Section: Clinical Microbiology

Original Research Article

PREVALENCE OF CYTOMEGALOVIRUS (CMV) AND EPSTEIN-BARR VIRUS (EBV) INFECTIONS AMONG SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) PATIENTS ATTENDING A TERTIARY CARE HOSPITAL IN SOUTH INDIA

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Received *: 10/12/2025*
Received in revised form *: 20/01/2026*
Accepted *: 06/02/2026*

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DOI: 10.70034/ijmedph.2026.1.220

Source of Support: Tamil Nadu State Research Committee (TNSRC) and Department of Health Research (DHR) – ICMR
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (1); 1256-1262

ABSTRACT

Background: Systemic Lupus Erythematosus (SLE) represents a complex autoimmune disorder with multifactorial etiology. Members of the Herpesviridae family, particularly Cytomegalovirus (CMV), Epstein-Barr virus (EBV) and Herpes Simplex virus (HSV) have been implicated as environmental triggers in SLE pathogenesis. The primary aim of this study was to determine the prevalence of CMV and EBV infections in SLE patients attending a tertiary care hospital in Chennai. This study also aims to determine the association between clinical manifestations and seropositivity of CMV, EBV and HSV in these patients.

Materials and Methods: Fifty patients with confirmed SLE were enrolled in this Cross-Sectional study conducted at a tertiary care hospital in South India, between February-July, 2024. Serum samples were tested for CMV, EBV, HSV IgG and IgM antibodies using ELISA.

Results: Among 50 SLE patients (90% were female, mean age 31.2 years), CMV IgG seropositivity was 88%, while CMV IgM was 38%. EBV IgG and IgM seropositivity rates were 86% and 4%, HSV IgG and IgM seropositivity rates were 76% and 32%, respectively. Co-infections were seen with CMV & EBV (2%), CMV & HSV (26%), CMV& EBV & HSV (2%). Statistical analysis revealed significant association between IgM seropositivity and disease activity in SLE patients.

Conclusion: High seroprevalence of CMV, EBV and HSV in patients with SLE suggest potential role of herpes viruses in SLE pathogenesis and clinical manifestations in South Indian population.

Keywords: CMV – Cytomegalovirus, EBV – Epstein-Barr virus, HSV – Herpes simplex virus, SLE – Systemic Lupus Erythematosus.

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic, multisystem autoimmune disorder characterized by loss of immunological tolerance, persistent inflammation, and the production of diverse autoantibodies. Although its precise etiology remains incompletely understood, SLE pathogenesis is widely recognized as the result of a multifactorial interaction involving genetic predisposition, hormonal influences, environmental triggers, and immune dysregulation.[1-3] Among the various environmental factors implicated, herpes viruses in particular have received considerable attention for their potential to initiate or exacerbate autoimmune responses.[4,5]

Epstein–Barr virus (EBV) is one of the most extensively studied infectious agents linked to SLE

development. Seminal studies revealed increased EBV seropositivity and viral load in young SLE patients, suggesting a possible etiologic role.[1] Subsequent studies have strengthened this association, reporting impaired immune control of latent EBV, molecular mimicry between EBV proteins and lupus autoantigens, and EBV-driven B-cell activation that contribute to loss of self-tolerance and autoantibody generation.[6-8] Dysregulated interferon responses triggered by EBV infection also support its critical involvement in the immunopathogenesis of SLE.[3]

Besides EBV, other herpes viruses including cytomegalovirus (CMV) and herpes simplex virus (HSV) have been implicated in autoimmune disease pathways. These viruses establish lifelong latency with the capacity to reactivate under immunosuppression, influencing both innate and adaptive immunity.[4] SLE patients experience increased frequency of herpes virus reactivation, which has been associated with disease flares and heightened clinical severity.[1,3] CMV infection, in particular, is recognized for its role in triggering lupus exacerbations and organ-specific complications, especially in patients on immunosuppressive therapy.[9-11] Molecular studies from diverse populations have confirmed higher detection rates of CMV DNA in SLE patients and demonstrated a correlation between active CMV infection and higher disease activity indices, including the SLEDAI score.[12]

