuity (UDVA), treatment outcomes, recurrence rates, and follow-up duration were collected.

Results. Ninety-eight (98) eyes of 97 patients were included in the study. The average patient age was 47 years, with 37% in the 41 to 60-year age group. A higher predilection for males (63%) was observed. The most common clinical presentation was epithelial keratitis (26%), followed by stromal keratitis (24%), keratouveitis (22%), stromal scarring (14%), and endothelial keratitis (13%). Ninety-nine percent of cases were unilateral, and 87% presented with decreased corneal sensation. The mean time from symptom onset to consultation was 6 weeks, with an average follow-up duration of 27 months. Epithelial keratitis responded well to topical antiviral in 92% of cases. Topical steroids combined with antiviral therapy showed good responses in stromal keratitis (41%), endothelial keratitis (92%), and keratouveitis (60%). Four eyes needed tectonic penetrating keratoplasty (PKP) for corneal perforation, while 5 eyes underwent optical PKP. The overall recurrence rate was 35%, with no recurrences in patients on prophylactic oral acyclovir (ACV), compared to 33% in those without (p = 0.001). The mean uncorrected distance visual acuity (UDVA) was 1.55 ± 1.07, which significantly improved to 1.20 ± 1.14 at the latest visit (p = 0.001).

Conclusion. HSV keratitis was more common in the middle-aged group, with epithelial keratitis being the leading presentation. Early diagnosis and appropriate treatment significantly improved visual outcomes and reduced corneal complications. One-third of cases recurred, highlighting the need for long-term monitoring. Prophylactic oral ACV may reduce recurrence rates, but further research is warranted to assess its cost-effectiveness.

Keywords: HSV keratitis, cornea, clinical profile, Philippines

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INTRODUCTION

Herpes simplex virus (HSV), a double-stranded DNA virus from the Herpesviridae family, can cause both asymptomatic and active ocular disease.[1] Herpes simplex virus type-1 (HSV-1) and type-2 (HSV-2) are responsible for ocular manifestations, including conjunctivitis, keratitis, iridocyclitis, and acute retinal necrosis. The global incidence of HSV keratitis is roughly 1.5 million, with 40,000 new cases of severe visual impairment annually.[2] In developed countries, HSV keratitis is a leading cause of infectious corneal blindness.[2] However, in developing countries, its impact on vision loss is often under-reported due to poor documentation.[3] A previous survey from the External Eye Disease Clinic of the Philippine General Hospital (PGH) showed HSV was the third most common cause of infectious keratitis from 1971 to 2000.[4]

HSV keratitis is typically diagnosed on its distinct clinical features, and additional laboratory tests, such as viral culture and serology, are rarely necessary. Furthermore, for immunologic manifestations of HSV keratitis, laboratory tests such as polymerase chain reaction (PCR) and culture will be negative due to absence of viral replication. The disease is classified into the following based on clinical presentation: epithelial keratitis, non-necrotizing stromal keratitis, necrotizing stromal keratitis, endothelial keratitis, and keratouveitis.[5] HSV epithelial keratitis presents variably from punctate keratitis to dendritic or geographic ulcer. Dendritic ulcer has a characteristic branching epithelial lesion with terminal bulbs. Non-necrotizing stromal keratitis or HSV immune stromal keratitis is a common, chronic recurrent manifestation of HSV and is the most common to cause visual impairment. Inflammation is thought to be from retained viral antigen in the stroma. It presents with stromal edema with DM folds with intact corneal epithelium, fine keratic precipitates, and corneal neovascularization, followed by lipid keratopathy, which can lead to further scarring. Necrotizing stromal keratitis is a rare manifestation of HSV that is thought to result from direct viral invasion of the corneal stroma. Clinically, necrosis, ulceration, and dense infiltration of the stroma with an overlying epithelial defect is present. The combination of replicating virus and severe host inflammation leads to thinning and perforation mimicking other causes of microbial keratitis such as bacterial and fungal. HSV endothelial keratitis is a relatively uncommon manifestation of HSV and presents with keratic precipitates underlying areas of epithelial and stromal edema. This can lead to local endothelial decompensation and permanent loss of endothelial cells. HSV keratouveitis clinically manifests as decreased corneal sensation, ciliary injection, corneal edema, epithelial defect, hypopyon, granulomatous/non-granulomatous keratic precipitates, anterior chamber cells and flare, iris atrophy, and increased IOP.[5,6]

