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Association Between Herpes Simplex Virus Type 1 IgG Seropositivity and Dementia at a University Hospital in Bangladesh

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Abstract

Introduction: Dementia has emerged as a significant global public health challenge among the aging population. Emerging evidence suggests that exposure to herpes simplex virus type 1 (HSV-1) immunoglobulin G (IgG) seropositivity has been associated with dementia in some epidemiological studies. This study aimed to examine the association between HSV-1 IgG seropositivity, dementia, and cognitive performance as measured by Mini-Mental State Examination (MMSE) scores among hospital-attending individuals presenting with memory complaints in the elderly population of Bangladesh.

Methods: This cross-sectional analytical study was conducted among 136 patients with complaints of memory loss during the period of November 2024 to April 2025. The study was conducted at the Department of Neurology and Virology at the Bangladesh Medical University (BMU). The patients were categorized as memory loss patients with or without dementia based on the MMSE. Additionally, blood samples were collected aseptically for the detection of anti-HSV-1 IgG seropositivity using the enzyme-linked immunosorbent assay (ELISA) method. Demographic, clinical, and laboratory results were collected and analyzed using IBM SPSS v25 (IBM Corp., Armonk, NY, USA) and Microsoft Excel (Microsoft Corp., Redmond, WA, USA). A p-value <0.05 was considered statistically significant.

Results: The mean age of memory loss patients with dementia infected with HSV-1 was 74.9 (±8.1), and 58 (85.3%) were HSV-1 IgG positive. Thirty-eight (88.4%) male and 20 (80.0%) female patients were HSV-1 IgG seropositive among memory loss patients with dementia (p=0.347). HSV-1 IgG-seronegative (median (interquartile range (IQR)): 26.0 (11.0-29.0)) individuals demonstrated significantly higher cognitive performance (MMSE) scores compared with seropositive (median (IQR): 25.0 (12.0-28.0)) individuals (p<0.05). However, this study could not found any significant association of dementia with HSV-1 IgG seropositivity (adjusted OR=0.865, 95% CI: 0.34-2.22, p=0.763), age (adjusted OR=0.974, 95% CI: 0.93-1.03, p=0.311), and male sex (adjusted OR=0.680, 95% CI: 0.34-1.37, p=0.283), respectively.

Conclusion: This study found no statistically significant association between prior HSV-1 IgG seropositivity and dementia or cognitive performance among hospital-attending individuals presenting with memory complaints, in the first study of its kind in Bangladesh. Nevertheless, multidimensional prospective studies are required to elucidate the potential infectious aetiology of dementia in older adults.

Categories: Neurology, Geriatrics, Public Health
Keywords: bangladesh , dementia, elderly people, herpes simplex-1 (hsv-1), mini-mental state examination (mmse)

Introduction

Dementia is a clinical syndrome characterized by a progressive decline in cognitive function, including impairments in memory, thinking, and the ability to perform activities of daily living. It arises from a variety of underlying causes, among which infectious agents are increasingly recognized as important contributors to brain damage [1]. Several infections, including human immunodeficiency virus (HIV), syphilis, Lyme disease, herpes simplex virus (HSV), as well as central nervous system (CNS) infections such as bacterial meningitis and viral encephalitis, have been implicated in neurodegeneration. Among these, herpes simplex virus type 1 (HSV-1) has gained attention as a potential risk factor for dementia. HSV-1 belongs to the α-herpesvirinae subfamily and is a neurotropic virus. The seropositivity for HSV-1 immunoglobulin G (IgG), primarily reflecting previous exposure, establishes lifelong latency in the trigeminal ganglia and is hypothesized to contribute to an elevated risk of developing dementia in later life [2,3]. However, HSV-1 IgG positivity does not provide evidence of active viral replication, viral reactivation, CNS involvement, or ongoing neuroinflammation.

