e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(8); 182-186

Original Research Article

# Clinical Predictors of Delayed Resolution in Herpetic Disciform Keratitis

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**Received: 01-05-2026 / Revised: 15-06-2026 / Accepted: 21-07-2026**
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**Conflict of interest: Nil**

**Abstract**

**Background:** Herpetic disciform keratitis is an immune-mediated manifestation of herpes simplex virus infection that may result in prolonged corneal inflammation, stromal scarring, and permanent visual impairment. Identification of factors associated with delayed clinical resolution is essential for improving patient outcomes.

**Objective:** To evaluate the clinical predictors of delayed resolution in patients with herpetic disciform keratitis.

**Methods:** This prospective observational cohort study included 130 patients with clinically diagnosed herpetic disciform keratitis. Baseline demographic characteristics, clinical findings, systemic comorbidities, and ophthalmic examination findings were recorded. All patients received standard antiviral therapy with topical corticosteroids under antiviral cover and were followed until complete clinical resolution. Delayed resolution was defined as persistence of active stromal inflammation beyond six weeks of treatment. Statistical analysis was performed using SPSS version 25.0.

**Results:** Delayed clinical resolution occurred in 42 (32.3%) patients. Diabetes mellitus, previous episodes of herpetic keratitis, symptom duration greater than seven days before presentation, raised intraocular pressure, extensive stromal edema, and poor baseline visual acuity were significantly associated with delayed recovery ($p<0.05$). Multivariate logistic regression identified extensive stromal edema (OR 4.15), delayed presentation (OR 3.68), previous herpetic keratitis (OR 3.21), diabetes mellitus (OR 2.84), raised intraocular pressure (OR 2.76), and poor baseline visual acuity (OR 2.43) as independent predictors of delayed resolution. Patients with delayed recovery had significantly longer treatment duration, poorer final visual acuity, and higher rates of corneal scarring, persistent stromal haze, and recurrence.

**Conclusion:** Delayed resolution in herpetic disciform keratitis is associated with several identifiable ocular and systemic factors. Early diagnosis, prompt treatment, and close monitoring of patients with these risk factors may reduce complications and improve visual outcomes.

**Keywords:** Herpetic Disciform Keratitis; Herpes Simplex Virus; Stromal Keratitis; Delayed Resolution; Clinical Predictors; Corneal Edema; Visual Outcome.

**DOI:** 10.25258/ijcpr.18.8.28



## Introduction

Herpes simplex virus (HSV) keratitis is one of the leading infectious causes of corneal blindness worldwide and remains an important cause of recurrent ocular morbidity. Following primary infection, HSV establishes lifelong latency in the trigeminal ganglion, with periodic reactivation leading to recurrent corneal disease. Repeated episodes of inflammation may result in progressive corneal scarring, thinning, neovascularization, and permanent visual impairment if not recognized and treated promptly. [1,2]

Herpetic stromal keratitis, particularly disciform keratitis, is an immune-mediated manifestation characterized by localized stromal edema, Descemet's membrane folds, keratic precipitates, and variable degrees of anterior chamber inflammation. Unlike epithelial keratitis, disciform keratitis primarily results from a delayed hypersensitivity response to viral antigens rather than active viral replication. The resulting endothelial dysfunction leads to stromal edema and significant visual deterioration. [3,4]

Current management consists of topical corticosteroids administered under antiviral cover, with oral or topical antiviral agents used to suppress viral replication and reduce recurrence.

Early initiation of therapy generally results in favorable outcomes; however, a subset of patients demonstrates delayed clinical resolution despite appropriate treatment. Persistent stromal edema and prolonged inflammation increase the risk of corneal scarring, endothelial dysfunction, irregular astigmatism, and permanent reduction in visual acuity. [5.6]

Several clinical factors, including delayed presentation, recurrent episodes, extensive stromal involvement, elevated intraocular pressure, reduced corneal sensation, diabetes mellitus, and poor treatment adherence, have been proposed as contributors to delayed recovery. Identification of these predictors is important because it may facilitate early risk stratification, optimize therapeutic strategies, and improve long-term visual outcomes. However, data regarding predictors of delayed resolution in herpetic disciform keratitis remain limited, particularly in the Indian population. [7]

Therefore, the present study was undertaken to evaluate the clinical predictors associated with delayed resolution in patients with herpetic disciform keratitis and to determine their relationship with treatment response and visual outcome.