There is a distinct mechanism of pathogenesis as HSV affects different corneal layers. In epithelial keratitis, there is direct replication of the virus in the corneal epithelial cells, while stromal keratitis is primarily immune-mediated.[5,6] Hence, proper choice of therapeutic intervention is dependent on proper classification of HSV keratitis.

Due to the lack of updated local data, this study aimed to describe the demographic profile, clinical presentations, treatments, disease course, recurrence rates, and visual outcomes of patients diagnosed with HSV keratitis at our hospital over the past ten years. The findings provide a clearer understanding of the disease's impact on vision and quality of life among Filipino patients and will help guide ophthalmologists in better recognizing and managing HSV keratitis to reduce visual loss and corneal damage.

METHODS

This single-center, cross-sectional, retrospective chart review was conducted at the External Disease & Cornea Clinic of the Philippine General Hospital from January 2013 to December 2023. The study included all available patient charts of those clinically diagnosed with HSV keratitis (HSV epithelial keratitis, HSV necrotizing and non-necrotizing stromal keratitis, HSV endotheliitis, HSV keratouveitis, HSV stromal leukoma/scar) by an External Disease & Cornea specialist, either through face-to-face or virtual consultations. Patients with less than 2 weeks of follow-up after initiating treatment or those with incomplete medical records (more than 50% missing data) were excluded.

Demographic data collected included age, gender, occupation, symptom onset, laterality, precipitating factors, HSV keratitis type, treatment, treatment outcomes, disease duration, number of recurrences, initial and latest uncorrected distance visual acuity (UDVA), and follow-up duration. Treatment response at two weeks post-initiation was classified as good response - recovery within 14 days; partial response - incomplete recovery by day 14 but resolution within one month; or poor response - no clinical improvement at one month. Patients with poor response were followed until the keratitis resolved. Follow-up visits were monitored for recurrence, defined as the appearance of new corneal lesions confirmed by an External Disease and Cornea specialist. The time to recurrence was also documented.

A possible confounder is the presence of visually significant complications of HSV keratitis at the initial consult, such as corneal scarring or lipid keratopathy, which could potentially affect visual outcomes.

A unique patient sequence number ensured privacy and confidentiality, with a master list kept separately in a password-protected electronic spreadsheet. Data extraction from patient charts was manually entered into an electronic spreadsheet, and analysis was performed using Stata 13 (StataCorp, Texas, USA).

The study complied with the Data Privacy Act of 2012 and followed the ethical standards of the 7th iteration of the Declaration of Helsinki, Good Clinical Practice of the WHO,

and the University of the Philippines Manila Research Ethics Board (2024-0179-01).

Data were presented using absolute and relative frequencies, measures of central tendency, and measures of spread. The Chi-square test was employed to compare outcome frequencies, with a significance level set up at p <0.05 for one-tailed comparisons. Multivariate analysis was performed using the latest visual acuity (logMAR), age, manifestation of HSV, treatment response, presence of recurrence, oral acyclovir use, and initial visual acuity (logMAR) variables. Kaplan-Meier analysis was used to check for recurrence-free survival in patients on prophylactic antiviral therapy.

RESULTS

Twenty-six patient charts were excluded due to incomplete medical records and inadequate follow-up. A total of 97 (79%) out of 123 charts of patients diagnosed with any form of HSV keratitis were included in the study. Among these, 97 patients had unilateral disease, and only one had sequential involvement, resulting in the analysis of 98 eyes from 97 patients.

Table 1 presents the demographic profile of patients with HSV keratitis. The mean age was 47 years (range 5 to 82 years). Males accounted for 63% of the population, and females 37%. Unemployed individuals (49%) and industrial workers (35%) were the most affected groups. Corneal sensation was decreased in 87% of patients and absent in 8%. Steroid use was the most common inciting factor, identified in 10% of cases. The mean interval from symptom onset to consult was 6 weeks (range 1 to 20 weeks).