Epidemiological evidence indicates that the burden of dementia varies considerably across regions. Temporal trends suggest a declining risk in several high-income countries (HICs), particularly in Europe and the United States, whereas the risk appears to be stable or increasing in many low-income countries (LICs)

[4,5]. Reported prevalence estimates show substantial variation ranging from approximately 1% to 15% in South-East Asian countries and from 2.3% to 23% in African countries [6]. Globally, Asia bears the highest number of dementia cases with an estimated 22.9 million affected individuals, more than double the number reported in Europe (10.5 million) and the Americas (9.4 million) [7].

Within South Asia, approximately 4.8 million people are living with dementia, including around 3.8 million in India (0.3%) and 0.4 million in Pakistan (0.2%) [8]. In Bangladesh, a national survey reported that approximately 8% of individuals aged 60 years and older (equivalent to about one in every 12 older adults) were affected by dementia [9].

Despite growing interest in the role of HSV-1 in neurodegeneration, there have been inconsistent findings regarding its association with dementia. Reactivation involves renewed viral activity, which may occur intermittently and, under certain circumstances, may lead to CNS involvement. Proposed mechanisms linking HSV-1 to neurodegeneration include neuroinflammatory responses, disruption of neuronal function, and potential interactions with amyloid-β and tau pathology [10]. These pathological processes may contribute to progressive cognitive impairment; however, the transition from HSV-1 exposure or reactivation to pathological changes and clinically diagnosed dementia remains uncertain. However, HSV-1 IgG seropositivity cannot necessarily be interpreted as evidence of ongoing viral activity or CNS infection. Despite biological and epidemiological interest in the potential relationship between previous exposure to HSV-1 and neurodegeneration, evidence regarding the association between peripheral HSV-1 IgG seropositivity and dementia remains inconsistent. Moreover, such evidence from South Asian populations, particularly in Bangladesh, is limited. Therefore, this study aimed to investigate whether any association exists between HSV-1 IgG seropositivity and dementia, along with cognitive performance using the Mini-Mental State Examination (MMSE), among a hospital-attending elderly population in Bangladesh.

Materials And Methods

Study design and population

This cross-sectional study was conducted at the Department of Neurology and Virology of the Bangladesh Medical University (BMU), Dhaka, between November 2024 and April 2025. During this period, a total of 136 participants were recruited from the inpatient and outpatient departments of Neurology among patients complaining of progressive memory loss due to causes other than trauma. Therefore, the study population primarily represents older adults seeking neurological care at this tertiary care setting as hospital-attending patients and should not be considered representative of the general elderly population of Bangladesh. The study sample size (n=136, with n=68 per group) was calculated using a power analysis for the comparison of two independent proportions. This was based on detecting differences in HSV-1 IgG seropositivity rates between patients with and without dementia [11,12]. Assuming equal allocation between the groups, a sample size of 68 participants per group provides 80% power at a significance level of alpha=0.05 to detect a hypothesized effect size equivalent to an odds ratio (OR) of approximately 3.0. Designing the study to detect a lower OR (<3.0) would necessitate a substantially larger sample size to identify a weaker association, which was beyond the scope of this project. For analytical purposes, 68 participants were included consecutively in each group, selected by convenience to maintain equal group sizes. The participants were clinically evaluated for study inclusion by a competent neurologist. The selected study population was categorized into participants with or without memory loss dementia using the MMSE [13]. A predesigned questionnaire with 11 tasks was used with a maximum total score of 30. Scores above 25 were labelled as without dementia, whereas participants with scores of 21-24, 10-20, and <10 were considered to have mild, moderate, and severe dementia.

Laboratory experiment

Peripheral venous blood samples were collected aseptically and centrifuged at 4000 rpm for 10 minutes. The separated plasma was stored at −20°C until further analysis. Anti-HSV-1 IgG antibodies were detected using an enzyme-linked immunosorbent assay (ELISA) method following the manufacturer's instructions (DRG International Inc., Springfield, NJ, USA). In brief, it is a solid-phase ELISA, where microtiter wells were coated with recombinant gG1 protein of HSV-1. During sample processing, HSV-1-specific antibodies of the positive samples were bound to the immobilized antigens. During washing to remove unbound material, horseradish peroxidase-conjugated anti-human IgG antibodies were added to the wells. After serial washing to remove the unbound conjugate from the immune complex, 3,3',5,5'-tetramethylbenzidine (TBM) substrate was added to produce a blue colour. The blue colour was turned into yellow by adding sulphuric acid as an enzymatic indicator. The intensity of colour was directly proportional to the amount of HSV-1-specific IgG antibody in the patient's sample, and this optical density (OD) value was read at 450 nm using an ELISA microtiter plate reader. The OD values were multiplied by 10 and divided by the cut-off control (mean OD) to obtain the DRG Unit (DU). The cut-off value for this assay is 10, and DU values <9, 9-11, and >11 were interpreted as negative, equivocal/borderline, and positive, respectively. All analysed samples fell within the labelled positive or negative reference ranges, and no equivocal or borderline results occurred during testing.