## Materials and Methodology

**Study Design:** This was a hospital-based prospective observational cohort study conducted to identify clinical predictors of delayed resolution in patients with herpetic disciform keratitis.

**Study Setting:** The study was conducted in the Department of Ophthalmology at a tertiary care teaching hospital.

**Study Duration:** The study was carried out over a period of 12 months.

**Sample Size:** A total of 130 patients with clinically diagnosed herpetic disciform keratitis were enrolled consecutively during the study period.

**Study Population:** Patients presenting to the ophthalmology outpatient department or emergency services with a clinical diagnosis of herpetic disciform keratitis were included.

### Inclusion Criteria

- Age 18 years or older.
- Clinical diagnosis of herpetic disciform keratitis based on slit-lamp examination.
- Presence of stromal edema with Descemet's membrane folds and endothelial keratic precipitates.
- Patients willing to provide written informed consent and comply with follow-up visits.

### Exclusion Criteria

- Active epithelial herpetic keratitis without stromal involvement.
- Bacterial, fungal, or acanthamoeba keratitis.
- Previous corneal transplantation.
- Severe ocular surface disorders affecting healing.
- Autoimmune keratitis or collagen vascular diseases.
- History of recent ocular trauma or intraocular surgery (<3 months).
- Immunocompromised patients (including HIV infection or systemic immunosuppressive therapy).
- Patients with incomplete follow-up data.

**Study Procedure:** After obtaining informed consent, demographic details including age, sex, occupation, affected eye, duration of symptoms, previous episodes of herpetic keratitis, systemic illnesses (diabetes mellitus, hypertension), and history of antiviral treatment were recorded.

A comprehensive ophthalmic examination was performed for all patients, including:

- Best-corrected visual acuity (BCVA) using LogMAR charts.
- Slit-lamp biomicroscopy.
- Corneal sensation assessment.
- Measurement of intraocular pressure using Goldmann applanation tonometry.
- Documentation of stromal edema, Descemet's membrane folds, keratic precipitates, epithelial defects, corneal neovascularization, anterior chamber reaction, and corneal scarring.
- Dilated fundus examination whenever media clarity permitted.

All patients received standard treatment consisting of topical corticosteroids under antiviral cover with oral acyclovir or valacyclovir according to institutional treatment protocols.

Cycloplegic agents and antiglaucoma medications were prescribed whenever indicated.

Patients were followed at 1 week, 2 weeks, 4 weeks, 6 weeks, and 3 months.

**Definition of Delayed Resolution:** Delayed resolution was defined as persistent stromal edema and/or anterior segment inflammation requiring more than six weeks of standard therapy to achieve complete clinical resolution, or persistence of active disease beyond the expected treatment period.

### Outcome Measures

### Primary Outcome

- Identification of clinical predictors associated with delayed resolution of herpetic disciform keratitis.

**Secondary Outcomes**

- Time to complete clinical resolution.
- Improvement in best-corrected visual acuity.
- Development of corneal scarring or neovascularization.
- Recurrence during follow-up.
- Requirement for prolonged corticosteroid therapy or additional interventions.

**Statistical Analysis:** Data were entered into Microsoft Excel and analyzed using SPSS version 25.0. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Independent Student's t-test or Mann-Whitney U test was used for comparison of continuous variables. Chi-square test or Fisher's exact test was used for categorical variables. Variables showing significant association on univariate analysis were entered into a multivariate logistic regression model to identify independent predictors of delayed resolution. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated, and a p-value <0.05 was considered statistically significant.

**Results**

A total of 130 patients with clinically diagnosed herpetic disciform keratitis were enrolled in the study. The mean age of the participants was 45.8 ± 13.6 years (range: 19–74 years). Males constituted 78 (60.0%) of the study population, while 52 (40.0%) were females. The mean duration of symptoms before presentation was 8.3 ± 4.2 days. Among the study population, 42 (32.3%) patients demonstrated delayed clinical resolution, whereas 88 (67.7%) achieved complete resolution within six weeks of standard therapy. Delayed resolution was significantly associated with recurrent disease, diabetes mellitus, and prolonged symptom duration before presentation, elevated intraocular pressure, and extensive stromal edema.

