Turkish Archives of Pediatrics

REVIEW
DOI: 10.5152/TurkArchPediatr.2023.23007

The Worldwide Prevalence of Herpes Simplex Virus Encephalitis and Meningitis: A Systematic Review and Meta-Analysis

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ABSTRACT

Given the relatively high frequency of central nervous system infections and considerable mortality and morbidity reported to be caused by herpes simplex viruses among the other viral agents, having a clear knowledge about their epidemiological profile seems necessary. This systematic review and meta-analysis aimed to determine the relative frequency and prevalence of herpes simplex encephalitis and meningitis in patients tested for viral etiologies. A comprehensive systematic review was performed in PubMed, Scopus, and Web of Science databases, searching for studies on the prevalence and relative frequency of herpes simplex virus 1 and herpes simplex virus 2 encephalitis and meningitis. Seventy-one studies were included. Overall, the prevalence of herpes simplex virus encephalitis among patients tested was 8% (95% confidence interval, 6%-11%; I^2 = 98%) and the prevalence of herpes simplex virus meningitis among aseptic patients tested was 4% (95% confidence interval, 3%-7%; I^2 = 95%), and a significant difference was observed by region. The results of our subgroup analysis for herpes simplex virus encephalitis revealed a prevalence of 8% for pediatric patients and adolescents and 12% for adults. The results for herpes simplex virus meningitis showed a prevalence of 4% for pediatric patients and adolescents and 9% for adults. We observed significant differences in the frequency of herpes simplex virus 1 and herpes simplex virus 2 detection rates by region. Having high rates of missed cases due to inadequate, highly sensitive paraclinical tests performed on patients with suspected viral central nervous system infection is one of the possible factors. More studies are needed to detect the possible flaws in the process of diagnosis in different regions.

Keywords: Herpesvirus, encephalitis, meningitis, HSV-1, HSV-2

INTRODUCTION

Encephalitis is referred to as inflammation of the brain parenchyma. It has various etiologies, including viral and nonviral (autoimmune, bacterial, and fungal), with a higher prevalence of autoimmune etiology in Western societies vs. Asian countries in which infectious agents are major causes of encephalitis. Management of encephalitis is very important considering the high risk of mortality and neurological sequelae observed as a consequence of it.[1] Meningitis is another type of central nervous system (CNS) infection in which inflammation takes place in the protective layer covering the brain and spine, caused by bacterial, viral, fungal, and noninfectious etiologies. Despite their differences in terms of pathophysiology and epidemiology, clinical presentations could be so similar, resulting in potential misdiagnosis.[2]

Until now, there are more than 30 distinct viral agents detected to cause CNS infections.[1,3] Enteroviruses and herpes simplex viruses (HSVs) are among the most common viruses

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Received: January 9, 2023
Accepted: June 21, 2023
Publication Date: August 9, 2023

Cite this article as: Rohani H, Arjmand R, Mozhgani S, Shafiee A, Javad Amini M, Forghani-Ramandi M. The worldwide prevalence of herpes simplex virus encephalitis and meningitis: A systematic review and meta-analysis. *Turk Arch Pediatr.* 2023;58(6):580-587.

detected in patients with meningitis. Besides, HSVs, in contrast to enteroviruses, which usually cause benign disease, are related to higher rates of mortality and morbidity.[4] Herpes simplex virus 1 and HSV-2 have infected a great portion of the population and are able to cause various complications like visual problems, mucocutaneous lesions, and also infections of CNS like encephalitis and meningitis in all age groups.[5]

Herpes simplex virus 1 is known to prominently influence the orofacial area; on the other hand, genitalia are the most common sites of HSV-2 infection. Herpes simplex virus 1 is one of the most prevalent agents responsible for recurrent aseptic meningitis and endemic fatal encephalitis.[6] Herpes simplex viruses are the most common etiology of sporadic infectious encephalitis in adults, which, despite the use of antiviral drugs, has moderate-to-high mortality rates (5%-30% in different countries).[7] Yearly incidence of herpes simplex encephalitis (HSE) is approximately 1 per 250 000-500 000 and had increased considerably during the past 20 years.[8,9] In total, up to 75% of HSE cases would end up in death or neurological sequelae.[10]

Considering the high mortality and morbidity rates of encephalitis and meningitis and the critical role of etiological agents' detection in the effectiveness of treatment, an epidemiological assessment of encephalitis and meningitis would benefit in clinical decision-making. In addition, this information is needed for health policymaking in terms of providing efficient distribution of resources and detection of the system-level flaws in the management of disease. Unfortunately, the available systematic review studies on the subject are not enough to cover all aspects of HSV-1 and HSV-2 epidemiology. Therefore, in this study, we aimed to investigate the prevalence and relative frequency of HSV-1- and HSV-2-induced meningitis and encephalitis using the results of reported studies published between 2000 and 2021 through a systematic review and meta-analysis.

MATERIALS AND METHODS

Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed to perform the study.[11] The protocol of this study has been prospectively registered with Alborz University of Medical Sciences with the number IR.ABZUMS.REC.1400.333.

Search Strategy

We searched 3 databases, PubMed, Scopus, and Web of Science, for studies published from 2000 to 2021 using the following combination of keywords and Boolean operators; ("meningitis" OR "encephalitis") and ("Herpes Simplex Virus 1" OR "Herpes Simplex Virus 2" OR "HSV-1" OR "HSV-2" OR "Human Herpesvirus 1" OR "Human Herpesvirus 2" OR "HHV-1" OR "HHV-2") and ("incidence" OR "prevalence" OR "relative frequency" OR "Etiology"). In addition, we reviewed the references from all the retrieved articles and relevant reviews to find the studies not captured by the search.