Statistical analysis

The descriptive statistics of the demographic and clinical data were presented as numbers and percentages,

and summarized using mean, standard deviation, and interquartile range (IQR). Categorical variables were assessed with the chi-square test/Fisher's exact test, and differences in continuous variables between memory loss patients with dementia and memory loss patients without dementia groups were assessed using the Mann-Whitney U test. The relationship between HSV-1 IgG in DU and MMSE score was evaluated using Spearman's correlation. Binary logistic regression was performed to determine whether HSV-1 IgG status or DU value was independently associated with dementia status, after adjustment for age and sex. Data were analysed using Statistical Package for the Social Sciences (SPSS) v25 (IBM Corp., Armonk, NY, USA) and Microsoft Excel (Microsoft Corp., Redmond, WA, USA), and a p-value <0.05 was considered statistically significant.

Ethical considerations

Informed consent was obtained prior to the inclusion of patients in the study, and individuals who declined to provide informed consent were excluded. All procedures were carried out in accordance with established ethical standards, ensuring strict confidentiality and anonymity. Ethical approval was obtained from the Institutional Review Board of BMU (Reference No.: BSMMU/2024/2661; Date: 06/03/2024).

Results

Among the 136 participants, the overall mean age (SD) was 75.5 (±7.0) years. In the cohort of memory loss patients without dementia, 46.3% (37/80) were male, and 55.4% (31/56) were female. Additionally, in the group of memory loss patients with dementia, 53.8% (43/80) were male, and 44.6% (25/56) were female. The demographic, clinical, and laboratory variables of the participants are detailed in Table *1*.

Demographic, clinical, and laboratory variables	Overall (N=136; 100%)		Memory loss patients without dementia (N=68; 50%)		Memory loss patients with dementia (N=68; 50%)		Test statistics (df)	p-Value
	n	%	n	%	n	%		
Age, mean (SD)	75.5 (7.0)	-	76.0 (5.8)	-	74.9 (8.1)	-	U=2163 (Z= -0.653)	0.514
Gender								
Male	80	58.8	37	46.3	43	53.8	χ^2=1.093 (1)	0.296
Female	56	41.2	31	55.4	25	44.6		
HSV-1 IgG seropositivity								
Positive	114	83.8	56	82.4	58	85.3	χ^2=0.217 (1)	0.641
Negative	22	16.2	12	17.6	10	14.7		
HSV-1 IgG (DU), median (IQR)	38.8 (33.3-41.4)	-	40.6 (31.2-42.9)	-	38.5 (33.4-40.2)	-	U=1795 (Z= -2.251)	0.024*
MMSE, median (IQR)	25.5 (19.0-27.0)	-	27.0 (26.0-28.0)	-	19.0 (16.3-23.0)	-	U=0.000 (Z=-10.117)	<0.001**
MMSE category								
Mild	-	-	-	-	28	41.2	-	-
Moderate	-	-	-	-	40	58.8	-	-
Severe	-	-	-	-	0	0.0	-	-

TABLE 1: Demographic, clinical, and laboratory variables of different study groups

df is reported for categorical variables analysed using Pearson's chi-square test. Standardized test statistic is reported for numerical variables analysed using Mann-Whitney U test. Dashes indicate that the statistic is not applicable.

*Implies p-value <0.05 and significant values; **Implies p-value <0.001 and highly significant values.