Figure 1 shows the frequency of diagnosis by clinical manifestation. The most common presentation was epithelial keratitis, observed in 26% of the eyes, followed by stromal keratitis (24%) and keratouveitis (22%). Endothelial keratitis was diagnosed in 13% of eyes, while 14% presented with stromal leukoma/scar.

Table 2 shows the summary of antiviral and steroid treatment for HSV keratitis. Table 3 presents the response to medical treatment by HSV keratitis type. For epithelial keratitis, patients receiving topical antiviral with the recommended dose of at least five times daily showed a good response in 91% of patients. Patients on a therapeutic dose of topical and oral antivirals showed a good response in 100% of patients. In non-necrotizing stromal keratitis, the recommended management is a therapeutic dose of topical steroids with a prophylactic dose of oral antiviral, which resulted in a 100% good response in patients who received this intervention. However, the most common treatment was topical acyclovir (ACV) with topical steroids, which achieved a good response in 78% of eyes, while 22% showed a partial response. For necrotizing stromal keratitis, 57% (4 out of 7 eyes) underwent penetrating keratoplasty, while 43% (3 eyes) were managed medically. The mainstay of management is oral antiviral therapy with a limited dose of topical steroids. One patient treated with topical ganciclovir (GCV) with steroids achieved a good response, while two patients treated with topical ACV alone showed partial and poor responses. For endothelial keratitis, the recommended management is

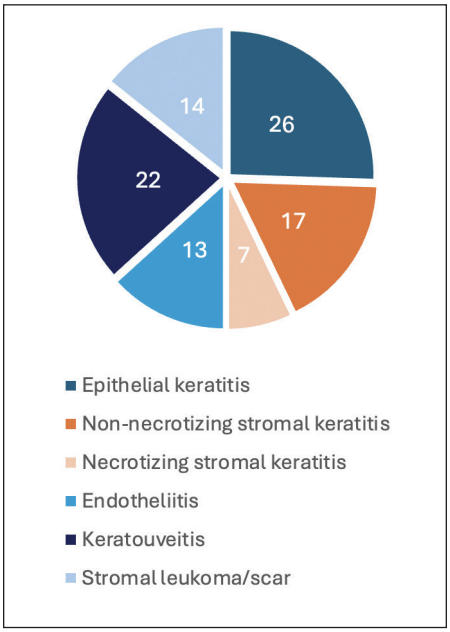

Figure 1. Frequency by HSV keratitis clinical manifestation (N = 98).

Table 1. Demographic Profile of Patients with HSV Keratitis (N = 97)

Patient Demographic	Patients, n (%)
Age (years), mean (range)	47 (5-82)
<18	9 (9%)
19 – 40	25 (26%)
41 – 60	35 (36%)
>60	28 (29%)
Sex	
Male	62 (64%)
Female	35 (36%)
Laterality	
Right	51 (53%)
Left	46 (47%)
Occupation	
Professionals	1 (1%)
Office workers	5 (5%)
Agricultural workers	4 (4%)
Industrial workers	34 (35%)
Student	6 (6%)
Unemployed	47 (49%)
Trigger factors	
Steroid use	10 (10%)
Ocular trauma	5 (5%)
Unknown/no reported	82 (85%)

Table 2. Summary of Antiviral and Steroid Treatment

Antiviral	
Prophylactic	• Oral Acyclovir 400mg twice per day or • Oral Valacyclovir 500mg once daily
Therapeutic	• Oral Acyclovir 400mg 5 times per day or • Topical acyclovir ointment 5 times per day or • Topical ganciclovir gel 5 times per day
Corticosteroid	
Limited	• Topical prednisolone acetate 2 times per day
Therapeutic	• Topical prednisolone acetate 4-8 times per day

Table 3. Medical Treatment and Response of HSV Keratitis per Clinical Manifestation (N = 77)