Eligibility Criteria

We collected original studies that met the following conditions: (1) studies with the population containing herpes simplex meningitis and/or encephalitis; (2) publications reporting the incidence, prevalence, or relative frequency of meningitis and/or encephalitis due to HSV-1 and/or HSV-2; and (3) studies available on PubMed, Scopus, and Web of Science databases published between 2000 and 2021. Studies published before 2000 and after 2021, concerning etiologies other than HSV-1 and HSV-2, and with a population of nonhuman beings and review or secondary analysis articles were excluded from the study.

Article Selection, Quality Assessment, and Data Extraction

Two investigators independently reviewed all identified titles, abstracts, and article texts to determine if a study was suitable for inclusion based on the eligibility criteria. If disagreements appeared, a third investigator helped to resolve the problem. In order to assess the quality of individual studies, we used "Quality Assessment Tool for Observational, Cohort and Cross-sectional Studies" provided by the National Heart, Lung, and Blood Institute.[12] The following data were extracted from each study: the first author's last name; country where the study was conducted; publication date; study population; study design; demographic information of patients like age; population of confirmed viral cases (if present); number of confirmed cases of encephalitis (if present); number of confirmed cases of meningitis (if present); and population of cases with confirmed infection of HSV, HSV-1, and HSV-2.

Outcome Measures

The main outcome in this study was to report the prevalence of HSV encephalitis and meningitis, as assessed by a positive result of polymerase chain reaction. Furthermore, we evaluated the prevalence of HSV-induced encephalitis and meningitis among the patients with virus-positive encephalitis and meningitis. The secondary outcome was to report the prevalence of HSV-1 and HSV-2 encephalitis and meningitis.

Statistical Analysis

A random-effects meta-analysis was performed to estimate the overall prevalence of HSV encephalitis and meningitis among patients who were tested for viral etiologies. Using a logit-transformed statistical model, the quantitative values of prevalence from each study were pooled separately. We used Cochran's Q statistic and the I^2 value to assess heterogeneity. I-squared statistic value >70% indicated a high amount of heterogeneity. We performed a subgroup analysis to estimate the prevalence of our outcomes in each continent separately. Publication bias was assessed by visual inspection of the funnel plot and Egger's regression test for funnel plot asymmetry. All analyses were statistically significant with a P <.05. The analyses were performed using R-4.1.3 software and meta package (R Core Team, Vienna, Austria; available at https://www.R-project.org/).

RESULTS

Search Results

Initial search identified 1051 studies after removing duplicates and publications before 2000 (Figure 1 presents the diagram of study selection process). After title and abstract screening, 154 articles fulfilled the criteria for further investigation, of which 83 were excluded (71 papers were excluded due to case definition not meeting the criteria and 12 papers with no outcomes of interest were excluded), and hence 71 were used

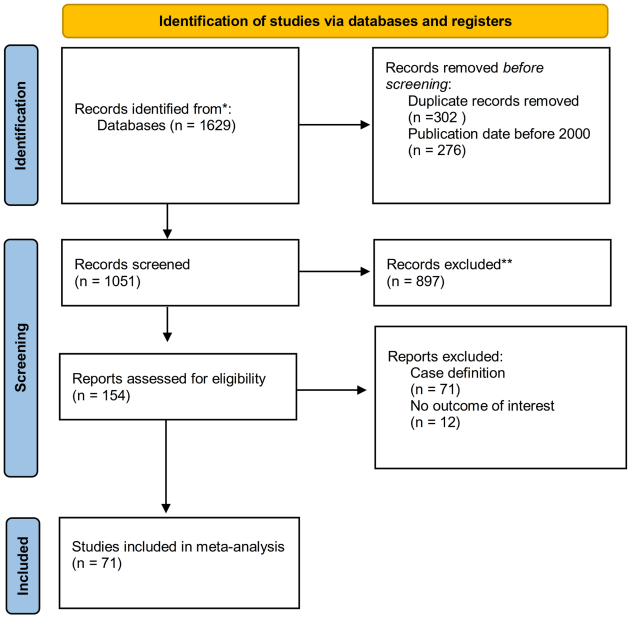

Figure 1. PRISMA flowchart of study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

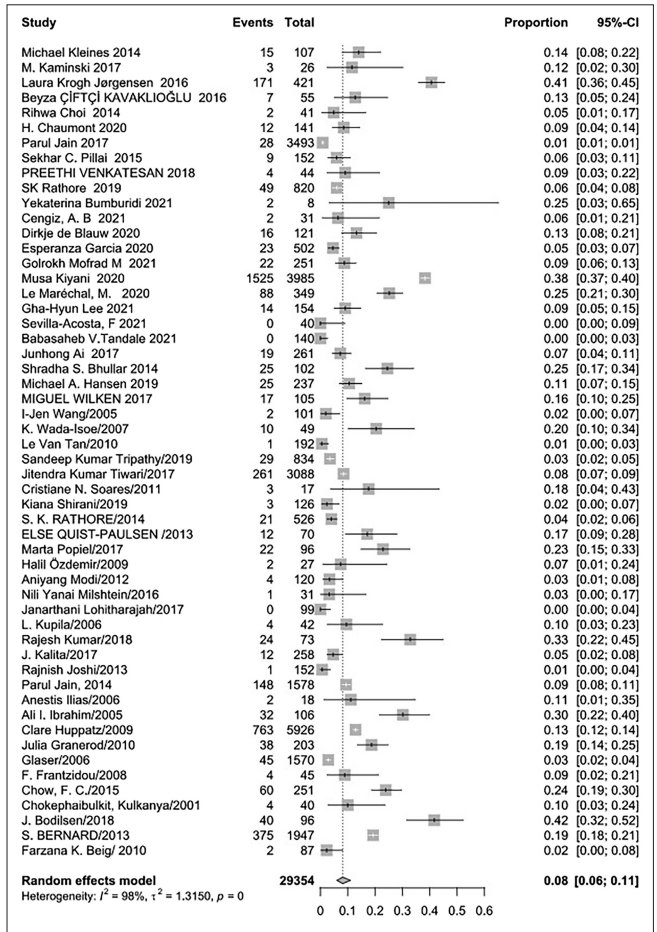

Figure 2. Forest plot of HSV encephalitis prevalence among patients tested. HSV, herpes simplex virus.

for data extraction.[4,13-83] Supplementary Table 1 presents more information on these papers.