DU, DRG unit; IQR, interquartile range; MMSE, Mini-Mental State Examination; χ^2, chi-square statistic; df, degrees of freedom; U, Mann-Whitney U; Z, standardized test statistic.

In binary logistic regression to assess gender-based differentiation in memory loss dementia, the OR for gender was 0.419 (95% CI: 0.165-1.063; B=−0.869, SE=0.475, p=0.067), which was not statistically significant. The model as a whole explained between 2.5% (Cox & Snell R-square) and 4.2% (Nagelkerke R-square) of the variance in gender status and correctly classified 83.8% of cases (Table *2*).

Predictor	B	SE	Adjusted OR	95% CI	p-Value
Gender (Male vs Female)	-0.869	0.475	0.419	0.165-1.063	0.067

TABLE 2: Logistic regression analysis predicting gender outcomes based on gender

Dependent variable: Dementia status (0 = memory loss patient without dementia, 1 = memory loss patient with dementia); Covariates entered: Gender. Statistical significance is indicated by a p-value <0.05 obtained from the binary logistic regression model.

B, regression coefficient; SE, standard error; Adjusted OR, adjusted odds ratio; CI, confidence interval.

In the memory loss patient without dementia cohort, 33 out of 37 (89.2%) male patients were HSV-1 IgG positive, while 23 out of 31 (74.2%) female patients were HSV-1 IgG positive. Additionally, four out of 37

(10.8%) male patients were HSV-1 IgG negative and eight out of 31 (25.8%) female patients were HSV-1 IgG negative. The difference was not statistically significant by Fisher's exact test (p=0.106). In the group of memory loss patients with dementia, 38/43 (88.4%) male patients and 20/25 (80.0%) female patients were HSV-1 IgG positive. In contrast, 5/43 (11.6%) male patients and 5/25 (20.0%) female patients were HSV-1 IgG negative (p=0.347) (Figure *1*).

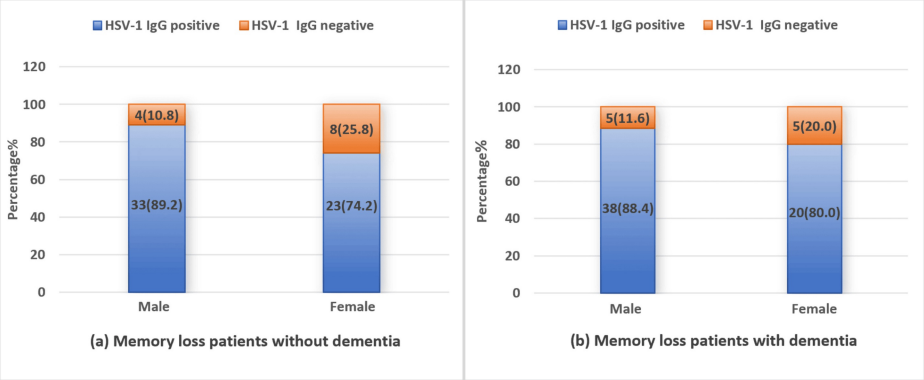


FIGURE 1: HSV-1 IgG serotype with gender-based categorization: group of memory loss patients without dementia (a) and group of memory loss patients with dementia (b)

HSV-1, herpes simplex virus type 1; IgG, immunoglobulin G.

The median HSV-1 IgG DU level was slightly higher (Mann-Whitney U test; p<0.05) in the group of memory loss patients without dementia (median (IQR): 40.6 (31.2-42.9)) than in the group of memory loss patients with dementia (median (IQR): 38.5 (33.4-40.2)) (Figure *2*).