	Good response, % (n)	Partial response, % (n)	Poor response, % (n)
Epithelial keratitis (n = 25)			
Therapeutic dose of topical antiviral (n = 25)	91% (20)	(9%) 2	0
Other intervention			
Therapeutic dose of topical and oral antiviral (n = 3)	100% (3)	0	0
Non-necrotizing stromal keratitis (n = 17)			
Therapeutic dose of topical steroid plus prophylactic dose of oral antiviral (n = 3)	100% (3)	0	0
Other intervention:			
Therapeutic dose of topical steroid plus therapeutic dose of topical antiviral (n = 9)	78% (7)	22% (2)	0
Therapeutic dose of topical antiviral (n = 2)	50% (1)	50% (1)	0
Therapeutic dose of topical steroid (n = 3)	67% (2)	33% (1)	0
Necrotizing stromal keratitis (n = 3)			
Limited dose of topical steroid plus therapeutic dose of oral antiviral (n = 0)	0	0	0
Other intervention:			
Limited dose of topical steroid plus therapeutic dose of topical antiviral (n = 1)	(100%) 1	0	0
Therapeutic dose of topical antiviral (n = 2)	0	50% (1)	50% (1)
Endothelial keratitis (n = 12)			
Therapeutic dose of topical steroid plus therapeutic dose of oral antiviral (n = 4)	100% (4)	0	0
Other intervention:			
Therapeutic dose of topical steroid plus therapeutic dose of topical antiviral (n = 8)	88% (7)	12% (1)	0
Keratouveitis (n = 20)			
Therapeutic dose of topical steroid plus therapeutic dose of oral antiviral (n = 13)	54% (7)	38% (5)	7% (1)
Other intervention:			
Therapeutic dose of topical steroid plus therapeutic dose of topical antiviral (n = 7)	71% (5)	29% (2)	0

therapeutic doses of both topical steroids and oral antivirals, which showed a good response in 100% of patients. In contrast, patients receiving topical steroids with topical antivirals had a good response in only 72% of cases. For keratouveitis, the recommended management consists of a therapeutic dose of topical steroids combined with a therapeutic dose of oral antivirals, resulting in a good response in 54% of patients and a partial response in 38%. In contrast, patients receiving therapeutic doses of topical steroids and topical antivirals had a good response in 71% and a partial response in 29%.

In the entire cohort, nine eyes (9%) underwent penetrating keratoplasty (PKP) as the initial treatment. Tectonic PKP was performed in four eyes for corneal perforation, while five eyes underwent optical PKP for corneal scarring. Recurrence of HSV keratitis on the graft occurred in three eyes (33%).

The overall recurrence rate was 35%. Figure 2 illustrates the frequency of recurrence by HSV keratitis type, with endothelial keratitis showing the highest recurrence rate.

For patients at high-risk of recurrence, such as multiple recurrences of any type of HSV keratitis or following any ocular surgery such as penetrating keratoplasty, a prophylactic dose of oral acyclovir 400mg twice daily was recommended. For a period of one year, only 13 of the 39 patients (31%) completed the prophylaxis regimen. Among these patients (n = 13), no recurrences were observed until after discontinuation of the prophylaxis, when 23% (3 patients) experienced recurrence. In contrast, 33% (28 patients) of those without prophylaxis had at least one recurrence during follow-up (n = 85). Figure 3 presents a Kaplan-Meier curve for recurrence, showing that patients without prophylaxis experienced a gradual decline in recurrence-free survival starting at five months. In contrast, those on prophylaxis for 12 months had no observed recurrences until the 18th month.

Figure 4 shows the distribution of UDVA at initial visit compared to latest visit. After treatment, at the latest visit, 41% achieved UDVA of 20/40 or better. The mean UDVA was 1.55 ± 1.07, which significantly improved to 1.20 ± 1.14 at the latest visit (p = 0.001).

Table 4 shows that among factors correlated with latest UDVA, only the initial UDVA was significant.