Quality Assessment

Based on our quality analysis carried out using "Quality Assessment Tool for Observational, Cohort and Cross-sectional Studies," 42, 20, and 8 papers were detected to have good, fair, and poor quality, respectively, and the quality of 1 study was not assessed as the full text was not available.

Herpes Simplex Virus Encephalitis

Fifty-four studies with an overall sample size of 29 354 patients were included. Overall, the prevalence of HSV encephalitis among patients tested was 8% (95% CI, 6%-11%; I^2 = 98%) (Figure 2). Furthermore, the prevalence of HSV encephalitis among patients with viral encephalitis was 29% (95% CI, 22%-38%; I^2 = 95%) (Supplementary Figure 1). The prevalence of HSV-1 and HSV-2 encephalitis was 10% (95% CI, 7%-14%; I^2 = 95%) and 2% (95% CI, 1%-3%; I^2 = 70%), respectively (Figure 3A and 3B).

Herpes Simplex Virus Meningitis

Twenty-eight studies with an overall sample size of 12 529 patients were included. Overall, the prevalence of HSV meningitis among patients tested was 4% (95% CI, 3%-7%; I^2 = 95%) (Figure 4). Furthermore, the prevalence of HSV meningitis among patients with viral meningitis was 16% (95% CI, 11%-23%; I^2 = 88%) (Supplementary Figure 2). The prevalence of HSV-1 and HSV-2 meningitis was 1% (95% CI, 1%-3%; I^2 = 89%) and 4% (95% CI, 2%-8%; I^2 = 96%), respectively (Figure 5A and 5B).

Subgroup Analysis

The detailed results regarding the subgroup analysis performed to assess the pooled prevalence based on geographical location of the published studies are available in Table 1. Most of the published records within this topic were from European and Asian countries. Herpes simplex virus encephalitis and meningitis were found to be mostly prevalent in North American and European countries, with a prevalence of 16% and 14%, respectively. Asian countries had reported the lowest prevalence compared with the results of other regions with regard to HSV encephalitis (pooled prevalence: 4%). The test for between-subgroup difference showed a significant difference regarding the prevalence of these diseases in each continent.

In order to investigate the prevalence of HSV encephalitis and meningitis in different age groups, we conducted a subgroup analysis based on the included study's sample size. We defined 3 subgroups: (1) studies including only pediatric and adolescent populations, (2) studies including only adults, and (3) studies including all populations without any age limitation on their inclusion criteria. The results of our subgroup analysis for HSV encephalitis revealed a prevalence of 8% for pediatrics and adolescents, 12% for adults, and 9% for studies without any age limitation (Supplementary Figure 3). The results for HSV meningitis showed a prevalence of 4% for pediatrics and adolescents, 9% for adults, and 2% for studies without any age limitation (Supplementary Figure 4).

Publication Bias

Visual inspection of the funnel plot and Egger's regression test showed possible sources of publication bias for the prevalence

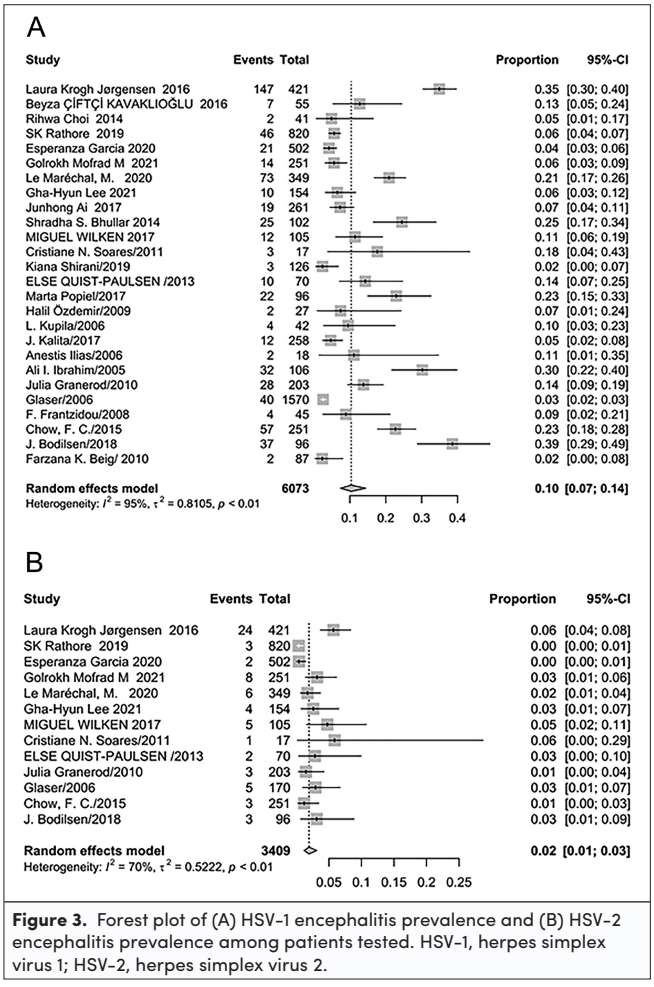

Figure 3. Forest plot of (A) HSV-1 encephalitis prevalence and (B) HSV-2 encephalitis prevalence among patients tested. HSV-1, herpes simplex virus 1; HSV-2, herpes simplex virus 2.