**Table 1: Baseline Demographic and Clinical Characteristics of the Study Population (n = 130)**

| Variable | Value |
|---|---|
| **Age (years)** | 45.8 ± 13.6 |
| **Gender** | |
| Male | 78 (60.0%) |
| Female | 52 (40.0%) |
| **Affected Eye** | |
| Right eye | 68 (52.3%) |
| Left eye | 62 (47.7%) |
| Duration of symptoms (days) | 8.3 ± 4.2 |
| Diabetes mellitus | 34 (26.2%) |
| Hypertension | 29 (22.3%) |
| Previous episode of HSV keratitis | 38 (29.2%) |
| Mean baseline BCVA (LogMAR) | 0.84 ± 0.39 |

The study population consisted predominantly of middle-aged adults with a slight male predominance. Approximately one-fourth of patients had diabetes mellitus, and nearly one-third had a previous episode of herpetic keratitis.

**Table 2: Comparison of Clinical Characteristics between Patients with Early and Delayed Resolution**

| Variable | Early Resolution (n=88) | Delayed Resolution (n=42) | p-value |
|---|---|---|---|
| Age (years) | 43.9 ± 12.8 | 49.7 ± 14.1 | 0.021 |
| Diabetes mellitus | 16 (18.2%) | 18 (42.9%) | 0.003 |
| Previous HSV keratitis | 18 (20.5%) | 20 (47.6%) | 0.001 |
| Symptoms >7 days before presentation | 24 (27.3%) | 24 (57.1%) | <0.001 |
| Raised IOP (>21 mmHg) | 12 (13.6%) | 16 (38.1%) | 0.002 |
| Extensive stromal edema | 20 (22.7%) | 22 (52.4%) | <0.001 |
| Corneal neovascularization | 10 (11.4%) | 12 (28.6%) | 0.015 |
| Baseline BCVA (LogMAR) | 0.72 ± 0.31 | 1.08 ± 0.42 | <0.001 |

Patients with delayed resolution were significantly older and had higher frequencies of diabetes mellitus, recurrent herpetic keratitis, delayed presentation, raised intraocular pressure, extensive stromal edema, corneal neovascularization, and poorer baseline visual acuity.

**Table 3: Clinical Outcome Following Treatment**

| Outcome | Early Resolution (n=88) | Delayed Resolution (n=42) | p-value |
|---|---|---|---|
| Mean time to resolution (weeks) | 4.3 ± 0.8 | 8.5 ± 1.6 | <0.001 |
| Final BCVA (LogMAR) | 0.18 ± 0.12 | 0.46 ± 0.24 | <0.001 |
| Corneal scarring | 18 (20.5%) | 24 (57.1%) | <0.001 |
| Persistent stromal haze | 10 (11.4%) | 18 (42.9%) | <0.001 |
| Recurrence during follow-up | 8 (9.1%) | 12 (28.6%) | 0.004 |
| Prolonged steroid therapy (>6 weeks) | 6 (6.8%) | 26 (61.9%) | <0.001 |

Patients with delayed resolution required significantly longer treatment, achieved poorer final visual acuity, and developed higher rates of corneal scarring, persistent stromal haze, recurrence, and prolonged corticosteroid therapy compared with those who responded early.

**Table 4: Multivariate Logistic Regression Analysis for Predictors of Delayed Resolution**

| Variable | Adjusted Odds Ratio (OR) | 95% Confidence Interval | p-value |
|---|---|---|---|
| Diabetes mellitus | 2.84 | 1.28–6.31 | 0.010 |
| Previous HSV keratitis | 3.21 | 1.42–7.25 | 0.005 |
| Symptoms >7 days before presentation | 3.68 | 1.61–8.39 | 0.002 |
| Raised intraocular pressure | 2.76 | 1.16–6.58 | 0.021 |
| Extensive stromal edema | 4.15 | 1.82–9.47 | <0.001 |
| Poor baseline BCVA (LogMAR >1.0) | 2.43 | 1.04–5.67 | 0.039 |

Multivariate logistic regression identified extensive stromal edema, delayed presentation, previous herpetic keratitis, diabetes mellitus, raised intraocular pressure, and poor baseline visual acuity as independent predictors of delayed clinical resolution in patients with herpetic disciform keratitis.