Herpes simplex virus (HSV) has also been investigated for its potential role in autoimmune modulation. Experimental and clinical observations indicate that HSV infections may alter immune pathways, induce autoreactive lymphocytes, and exacerbate inflammatory responses, thereby contributing to autoimmunity in susceptible individuals.[13,14] More broadly, herpes viruses with their capacity for lifelong latency, periodic reactivation, and profound effects on both innate and adaptive immunity represent biologically plausible contributors to the development and exacerbation of autoimmune diseases, including SLE.[14,15] Molecular and serological studies have identified correlations between active herpes virus infections and increased disease activity scores such as SLEDAI-2K, reinforcing the clinical importance of viral monitoring in SLE patients.[5,7,12]

Beyond their potential involvement in disease initiation, viral infections remain a major cause of morbidity and mortality in SLE patients. Immunosuppressive therapies increase susceptibility to opportunistic viral reactivation and severe infections, complicating clinical management and sometimes mimicking lupus flares.[5,16] Several studies have demonstrated that active herpes virus infections correlate with higher disease activity, increased hospitalization, and poorer overall outcomes.[11,12]

Despite accumulating global evidence, regional data on herpes virus prevalence among SLE patients from the Indian subcontinent, particularly from South India, are scarce. Considering regional differences in viral epidemiology, genetic backgrounds, and environmental exposures, it is critical to understand the burden and clinical impact of these infections in the local population for improving diagnostic accuracy, risk stratification, and tailored clinical management.

The present study aims to determine the seroprevalence of CMV, EBV, and HSV infections among SLE patients attending a tertiary care hospital in South India and to evaluate the association between active herpes virus infection and disease activity. This work contributes to the growing understanding of viral triggers in SLE pathogenesis and may support improved diagnostic and therapeutic strategies tailored to the regional patient population.

MATERIALS AND METHODS

Ethical Considerations: Ethical clearance and approval were obtained from the Institutional Ethics Committee prior to initiation of the study (Institutional Ethics Committee, Madras Medical College; Approval No. 02012024). Written informed consent was obtained from all participants before enrolment.

Study Design and Setting: This cross-sectional study was conducted at the Virus Research and Diagnostic Laboratory (VRDL), Institute of Microbiology, in collaboration with the Institute of Rheumatology, Madras Medical College & Rajiv Gandhi Government General Hospital (MMC & RGGGH), Chennai. The study period spanned six months, from February 2024 to July 2024.

Study Population: A total of 50 patients with confirmed SLE, attending the Institute of Rheumatology at this tertiary care center in South India were enrolled. Demographic details, clinical characteristics, co-morbidities, laboratory parameters, and treatment history were collected using a standardized data collection form following written informed consent.

Sample Collection and Processing: Two milliliters of venous blood were collected aseptically from each participant. Samples which were stored at 2°C – 8°C until testing, were centrifuged at 3000 rpm for 10 minutes to separate serum. Serum samples were analyzed for CMV, EBV, and HSV IgG and IgM antibodies using commercial ELISA kits (Euroimmun, Germany). Optical density (OD) values were measured at 450 nm with a reference wavelength between 620 nm and 650 nm. Results were interpreted according to the manufacturer's instructions.

Statistical Analysis: Data were analyzed using SPSS version 21 (IBM Corp., Armonk, NY). Descriptive statistics, including frequencies and measures of central tendency, were calculated. Categorical variables were analyzed using the chi-square test or

Fisher's exact test, as appropriate. A p-value < 0.05 was considered statistically significant.

RESULTS

Fifty patients with Systemic Lupus Erythematosus (SLE) attending a tertiary care hospital in South India were included in the study. The demographic profile, clinical manifestations, associated co-morbidities, and treatment details of the participants are summarized in [Table 1].

The study population consisted predominantly of women (90%), with men accounting for 10% of the cohort. The mean age was 30.03 ± 11.72 years (range: 8 – 58 years). The highest proportion of SLE cases was observed in the 31–40 years age group (30%), followed by the 21–30 years (26%) and 11–20 years (24%) age groups.

Arthritis was the most commonly reported manifestation, affecting 29 patients (58%). Fever (48%) and skin rash (46%) were also frequent. Mucosal ulcers were present in 20 patients (40%), and alopecia in 14 (28%). Other clinical features included myositis in 9 (18%), pleurisy in 8 (16%), vasculitis in 4 (8%), lupus headache in 3 (6%), and seizures in 3 (6%). Less common manifestations included psychosis in 2 (4%), visual disturbances in 2 (4%), pericarditis in 1 (2%), and cerebrovascular accident in 1 (2%).