of HSV encephalitis (linear regression test of funnel plot asymmetry: P = .0026) and meningitis (linear regression test of funnel plot asymmetry: P = .0362) (Figure 6). Visual inspection of funnel plot and the results of Egger's regression test for

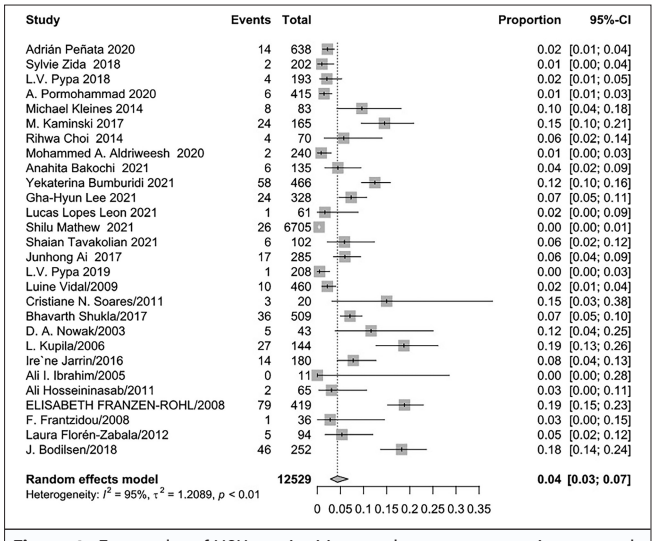

Figure 4. Forest plot of HSV meningitis prevalence among patients tested. HSV, herpes simplex virus.

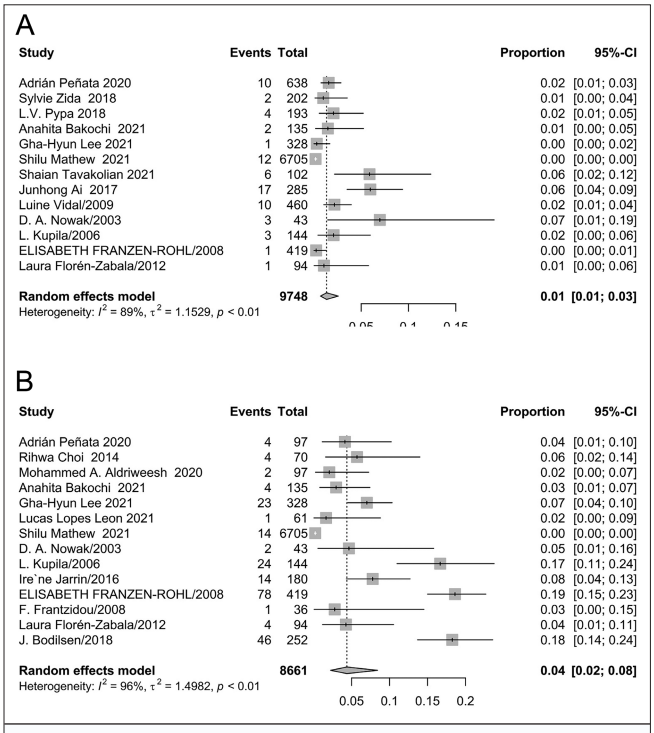

Figure 5. Forest plot of (A) HSV-1 meningitis prevalence and (B) HSV-2 meningitis prevalence among patients tested. HSV-1, herpes simplex virus 1; HSV-2, herpes simplex virus 2.

secondary outcomes did not show any asymmetry of the funnel plot (Supplementary Figures 5-10).

DISCUSSION

The present study provides estimations for the prevalence and relative frequency of HSV-1 and HSV-2 encephalitis and meningitis (using available records between 2000 and 2021) across different regions of the world. Considering the fact that a relatively high proportion of viral encephalitis and meningitis cases are caused by HSVs (especially HSV-1 and HSV-2), having clear data on their epidemiological features and essentially burden of disease seemed necessary, and to the best of our knowledge, this is the first systematic review and meta-analysis to address this issue.

Our analysis indicated that overall, 8% of encephalitis patients tested were HSV-1/2 positive, and HSV was the infectious agent responsible for 4% of aseptic meningitis cases. In addition, our results showed significant differences regionally, identifying North America with the highest frequency of HSV-positive viral encephalitis cases (16%) and Asia to be the region with the lowest rate, by a frequency of 4%. On the other hand, among patients with aseptic meningitis, Europe was detected to have the highest rate of HSV-positive cases with a prevalence of 6%, and South America and Asia were the regions with the lowest rates of HSV as the etiological factor. In comparison with HSV-2, HSV-1 was the predominant HSV found in patients with encephalitis (10% vs. 2%), and in meningitis cases, HSV-2 was the major infectious factor, with an overall prevalence of 4% in comparison to HSV-1, which was responsible for meningitis in 1% of cases.

Table 1. Subgroup Analysis Based on Geographical Region

	Number of Studies	Sample Size	Pooled Prevalence (%) (95% CI)	I^2 (%)	Test for Subgroup Differences
HSV encephalitis					
Europe	20	5729	14 (10-19)	95	$P < .01$
Asia	25	12410	4 (3-7)	93	
Oceania	2	6078	10 (6-17)	84	
North America	4	4975	16 (7-32)	99	
South America	3	162	8 (2-31)	0	
HSV meningitis					
Europe	14	2165	6 (3-11)	84	$P < .01$
Asia	9	8675	3 (1-6)	97	
North America	1	509	7 (5-10)	–	
South America	4	1179	2 (2-3)	70	

HSV, herpes simplex virus.