**Discussion**

The present study evaluated the clinical predictors of delayed resolution in patients with herpetic disciform keratitis and found that 32.3% of patients experienced delayed clinical resolution despite receiving standard antiviral and corticosteroid therapy. Delayed recovery was significantly associated with diabetes mellitus, previous episodes of herpetic keratitis, prolonged duration of symptoms before presentation, raised intraocular pressure, extensive stromal edema, and poor baseline visual acuity. Patients with delayed resolution also had significantly longer treatment duration, poorer final visual acuity, and a higher incidence of corneal scarring and recurrent disease.

The landmark Herpetic Eye Disease Study (HEDS) demonstrated that oral acyclovir significantly reduces recurrent herpes simplex ocular disease and improves long-term outcomes, emphasizing the importance of suppressing recurrent viral activity in stromal keratitis. [8] In the present study, previous episodes of herpetic keratitis emerged as an independent predictor of delayed resolution, supporting the concept that recurrent immune-mediated inflammation contributes to prolonged stromal healing and persistent endothelial dysfunction. The HEDS investigators also showed that topical corticosteroids administered together with antiviral therapy accelerate the resolution of stromal inflammation and reduce treatment failure in herpes simplex stromal keratitis. [9] Despite receiving similar treatment protocols, approximately one-third of patients in the present study demonstrated delayed clinical resolution, indicating that disease severity and host-related factors substantially influence therapeutic response beyond standard treatment.

The systematic review by Wilhelmus [10] concluded that prompt antiviral therapy combined with carefully monitored corticosteroid treatment remains the cornerstone of stromal herpes simplex keratitis management, although patients with severe stromal involvement often require prolonged therapy. Our findings are consistent with this observation, as extensive stromal edema was the strongest independent predictor of delayed resolution and prolonged corticosteroid use.

Rowe et al. [11] described the complex immunopathogenesis of herpes simplex stromal keratitis, highlighting that excessive host inflammatory responses, endothelial dysfunction, and cytokine-mediated tissue injury play major roles in persistent corneal edema and scarring. Similar mechanisms may explain the poorer visual outcomes observed in the present study among patients with delayed resolution, who developed significantly higher rates of corneal scarring and persistent stromal haze.

The epidemiological study by Labetoulle et al. [12] reported that recurrent herpetic keratitis remains an important cause of chronic corneal morbidity and visual impairment. Their findings emphasized the importance of early diagnosis and close follow-up to prevent permanent structural damage. In agreement with these observations, patients presenting later than seven days after symptom onset in the present study had a significantly

greater risk of delayed clinical recovery, underscoring the value of early ophthalmic intervention.

Similarly, Azher et al. [13] highlighted that delayed diagnosis, recurrent disease, associated systemic illnesses such as diabetes mellitus, and elevated intraocular pressure contribute to poor clinical outcomes in herpes simplex keratitis. The present study supports these findings by demonstrating that diabetes mellitus, raised intraocular pressure, recurrent disease, and poor baseline visual acuity independently predicted delayed resolution. Diabetes may impair corneal epithelial healing, alter immune responses, and increase susceptibility to prolonged inflammation, thereby delaying recovery. Overall, the present study demonstrates that delayed resolution in herpetic disciform keratitis is influenced by both ocular and systemic factors. Early diagnosis, prompt initiation of antiviral and corticosteroid therapy, careful monitoring of intraocular pressure, and optimal management of systemic comorbidities, particularly diabetes mellitus, may improve treatment response and reduce the risk of permanent visual impairment. Identification of high-risk patients at presentation allows clinicians to individualize follow-up schedules and institute timely interventions to prevent long-term corneal complications.

## Conclusion

Delayed resolution occurred in nearly one-third of patients with herpetic disciform keratitis and was significantly associated with diabetes mellitus, previous episodes of herpetic keratitis, delayed presentation, raised intraocular pressure, extensive stromal edema, and poor baseline visual acuity. Patients with delayed recovery experienced prolonged treatment, poorer visual outcomes, and higher rates of corneal scarring and recurrence. Early recognition of these clinical predictors can help ophthalmologists identify high-risk patients, optimize treatment strategies, ensure closer follow-up, and improve long-term visual prognosis. Appropriate antiviral therapy combined with judicious corticosteroid use and management of associated systemic conditions remains essential for successful clinical outcomes.

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