Hyperthyroidism was the most frequently associated co-morbidity (16%), followed by hypertension (14%) and tuberculosis (10%). Diabetes mellitus and epilepsy were reported in 2 patients each (4%), while asthma was noted in 1 patient (2%).

Regarding treatment, 49 of 50 patients (98%) were receiving hydroxychloroquine (HCQ), and 23 patients (46%) had been initiated on dexamethasone. Laboratory parameters are detailed in [Table 2]. Renal involvement with proteinuria was observed in 20 patients (40%), and urinary casts in 3 patients (6%). Low complement levels were seen in 13 (26%), and increased protein binding in 17 (34%). Hematological abnormalities included severe anemia in 28 patients (56%), leukopenia in 5 patients (10%) and thrombocytopenia in 2 patients (4%).

Seropositivity for CMV, EBV, and HSV is presented in [Table 3]. CMV IgG antibodies were detected in 44 patients (88%), and CMV IgM in 19 patients (38%). EBV IgG and IgM seropositivity were 43 (86%) and 2 (4%), respectively. HSV IgG and IgM seropositivity were 38 (76%) and 16 (32%).

Among patients with IgM seropositivity, four showed isolated CMV IgM positivity, two showed isolated HSV IgM positivity, one patient tested positive for both CMV and EBV IgM, thirteen patients were positive for both CMV and HSV IgM, and one patient demonstrated triple IgM positivity for CMV, EBV, and HSV.

Disease activity was assessed using the SLEDAI-2K scoring system [Table 4]. Among the 29 patients who were seronegative for CMV, EBV, and HSV IgM, 9 had mild disease activity, while 10 each presented with moderate and high disease activity.

Of the four patients with CMV IgM positivity, one had moderate disease activity, two had high disease activity, and one exhibited very high disease activity. Among the two patients with isolated HSV IgM positivity, one showed moderate and one showed high disease activity.

Among the 15 patients with combined IgM seropositivity (multiple herpesvirus infections), 11 (73.3%) exhibited high disease activity, and 4 (26.7%) showed very high disease activity.

As shown in [Table 5], there was a significant association between active herpes virus infection and higher SLEDAI-2K scores. Among the 21 patients with active infection (IgM seropositivity for CMV, EBV and HSV), 14 demonstrated high disease activity and 5 demonstrated very high disease activity. This association was statistically significant, indicating that acute herpes virus infection correlates with increased disease severity in SLE patients.

Table 1: Demographic and Clinical Characteristics of SLE Patients (n=50)

Characteristics	Categories	Number (n)	Percentage (%)
Age Group (in years)	1-10	1	2.0
	11-20	12	24.0
	21-30	13	26.0
	31-40	15	30.0
	41-50	6	12.0
	51-60	3	6.0
Gender	Female	45	90.0
	Male	5	10.0
Clinical Manifestations	Seizures	3	6.0
	Psychosis	2	4.0
	Cerebrovascular Accident	1	2.0
	Visual Disturbance	2	4.0
	Lupus Headache	3	6.0
	Vasculitis	4	8.0
	Arthritis (≥2 joints with swelling/tenderness)	29	58.0
	Myositis	9	18.0
	Rash	23	46.0
	Alopecia	14	28.0
	Mucosal Ulcers	20	40.0
	Pleurisy	8	16.0
	Pericarditis	1	2.0

	Fever (>38°C)	24	48.0
Co-morbidities	Diabetes mellitus	2	4.0
	Tuberculosis	5	10.0
	Epilepsy	2	4.0
	Asthma	1	2.0
	Hypertension	7	14.0
	Hyperthyroidism	8	16.0
Drug Regimen	Hydroxychloroquine (HCQ)	49	98.0
	Dexamethasone	23	46.0

Table 2: Laboratory Parameters in SLE Patients (n=50)

Parameter	Number (n)	Percentage (%)
Severe Anemia (<8 g/ dl)	28	56
Leukopenia (<3,000/mm³)	5	10.0
Thrombocytopenia (<100,000/mm³)	2	4.0
Low Complement (C3, C4)	13	26.0
Increased DNA Binding	17	34.0
Proteinuria (>0.5 gm/24 h)	20	40.0
Urinary Casts	3	6.0

Table 3: Seroprevalence of CMV, EBV, and HSV in SLE Patients (n=50)