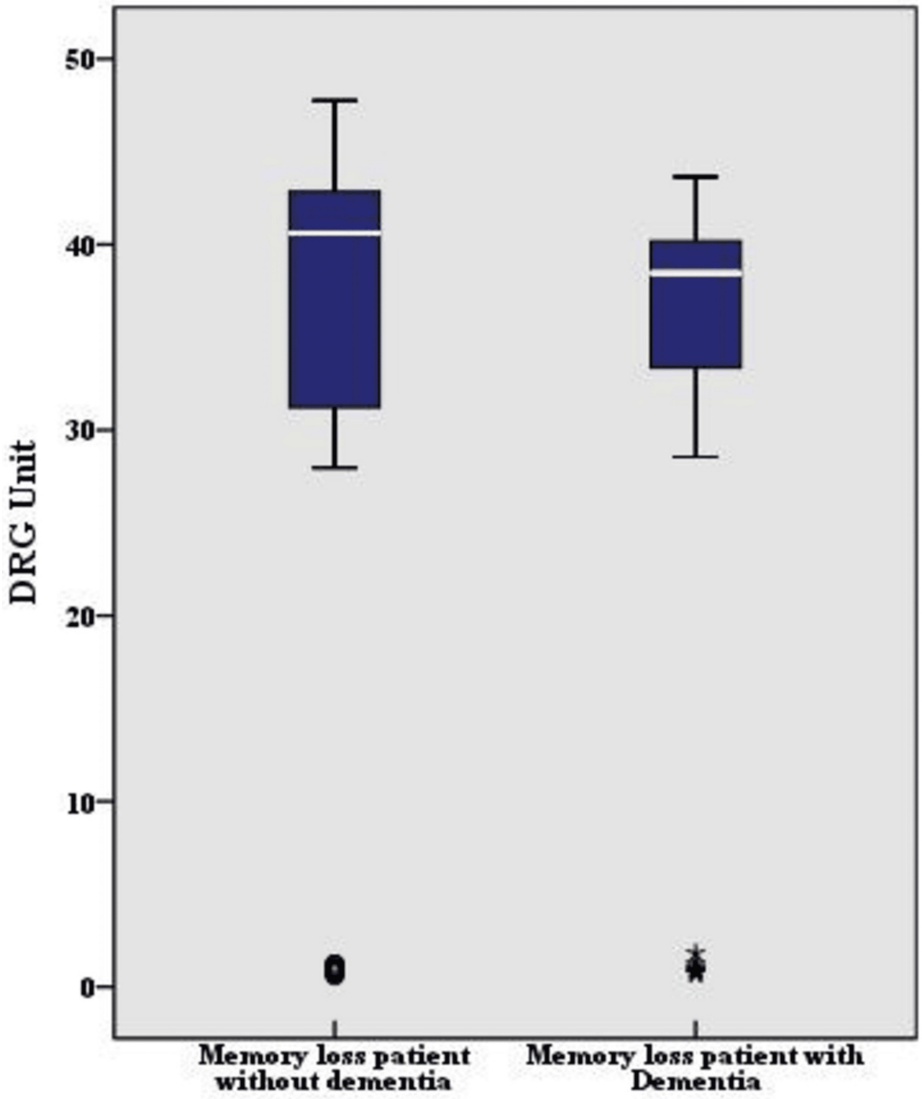


FIGURE 2: Distribution of HSV-1 IgG DRG Unit value according to memory loss dementia status

HSV-1, herpes simplex virus type 1; IgG, immunoglobulin G.

HSV-1 IgG-negative individuals had slightly higher MMSE scores (median 26.0, IQR 11.0-29.0) than HSV-1 seropositive individuals (median 25.0, IQR 12.0-28.0) (Mann-Whitney U test; $p<0.05$) (Figure *3*).