DISCUSSION

This study aimed to describe the clinical profile and treatment outcomes of HSV keratitis in patients referred to our institution. The average patient age was 47 years, with 63% of cases occurring in the 20 to 60 age group, consistent with previous reports that suggest HSV keratitis is most common in adults under 60.[7] This indicates that HSV keratitis predominantly affects the working-age population,

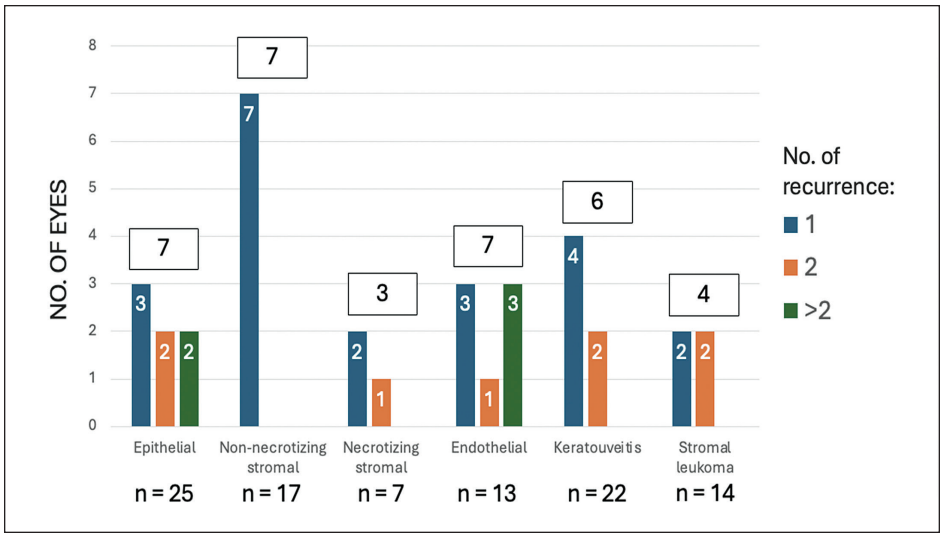

Figure 2. Frequency of recurrences per HSV clinical manifestation (N = 98).

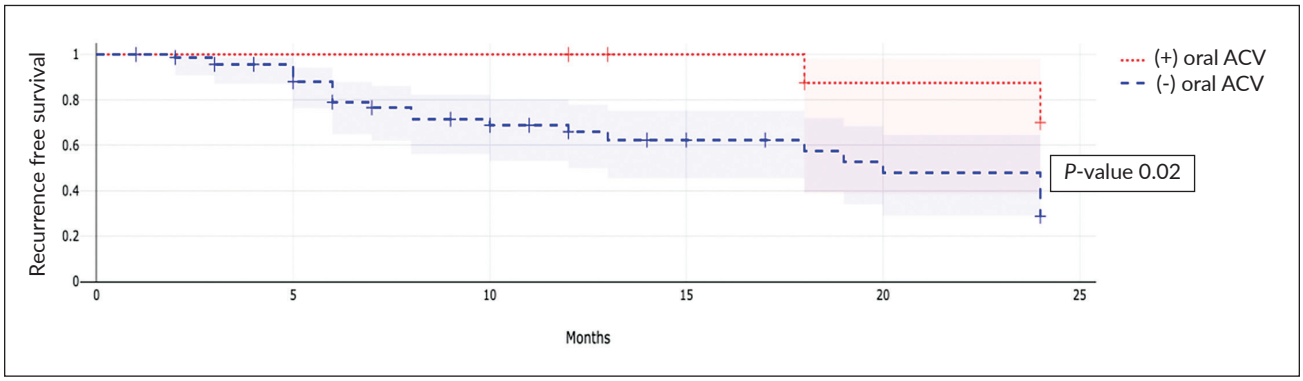

Figure 3. Kaplan-Meier curve for recurrence in patients taking oral acyclovir compared to those without prophylaxis.

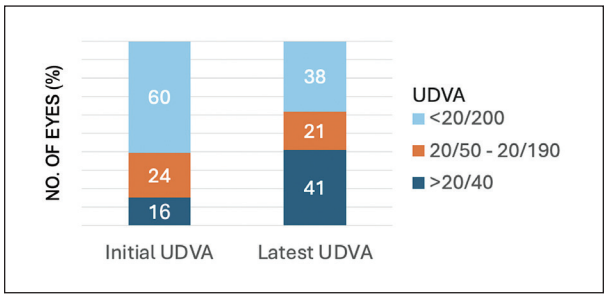

Figure 4. Distribution of UDVA at initial compared to latest visit (N = 98).