Virus	Antibody Class	Number of Positives	Percentage (%)
CMV	IgG	44	88.0
	IgM	19	38.0
EBV	IgG	43	86.0
	IgM	2	4.0
HSV	IgG	38	76.0
	IgM	16	32.0
Active CMV, EBV and HSV Infection in SLE patients			
CMV	IgM	4	8.0
EBV	IgM	0	0
HSV	IgM	2	4.0
CMV + EBV	IgM	1	2.0
CMV + HSV	IgM	13	26.0
CMV + EBV + HSV	IgM	1	2.0

Table 4: Association Between Disease Activity (SLEDAI 2K Score) and Acute Infection

IgM Positivity for CMV,EBV, HSV	Number (n)	Disease Activity based on SLEDAI 2K Score			
		Mild (1-5)	Moderate (6-10)	High (>10)	Very High(>20)
NEGATIVE	29	9	10	10	0
CMV	4	0	1	2	1
EBV	0	0	0	0	0
HSV	2	0	1	1	0
CMV + EBV	1	0	0	1	0
CMV + HSV	13	0	0	9	4
CMV+EBV + HSV	1	0	0	1	0

Table 5: Distribution of Patients according to SLEDAI-2K Severity Score and Test Positivity (n = 50)

SLEDAI-2K Severity Category	Negatives (n)	Positives (n)	Total (n)	Chi-square (χ^2) value	p-value
Mild (1–5)	9	0	9	19.212	0.0002*
Moderate (6–10)	10	2	12		
High (11–19)	10	14	24		
Very High (≥20)	0	5	5		
Total	29	21	50		

*$p<0.05$ is considered statistically significant. Fischer's exact test was applied where expected cell counts were <5.

DISCUSSION

Systemic Lupus Erythematosus (SLE) is an autoimmune, chronic inflammatory disease with multi-system involvement characterized by episodes of remission and exacerbation. Various exogenous and endogenous factors contribute to the pathogenesis of SLE. Viral infections due to Cytomegalovirus, Epstein-Barr virus and Herpes simplex virus may trigger the development or exacerbation of SLE in genetically predetermined individuals.[17,18]

In this study involving 50 SLE patients from a tertiary care hospital in South India, we observed a high burden of herpes virus seropositivity and a significant association between active infection and increased disease activity. The demographic profile, dominated by young women, aligns with the well-established epidemiology of SLE, which disproportionately affects females of reproductive age.[3,19] The clinical

manifestations observed particularly arthritis, mucocutaneous involvement and fever are consistent with the global spectrum of SLE presentations reported in earlier studies.[3,19]

Nearly all patients in this cohort were receiving hydroxychloroquine (HCQ), with 49 out of 50 individuals (98%) on HCQ therapy. The high prevalence of HCQ prescription (98%) aligns with global treatment guidelines, emphasizing its disease-modifying properties, immunomodulatory effects and ability to reduce SLE progression.[17] Evidence also suggests that sustained HCQ therapy lowers flare frequency, decreases cumulative disease burden, and reduces cardiovascular complications among SLE patients.[20,21] In addition, 23 patients (46%) were receiving dexamethasone, indicating that almost half the cohort required systemic corticosteroids likely reflecting active disease, moderate to severe flares, or organ-threatening manifestations such as lupus nephritis or systemic inflammation.[22] Although glucocorticoids remain central to the rapid control of SLE activity, long-term therapy is associated with significant adverse effects, including osteoporosis, metabolic disturbances such as diabetes, and increased susceptibility to infections.[23,24] These findings highlight that, despite widespread HCQ use, many patients still require corticosteroids, underscoring the importance of implementing effective immunosuppressive therapies.

Renal involvement was noted in 40% of patients, comparable to prevalence rates described in previous cohorts, particularly from Asian populations where lupus nephritis tends to be more common and severe (25,26). 56% of patients presented with severe anemia, a well-documented hematological manifestation of SLE that may result from chronic inflammation, autoimmune hemolysis, or renal insufficiency. 10 % of the patients showed leucopenia which is frequently observed in SLE and may result from immune-mediated destruction or medication effects. While the majority of patients maintained platelet counts within normal limits, 4% exhibited thrombocytopenia, a common hematologic abnormality in SLE that may be attributed to immune-mediated platelet destruction or bone marrow suppression due to disease activity or immunosuppressive therapy. The hematological abnormalities, including severe anemia, leukopenia and thrombocytopenia reflect classic immune-mediated cytopenia characteristic of SLE pathology.[27]