Since these numbers represent the relative frequency of HSV encephalitis and meningitis, the regional differences observed in this study can reflect the regional variations in the prevalence of HSV infections and other viral agents simultaneously. Based on a comprehensive systematic review on the distribution of HSV infection, the WHO African Region has the highest prevalence of HSV-2 infections followed by Region of the Americas, Western Pacific Region, European Region, South-East Asia Region, and Eastern Mediterranean Region.[84] The region with highest prevalence of HSV-1 infections is the WHO African Region, followed by Western Pacific Region, Eastern Mediterranean Region, European Region, South-East Asia Region, and Region of the Americas.[84] As HSV-2 is mainly responsible for meningitis, our results on regional meningitis etiologies are in agreement with that of the seroprevalence of HSV-2. On the other hand, the distribution of HSV-1 encephalitis is incompatible with the regional prevalence of HSV-1 infection.

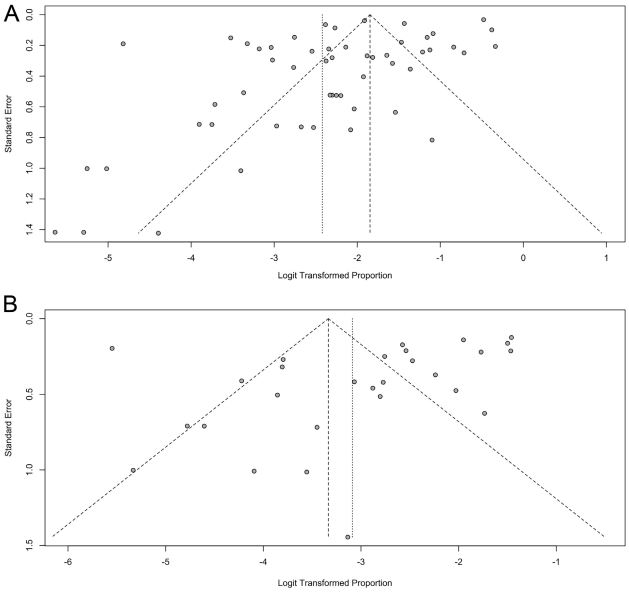

Figure 6. Funnel plot of eligible studies on prevalence of (A) HSV encephalitis and (B) HSV meningitis. HSV, herpes simplex virus.

The significant predominance of encephalitis due to Japanese encephalitis virus infection in Eastern Asia[85] may be responsible for the lower frequency of HSV encephalitis in Asian countries.

One additional factor possibly related to the difference observed in the frequency of HSV detection from region to region is potential flaws in diagnostic techniques and tools used in each study, considering the fact that regions with better economic status have overall higher rates. Due to the higher rates of mortality and neurological sequels as a result of HSV encephalitis and meningitis in contrast to other viruses, more studies are needed to test this hypothesis and to identify other possible factors causing this difference.

In the CNS, HSV infection can result in HSE, aseptic meningitis, myelitis, and radiculitis.[3] Herpes simplex encephalitis can affect the median temporal cortex and limbic and orbitofrontal regions and results in a high mortality rate of 70% in patients who do not receive treatment.[9,86] Herpes simplex virus is the first viral etiological agent of sporadic encephalitis in Western societies and possibly worldwide.[87] Among HSE cases, one-third are younger than 20 years and one-half are patients older than 50 years.[86] A hospital admission rate of 5-15 cases per 100 000 per year due to viral meningitis highlights it as an important health issue.[3] Herpes simplex virus is one of the most common viral agent detected in patients with viral meningitis.[3] Although HSV-1 is the major cause of HSE, meningitis is predominantly caused by HSV-2.[88] Recurrent aseptic meningitis (also known as Mollaret's meningitis) is the predominant form of meningitis caused by HSV-2,[86] and complications of the neurologic system are more common in the meningitis caused by HSV-2 than in other viral meningitis cases.[89] When a patient is suspected to have encephalitis, a complete workup, including complete blood count with differential, blood culture, renal and liver function tests, electrolytes and serological tests for specific organisms (varies in different populations like children and immunocompromised patients), and lumbar puncture (if not contraindicated) should be obtained to detect the etiology of disease.[90] Herpes simplex virus encephalitis cerebrospinal fluid profile can vary a lot, but in most cases, it shows moderately elevated protein and lymphocyte counts with a normal glucose level.[91] The first step in the management of a patient with encephalitis is the detection and treatment of potentially

life-threatening issues.[90] For a patient whose clinical and initial laboratory findings are suggestive of HSE, an empirical treatment with intravenous acyclovir in combination with broad-spectrum antibiotics (until the exclusion of bacterial infection) is recommended.[92,93]

Our study has several strengths. First, we thoroughly searched the databases regarding any article that assessed the etiological causes of encephalitis between 2000 and 2021. Second, we performed a meta-analysis to provide an estimate regarding the prevalence and the relative frequency of HSV encephalitis and meningitis among patients with these diseases. Furthermore, we evaluated the prevalence of HSE and meningitis among virus-positive cases of encephalitis and meningitis. Third, we performed a subgroup analysis to evaluate the prevalence in each individual region. The results of our subgroup analysis showed the low prevalence of HSE/meningitis, albeit considerable amount of records were available. Our study has also some limitations. First, the amount of heterogeneity observed was high. Second, our primary outcomes were subjected to possible publication bias. Therefore, more studies on this topic are recommended. Finally, the quality assessment of the included studies showed that several studies were not of enough quality, which should be noted by future researches on this topic.