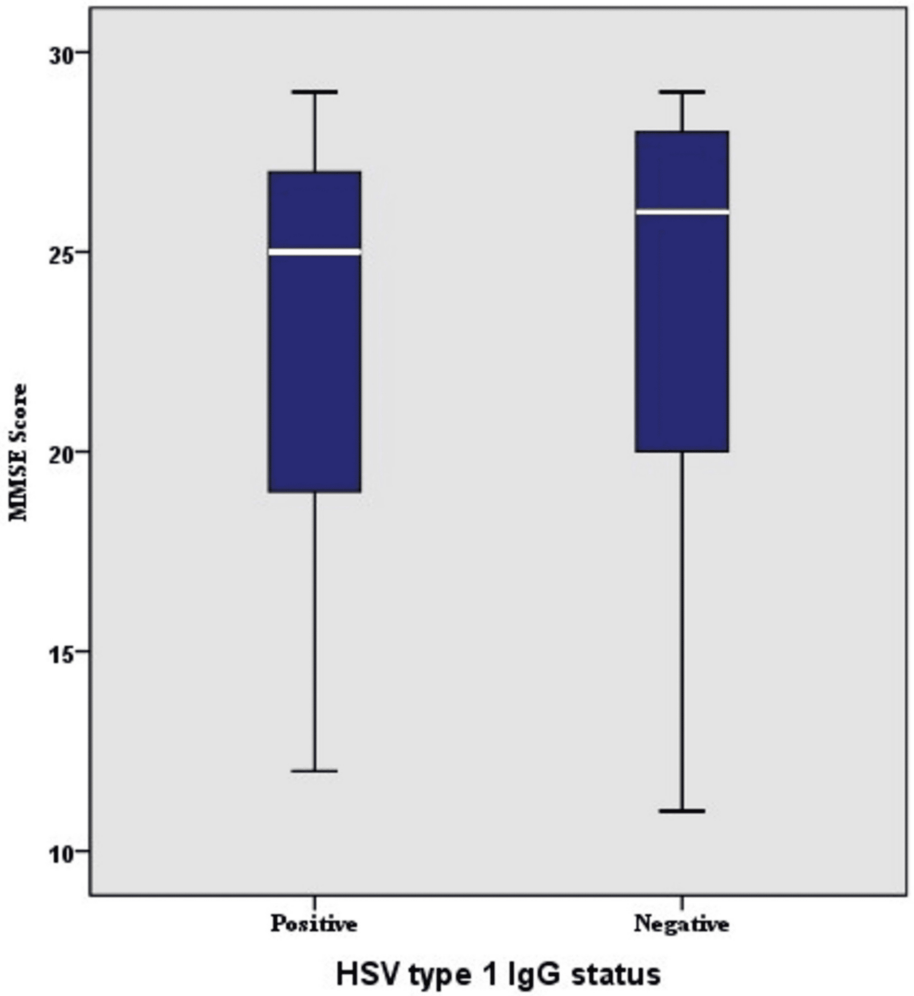


FIGURE 3: Distribution of MMSE score values according to HSV-1 IgG seropositivity

HSV-1, herpes simplex virus type 1; IgG, immunoglobulin G; MMSE, Mini-Mental State Examination.

Spearman's rank correlation analysis demonstrated a weak positive correlation between HSV-1 IgG DRG Unit and overall cognitive test score (Spearman's ρ=0.211, 95% CI: 0.05-0.36, p=0.014) (Figure *4a*). A weak positive correlation was observed between MMSE scores and HSV-1 IgG DRG Unit in the group pf memory loss patients without dementia (Spearman's ρ=0.241, 95% CI: -0.053 to 0.400, p=0.047) (Figure *4b*), whereas no statistically significant correlation was observed between MMSE scores and HSV-1 IgG DRG Unit in the group of memory loss patients with dementia (Spearman's ρ=-0.91, 95% CI: -0.318 to 0.131, p=0.462) (Figure *4c*).

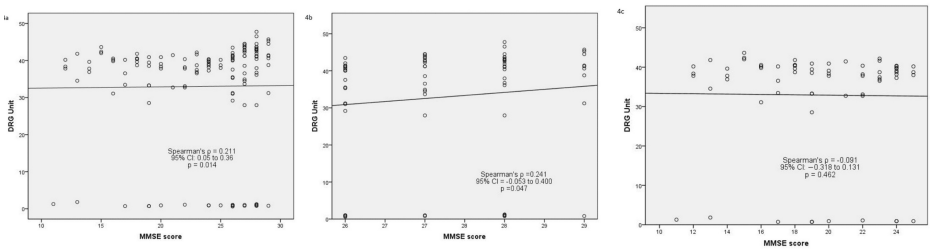


FIGURE 4: Spearman's correlation between HSV-1 IgG DRG units and MMSE scores in the overall study population (a), the group of memory loss patients without dementia (b), and the group of memory loss patients with dementia (c)

HSV-1, herpes simplex virus type 1; IgG, immunoglobulin G; MMSE, Mini-Mental State Examination.