Table 4. Factors Associated with Latest Uncorrected Distance Visual Acuity (UDVA)

Independent variables	Estimate	95% CI	*P*-value
Initial UDVA, logmar	0.63	0.42, 0.84	<0.001
Age	0.01	-0.002, 0.2	0.13
Clinical manifestation	0.33	-0.67, 0.44	0.97
Response to treatment	0.20	-0.34, 0.70	0.74
Recurrence	0.19	-0.23, 0.61	0.38
(+) Oral acyclovir prophylaxis	0.17	-0.24, 0.58	0.42

with potential productivity loss due to corneal scarring. We have observed a higher predilection for males in this cohort, which was also reported in a previous local study.[4] However, multicenter studies have found HSV keratitis to have no sexual predilection.[7,8] 99% had unilateral involvement with associated reduced or absent corneal sensation compared to the unaffected eye due to HSV's reactivation pattern along sensory nerves, causing unilateral keratitis.

The most common clinical presentations were HSV epithelial keratitis (26%), followed by stromal keratitis (24%) and keratouveitis (22%), consistent with other international studies.[4,7-10] The lower incidence of stromal keratitis compared to older local studies may reflect an improved classification of HSV types, with endothelial keratitis recognized as a distinct entity, as well as an increase in referrals to subspecialists elsewhere. Epithelial and endothelial keratitis had faster resolution times, with 92%

healing within two weeks, compared to stromal keratitis (80%) and keratouveitis (60%), which took longer to resolve. This difference may be due to the immune-mediated nature of stromal keratitis and keratouveitis, whereas epithelial and endothelial keratitis are caused by direct viral replication and respond better to antiviral treatment.[8] Topical antivirals were effective for epithelial keratitis, while patients with stromal and endothelial keratitis and keratouveitis required topical corticosteroids in combination with oral or topical antivirals to control the immune response and prevent viral replication.[6]

HSV necrotizing stromal keratitis is especially difficult to manage given its capacity to quickly progress to corneal perforation. In our cohort, 57% (4 out of 7) underwent corneal transplant due to corneal perforation at presentation. In Valenton's local survey, necrotizing stromal keratitis comprised 66% (236 eyes of 354) of all stromal keratitis cases, with 33 patients (9%) presenting with corneal perforation. Of these, 16 patients underwent conjunctivoplasty with peripheral iridectomy, while 2 had penetrating keratoplasty. This is in contrast to the Herpetic Eye Disease Study (HEDS), where only 9 – 13 patients (10 - 12%) with stromal keratitis were classified as necrotizing stromal keratitis. The treatment and outcomes primarily for HSV necrotizing stromal keratitis have not been studied adequately in randomized clinical trials due to the limited number of patients, but evidence suggests a role for oral antiviral combined with judicious use of topical corticosteroids.[6] One case series of 7 patients reported success in combining amniotic membrane graft with topical corticosteroid and antiviral treatment. The ulcerated corneas healed, but final visual acuity remained worse than 20/100 in 6 of 7 eyes due to scar formation.[11]

In our HSV endothelial keratitis patients, one showed a partial response to topical GCV combined with steroids, while a good response was observed in those treated with topical or oral ACV and steroids. This may be due to GCV's insufficient corneal penetration as compared to ACV.[6] Therefore, oral ACV is recommended for HSV endothelial keratitis to ensure adequate drug penetration into the cornea.[6]

Based on our data, oral antivirals, whether in therapeutic dose for keratouveitis and endothelial keratitis, or prophylactic dose for non-necrotizing stromal keratitis, appear to achieve a good response in most cases. Furthermore, studies have found that even in patients with HSV epithelial keratitis, therapeutic doses of oral acyclovir were as effective as topical acyclovir.[6] Adequate corneal and aqueous humor levels have been reported with oral antivirals, with the advantage of avoiding ocular surface toxicity, especially in cases where prolonged antivirals are required. Once the disease is under control, the oral antiviral is reduced to prophylactic dose and maintained as long as topical corticosteroids are in use.[6] In this cohort, only 2 patients had poor response to treatment. This may suggest either failure to reach therapeutic levels of antiviral or acyclovir-resistant HSV. The latter cannot be confirmed due to lack of virologic testing.