CONCLUSION

The results of this study identified the relative frequency of HSV-1 and HSV-2 encephalitis and meningitis in patients tested for viral agents. In addition, we examined the relative frequency of HSV CNS infections by region which showed significant differences.

Data Availability: All data generated or analyzed during this study are included in this published article and its supplementary files.

Ethics Committee Approval: The protocol of this study has been prospectively registered with Alborz University of Medical Sciences with the number IR.ABZUMS.REC.1400.333.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.R., R.A.,S.M.; Design – H.R., R.A.,S.M.; Data Collection and/or Processing – A.S., M.M.; Analysis and/or Interpretation – A.S., M.M.; Literature Search – A.S., M.M.; Writing Manuscript – M.A. M.M., A.S.; Critical Review – M.A. M.M., A.S.

Declaration of Interests: The authors declare that they have no competing interests.

Funding: This study received no funding.

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Supplementary Table 1. Characteristics of the Included Studies

Author/Year	Country	Type of Study	Population	Quality
Peñata et al[61]	Colombia	Prospective study	Patients with suspected meningitis and meningoencephalitis in a tertiary referral complex in Medellín, Colombia.	Good
Zida et al[83]	France	Cohort	atients with aseptic meningitis	Poor
Pypa et al[65]	Ukraine	Prospective analysis	Patients with serous meningitis	Good
A. Pormohammad et al[4]	Iran	Cohort	Individuals with suspected meningitis	Good
Kleines et al[47]	Germany	Retrospective study	Assumed CNS infection	Good
Kaminski et al[45]	Germany	Cohort	Patients with aseptic meningitis or encephalitis/me ningoencephalitis	Good
Jørgensen et al[42]	Denmark	Cohort study	All adults hospitalized with a first-time diagnosis of HSE in Denmark during 2004–2014	Good
Çiftçi Kavaklioğlu et al[26]	Turkey	Retrospective	Patients hospitalized with a clinical syndrome of encephalitis	Goo
Choi et al[23]	Korea	Retrospective	Patients who presented with suspicion of acute viral meningitis and/or encephalitis	Fair
Chaumont et al[22]	France	Retrospective	Patients presenting an acute infectious myelitis/ encephalitis	Fair
Jain et al[40]	India	Observational cross-sectional	Patients with a clinical diagnosis of AES	Poor
Pillai et al[62]	Australia	Retrospective single-center cohort	Patients with encephalitis	Good
Venkatesan et al[77]	India	Cohort	Clinically suspected cases of viral encephalitis	Good
Rathore et al[68]	India	Cohort	Suspected AES cases	Fair
Aldriweesh et al[14]	Saudi Arabia	Retrospective cohort study	Patients who fit the definition of aseptic meningitis	Good
Bakochi et al[15]	Sweden	Cohort	Patients admitted to the hospital with the suspicion of meningitis	Poor
Bumburidi et al[20]	Kazakhstan	Cohort	Patients who met the EM case definition and had CSF laboratory studies consistent with EM were enrolled in the study	Good
Cengiz et al[21]	Turkey	Prospective study	Children hospitalized with the diagnosis of acute encephalitis	Poor
de Blauw et al[27]	Netherlands	Retrospective cohort study	Included children diagnosed with encephalitis <18 years of age admitted to 1 of the 8 pediatric intensive care units (PICU) in the Netherlands between January 2003 and December 2013	Fair
Garcia et al[31]	Mexico	A retrospective observational cross-sectional study	Patients with clinically suspected encephalitis	Good
Golrokh Mofrad et al[58]	Iran	Cohort	Patients with clinical suspicion of viral encephalitis	Poor
Kiyani et al[46]	USA	Retrospective?	Patients with a primary diagnosis of viral encephalitis	Fair
Le Maréchal et al[50]	France	Prospective cohort study	Patients presenting with a documented or suspected acute infectious encephalitis	Good
Lee et al[52]	Korea	Retrospective	The study population was composed of adults (≥16 years old) whose cerebrospinal fluid (CSF) samples were obtained for HSV-1, HSV-2, and VZV detection using PCR methods following presentation at the emergency department with the clinical suspicion of CNS infection	Good
Leon et al[53]	Brazil	A descriptive, single-center, cross-sectional study	Adult patients with viral acute neurological syndrome	Fair
Mathew et al[55]	Qatar	Retrospective	Patients with suspected meningitis	Good
Sevilla-Acosta et al[69]	Costa Rica	Prospective, observational study	Children <13 years and >1 month with the diagnosis of acute encephalitis	Fair
Tandale et al[73]	India	Cohort	AES cases suspected of viral etiologies	Fair