In this study, a logistic regression model was utilized to predict dementia outcomes based on HSV-1 IgG positivity, age, and male sex. The model as a whole explained between 1.6% (Cox & Snell R-squared) and 2.2% (Nagelkerke R-squared) of the variance in dementia status and correctly classified 55.9% of cases. As shown in Table *3*, this study did not detect a statistically significant association between HSV-1 IgG seropositivity and dementia (adjusted OR=0.865, 95% CI: 0.34-2.22, p=0.763). Similarly, age (adjusted OR=0.974, 95% CI: 0.93-1.03, p=0.311) and male sex (adjusted OR=0.680, 95% CI: 0.34-1.37, p=0.283) did not show any significant association.

Predictor of dementia outcome	B	SE	Adjusted OR	95% CI	p-Value
HSV-1 IgG seropositive	-0.15	0.48	0.865	0.34-2.22	0.763
Age	-0.03	0.03	0.974	0.93-1.03	0.311
Male sex	-0.39	0.36	0.680	0.34-1.37	0.283

TABLE 3: Logistic regression analysis predicting dementia outcomes based on the predictors

Dependent variable: Dementia status (0 = memory loss patient without dementia, 1 = memory loss patient with dementia); Covariates entered: HSV-1 IgG status, Age, Sex. Statistical significance is indicated by a p-value <0.05 obtained from the binary logistic regression model.

B, regression coefficient; SE, standard error; Adjusted OR, adjusted odds ratio; CI, confidence interval; HSV-1: herpes simplex virus type 1; IgG: immunoglobulin G.

Discussion

This cross-sectional study evaluates associations between HSV-1 IgG serostatus and memory loss in patients with dementia but cannot establish temporal relationships, causality, or whether HSV-1 infection contributes to future dementia development among older patients. In this study, we did not observe a statistically significant association between previous HSV-1 exposure and memory loss in patients with dementia. However, given the limited number of HSV-1 seronegative participants and the resulting uncertainty in effect estimates, a clinically relevant association cannot be excluded.

The discrepancy between our results and previous reports of a doubled dementia risk in anti-HSV-1 IgG-positive individuals [14] may be attributed to cohort differences. Prior studies featured longer follow-up and included younger or more age-diverse participants. Because age profoundly influences dementia risk, controlling for it entirely in statistical models is challenging. The groups had similar mean ages, and no statistically significant association was found between age and memory loss in the group of patients with dementia, as observed in the logistic regression analysis. Although the groups had comparable mean ages, reducing the likelihood of substantial confounding by age, age was also adjusted for in the multivariable regression model to account for any residual confounding in this study. The mean age of patients with dementia was 74.9 years, which is in agreement with earlier research findings [15,16]. In Bangladesh, increasing life expectancy from 66 years in 2000 to 72.3 years in 2023, according to the Bangladesh Bureau of Statistics, has resulted in a growing proportion of older adults, thereby contributing to an increased burden of age-related conditions such as dementia [17]. Projections further suggest that the number of individuals living with dementia in Bangladesh will more than double by 2051, reflecting global demographic

trends [9].

Notably, this study found a much higher rate of anti-HSV-1 IgG seropositivity among male participants than among female participants in both the memory loss patients with dementia and those without dementia. In contrast, a US-based study reported no significant sex-based difference in dementia risk associated with HSV-1 or HSV-2 infection, although male patients with HSV-2 infection had a higher risk than female patients [18]. However, this difference may depend on the study design.

In the present study, we observed two apparently contrasting findings regarding HSV-1 serostatus, HSV-1 IgG values, and cognitive performance, rather than evidence of active infection-related mechanisms. HSV-1 IgG seropositivity reflects previous exposure to HSV-1 and does not directly indicate active viral replication, viral reactivation, or the timing of infection. This apparent conflict may align with previous studies that have proposed that HSV-1 may contribute to the pathogenesis of neurodegenerative diseases such as Alzheimer's disease, potentially through viral reactivation, amyloid deposition, or neuronal injury [19]. However, these mechanisms were not directly assessed in our study.