Recurrence was observed in 35% of patients, which is within the range reported in other studies (20 to 65%) and with the intervals between recurrences shortening over time.[7,8] Interestingly, 83% of patients with more than two recurrences maintained a visual acuity of 20/60 or better at the latest visit, suggesting that recurrence does not necessarily correlate with poor visual outcomes when managed appropriately. We observed more recurrences in HSV endothelial keratitis, whereas other studies typically found epithelial keratitis to have the highest recurrence rate. Both epithelial and endothelial keratitis are thought to recur due to viral replication, and immune dysregulation may trigger recurrences easily. Additionally, recurrences in the epithelial keratitis group may have been overlooked due to shorter follow-up and fewer symptoms compared to endothelial keratitis cases.

For patients at high risk of recurrence, oral ACV prophylaxis at 400 mg twice daily was started, though only 13 of the 39 patients (31%) completed the 1-year regimen, with the rest citing financial constraints and difficulty obtaining the medication as reasons for non-compliance. No recurrences occurred in patients still on prophylaxis, while 23% (3 eyes) had recurrences within 12 months (range 6 – 24 months) after discontinuing ACV. In contrast, 33% of patients without prophylaxis had recurrences, with a mean onset of 16 months (range 2–72 months). The continuous prophylactic regimen appeared protective, with a suppressive effect for at least 6 months after discontinuation. However, given the high cost (PhP 29,200.00 or USD 514.00 annually), treatment decisions must balance visual impact and affordability. For younger patients with immune-mediated HSV keratitis such as stromal keratitis, ACV prophylaxis may be more cost-effective compared to treating all high-risk patients.

Visual outcomes showed that 60% of patients initially had UDVA worse than 20/200, improving to 38% after treatment. However, 55% of those with initial UDVA worse than 20/200 retained poor vision at the latest visit. This contrasts with Moorfields and HEDS, where only 3 to 10% had similarly poor vision.[1] This discrepancy may be due to delayed consultation in our cohort (6 weeks from symptom onset versus 15 days in other studies) and the presence of more severe cases.[12] Delay in diagnosis and appropriate management may lead to permanent scarring and reduced corneal transparency, emphasizing the importance of timely treatment to prevent irreversible visual impairment.

This study has several limitations. First, being retrospective, it relied on the accuracy and completeness of medical records. Second, as a tertiary referral hospital, we typically handle more severe cases, which may skew our findings. Finally, we may not have captured all recurrences, as some patients might have missed follow-up visits or sought care elsewhere.

Moving forward, we recommend developing a local preferred practice pattern and treatment algorithm in the management of HSV keratitis, as treatment approaches

still vary among cornea specialists. Based on our study data, therapeutic doses of oral ACV are recommended, as they are more effective in treating all forms of HSV keratitis compared to topical antivirals. Furthermore, initiating prophylactic oral ACV at the initial visit is strongly suggested for patients with HSV endothelial keratitis due to their high risk of recurrence. Finally, we recommend reassessing compliance barriers and evaluating the cost-effectiveness of long-term antiviral therapy.

CONCLUSION

We presented updated clinical data of HSV keratitis seen and treated at a tertiary hospital with emphasis on treatment response and the role of oral prophylaxis. HSV keratitis primarily affects patients under 60 years old, manifesting unilaterally with decreased corneal sensation. Epithelial keratitis is the most common presentation, followed by stromal keratitis and keratouveitis. Timely diagnosis and appropriate treatment lead to significant improvements in visual acuity and help prevent corneal complications. Recurrences occur in one-third of patients, highlighting the need for long-term monitoring. Although prophylactic oral ACV seems protective against HSV recurrences, our data cannot conclusively support this due to the small number of patients completing the one-year regimen.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

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