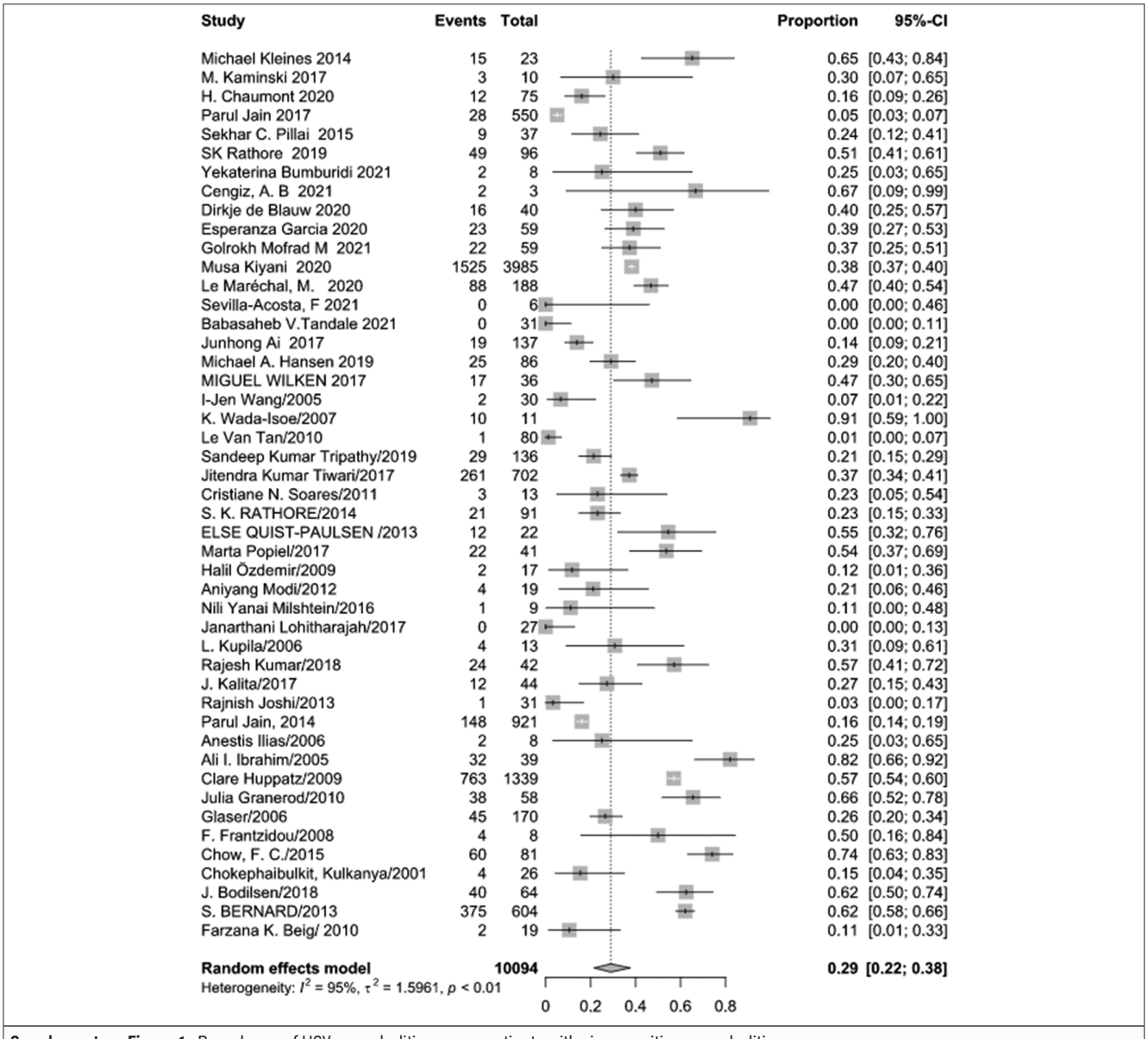
(*Continued*)

Supplementary Table 1. Characteristics of the Included Studies (Continued)