In our cohort of 50 SLE patients, we observed high IgG seroprevalence for CMV (88%), EBV (86%), and HSV (76%), which aligns with global reports indicating that most adults harbor latent herpes viruses (28). High IgM seropositivity particularly for CMV (38%), EBV (4%) and HSV (32%) suggests a substantial burden of active or reactivated infections. This pattern is consistent with evidence that SLE patients may have increased susceptibility to viral reactivation due to intrinsic immune dysregulation or immunosuppressive therapy.[6] Similar findings have been reported in earlier studies showing high seroprevalence rates of EBV, CMV, and HSV activity in SLE compared with healthy controls.[12,29,30]

CMV reactivation is a recognized concern in SLE patients, often leading to opportunistic infections and complications such as vasculitis.[31] CMV reactivation can mimic SLE flares, complicating diagnosis and management. Both EBV and HSV can evade immune surveillance, leading to prolonged latent infections and periodic reactivation, which may contribute to immune dysregulation in autoimmune diseases.[32] Stimulation of autoreactive B cells by EBV and impact of HSV on inflammatory responses may have synergistic effects, increasing the risk of SLE flares.

CMV and HSV co-infection had the highest prevalence, with 13 patients (26%) testing positive for both viruses. This elevated prevalence may stem from the immunosuppressive state inherent to SLE or result from treatments involving corticosteroids and other immunosuppressants. CMV and EBV are known to contribute to autoimmune diseases through molecular mimicry and chronic immune activation.[6,15] In this study, CMV + EBV IgM positivity was observed in 2% of patients, indicating recent or reactivated infection.

The detection of triple infection with CMV + EBV + HSV in 1 patient (2%) underscores a rare but clinically significant event. The concurrent presence of Herpes viruses such as Cytomegalovirus (CMV), Epstein-Barr virus (EBV) and Herpes Simplex Virus (HSV) can severely impact immune function, increasing the risk of severe complications including opportunistic infections, persistent inflammation and development of flare in systemic lupus erythematosus (SLE). A study by Lino K et al,[33] reported that 45% of hospitalized SLE patients had co-infections with multiple herpes viruses, with EBV being the most frequently detected while our study showed higher prevalence of CMV followed by HSV. These co-infections were associated with renal dysfunction, highlighting the potential for severe complications in SLE patients with multiple viral infections.

Possibility of false positivity cannot be ruled out in cases with multiple seropositivity. Rather than true antigenic cross reactivity, false positive reaction could be due to presence of interfering substances such as autoantibodies, heterophile antibodies, and serum binding proteins. Hence care must be taken in interpretation of such results. There are no clear guidelines on interpretation of such cases presenting a diagnostic conundrum.[34] Additional tests like IgG avidity test, viral load and clinical correlation can guide us in diagnosing such cases.

Table 4 highlights the association between acute infections due to Herpes viruses and SLE disease activity. Statistical analysis in [Table 5] revealed significant association between IgM seropositivity and disease activity in SLE patients. Patients with combined seropositivity showed high to very high

disease activity similar to study by Reis et al. who demonstrated a significant correlation between active herpes virus infections and elevated SLEDAI scores,[12] findings that are closely mirrored in our data..[12]

The association between active CMV infection and lupus flares is supported by evidence showing that CMV reactivation increases inflammatory cytokine release and may precipitate renal or hematologic complications in SLE patients.[9-11] These findings highlight the significant impact of viral infections on clinical manifestations in SLE patients.

Limitations: This study has some limitations. First, the diagnosis of acute viral infection was based solely on IgM serology, which is not fully reliable. IgM antibodies may persist, reappear during non-specific immune activation or produce false-positive results due to interfering substances such as rheumatoid factor or heterophile antibodies especially in patients with high autoimmune antibody levels. Confirmatory molecular test, such as PCR-based viral load quantification, was not performed, limiting the accuracy of distinguishing true reactivation from false positivity. Additionally, the study involved only 50 patients from a single centre, which may reduce its generalizability to the wider South Asian SLE population. Finally, the absence of age and sex matched controls prevents determination of the true excess burden of CMV, EBV and HSV seropositivity attributable specifically to SLE.

CONCLUSION

This study assessed the seroprevalence of acute CMV, EBV, and HSV infections in patients with active SLE using IgM ELISA and examined their potential associations with disease activity. These findings provide preliminary insights into the burden of these viral infections among SLE patients attending a tertiary care centre in South India. The results highlight the importance of comprehensive viral screening in immunocompromised individuals with SLE to support timely diagnosis and management, ultimately improving patient outcomes.

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