Although the group of memory loss patients with dementia had a slightly lower median HSV-1 IgG DU than the group of memory loss patients without dementia, quantitative peripheral HSV-1 IgG levels do not directly reflect viral reactivation, viral replication, or CNS involvement. The magnitude of the antibody response may vary between individuals and may not correspond to the level of HSV-1 activity in the nervous system [20]. Therefore, the observed direction of the difference should not be interpreted as evidence for or against a mechanistic role of HSV-1 reactivation in memory loss in patients with dementia.

In addition, when baseline cognitive function was assessed with the MMSE in this study, no significant association was observed between HSV-1 IgG positivity and MMSE scores among patients with memory loss and dementia. This finding is supported by a study based in Uppsala, Sweden, in which anti-HSV-1 IgG carriage was associated with worse MMSE performance [21], though future studies incorporating comprehensive neuropsychological assessments and clinical diagnostic criteria are warranted.

Although the overall sample size was adequate for the primary analyses, the number of HSV-1-seronegative participants was relatively small (n=22), which may have limited statistical power to detect modest differences between seropositive and seronegative groups and led to wide confidence intervals around the effect estimates. Therefore, the absence of statistically significant findings should not be interpreted as definitive evidence of no association.

The findings of this study should be interpreted in the context of the study population. Our participants were hospital attendees presenting with memory complaints and may therefore differ from the general elderly population of Bangladesh in terms of health status, healthcare-seeking behaviour, comorbidities, and socioeconomic characteristics. Consequently, the present findings should not be generalised to the broader elderly population of Bangladesh. Further community-based studies involving representative samples of older adults are warranted to establish the prevalence and determinants of memory complaints in the general elderly population.

An important limitation is the possibility of residual confounding. We did not systematically collect information on several potentially relevant factors, including educational and socioeconomic status, vascular and metabolic comorbidities, smoking and alcohol use, depression, medication use, apolipoprotein E genotype, other infections, and neurological diagnoses. Consequently, we could not assess or adjust for their potential effects. Furthermore, the cross-sectional design limits the ability to determine temporal relationships or causality. It remains unclear whether HSV-1 exposure preceded cognitive decline or whether other biological, gender-based demographic or vascular factors influenced both HSV-1 serostatus and cognitive outcomes. Although HSV-1 has been proposed to contribute to neurodegenerative pathways, our study assessed only peripheral HSV-1 IgG seropositivity, which indicates previous exposure rather than active infection or CNS involvement. As we did not evaluate viral activity, such as HSV DNA detection, neuroinflammatory markers, amyloid/tau pathology, neuroimaging, or brain tissue changes, mechanistic interpretations should be considered hypothesis-generating rather than demonstrated by our findings. Moreover, dementia classification was primarily based on MMSE scores, which may not capture all aspects of cognitive impairment, and some degree of misclassification cannot be excluded. Future studies incorporating comprehensive assessment of these factors and appropriately specified multivariable models are needed to determine whether the observed association remains after accounting for these potential confounders.

Conclusions

Our findings, based on hospital-attending older patients presenting with memory concerns, suggest that HSV-1 IgG seropositivity was not independently associated with dementia among patients with memory loss in Bangladesh. However, because of the cross-sectional design, hospital-based nature, limited seronegative sample size, and potential limitations of cognitive assessment, these results should be considered preliminary. Longitudinal studies with larger and more diverse populations are needed to clarify the

potential role of viral activity, CNS involvement, and neurodegenerative pathways in cognitive decline and dementia progression.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: S M Rashed Ul Islam, Md. Masud Rana

Drafting of the manuscript: S M Rashed Ul Islam, Farzana Laila

Critical review of the manuscript for important intellectual content: S M Rashed Ul Islam, Farzana Laila, Md. Masud Rana

Supervision: S M Rashed Ul Islam

Acquisition, analysis, or interpretation of data: Farzana Laila, Md. Masud Rana

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Institutional Review Board (IRB), Bangladesh Medical University (BMU) issued approval BSMMU/2024/2661 dated 06/03/24. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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