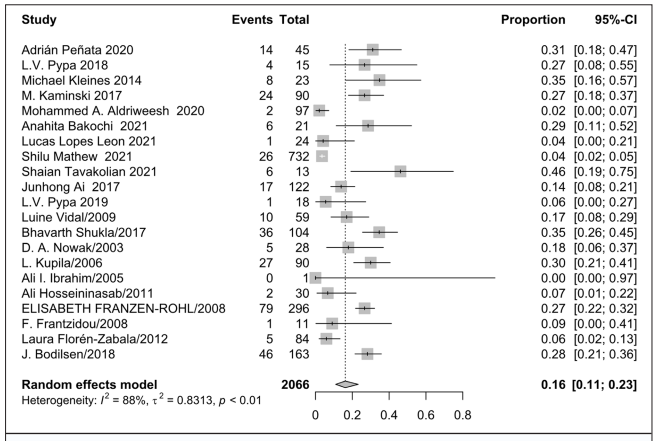
Author/Year	Country	Type of Study	Population	Quality
Tavakolian et al[74]	Iran	Cross-sectional study	Patients suffering from the loss of consciousness, seizures, muscle weakness, fever, headache, rash, and sudden severe dementia from Emam Hossin, Loghman, and Mofid Hospitals	Good
Ai et al[13]	China	Multicenter prospective	Inpatients suspected of viral encephalitis or meningitis	Good
Bhullar et al[18]	India	Retrospective	Patients with suspicion of HSE	Good
Hansen et al[34]	USA	Retrospective cohort study	Patients with confirmed encephalitis	Good
Pypa et al[64]	Ukraine	Prospective	Patients with aseptic meningitis	Good
Wilken et al[81]	Argentina	Cohort	Adult patients admitted to authors' hospital with a suspected diagnosis of encephalitis	Good
Wang et al[80]	Taiwan	Cohort	Patients diagnosed to have encephalitis had to have at least one symptom or sign of parenchymatous brain dysfunction	Good
Wada-Isoe et al[79]	Japan	Cross-sectional	Patients diagnosed with acute encephalitis	Poor
Vidal et al[78]	Brazil	Cohort	Children and adult patients clinically diagnosed with meningitis	Good
Van Tan et al[82]	Vietnam	Cohort	Children with suspected acute encephalitis of viral origin, based on the clinical judgment of admitting physicians	Good
Tripathy et al[76]	India	Cohort	Children patients clinically diagnosed with encephalitis	Fair
Tiwari et al[75]	India	Cohort	Patients clinically diagnosed with acute Encephalitis	Good
Cristiane N. Soares et al[72]	Brazil	Review	Adults and adolescents with diagnoses of viral encephalitis or meningitis	Poor
Shukla et al[71]	USA	Cohort	Children and adults patients clinically diagnosed with aseptic meningitis	Good
Shirani et al[70]	Iran	Cross-sectional	Patients with the clinical diagnosis of HSV-1 meningoencephalitis	Fair
Rathore et al[67]	India	Cohort	AES cases admitted to the tertiary-care referral hospitals in Odisha	Good
Quist Paulsen et al[66]	Norway	Cohort	Adult patients hospitalized and diagnosed with infectious encephalitis	Fair
Popiel et al[63]	Poland	Cohort	Patients meeting the initial criteria for encephalitis	Good
Özdemir et al[60]	Turkey	Cohort	Children patients diagnosed with encephalitis	Fair
Nowak et al[59]	Germany	Cohort	Adult patients with acute aseptic meningitis	Good
Modi et al[57]	India	Cross-sectional	Patients aged 14 years or above who were admitted with AFE	Fair
Milshtein et al[56]	Israel	Cohort	Hospitalized children patients with the diagnosis of acute encephalitis	Good
Lohitharajah et al[54]	Sri Lanka	Cross-sectional	Patients with a clinical syndrome of encephalitis/me ningoencephalitis	Good
Kupila et al[49]	Finland	Cohort	All consecutive immunocompetent adults treated for acute aseptic meningitis or encephalitis	Good
Kumar et al[48]	India	Cohort	Children patients fulfilling the criteria for AES	Fair
Kalita et al[44]	UK	Cohort	Children patients with the diagnosis of AIES	Good
Joshi et al[43]	India	Cohort	Hospitalized adults with AES	Good
Jarrin et al[41]	France	Cohort	Patients fulfilling the criteria for aseptic meningitis with or without encephalitis.	Good
Jain et al[39]	India	Cohort	Patients with diagnosed acute encephalitis syndrome	Good
Ilias et al[38]	Greece	Cohort	Children hospitalized for encephalitis	Fair
Ibrahim et al[37]	Germany	Cross-sectional	Patients clinically diagnosed with encephalitis/ meningitis	Fair
Huppatz et al[36]	Australia	Cohort	Hospitalized patients with encephalitis	Poor
Hosseininasab et al[35]	Iran	Cohort	Children meningitis patients with a clinical diagnosis	Good
Granerod et al[33]	England	Cohort	Patients of all ages and with symptoms suggestive of encephalitis	Good
Glaser et al[32]	USA	Cohort	Encephalitis patients in California Project	Fair

(*Continued*)

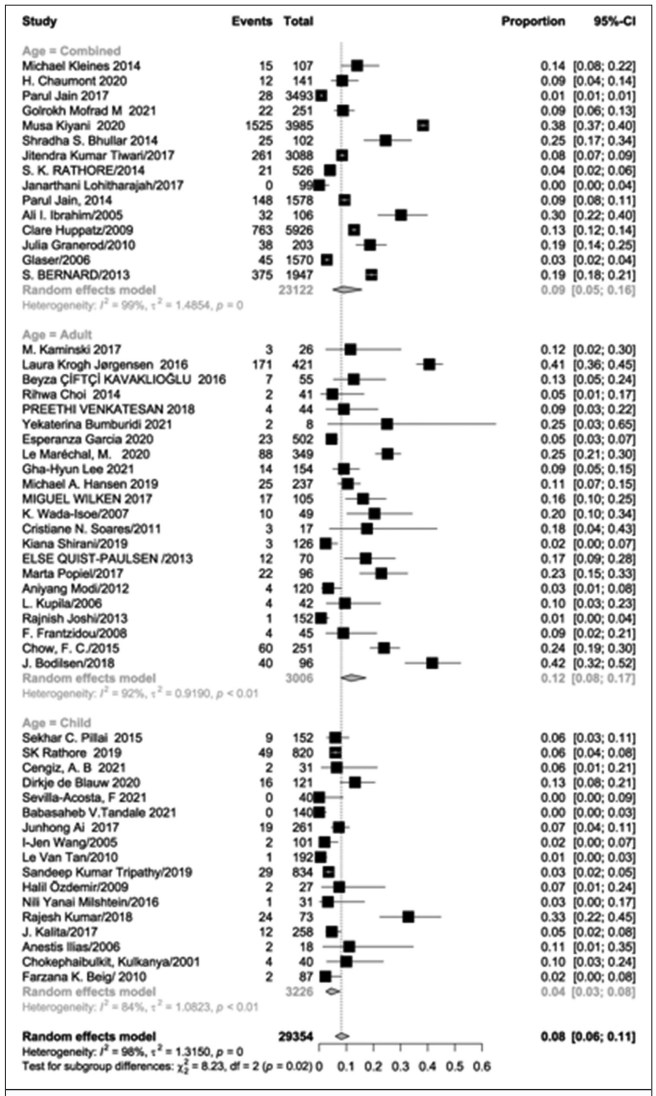
Supplementary Table 1. Characteristics of the Included Studies (Continued)				
Author/Year	**Country**	**Type of Study**	**Population**	**Quality**
Franzen-Rohl et al[30]	Sweden	Cohort	Patients clinically diagnosed with meningitis	Fair
Frantzidou et al[29]	Greece	Cohort	Adults patients presented with aseptic meningitis or encephalitis	Fair
Florén-Zabala et al[28]	Spain	Cohort	Adults patients who presented with aseptic meningitis	NA
Chow et al[25]	USA	Cohort	Adults patients who presented with TL encephalitis	Good
Chokephaibulkit et al[24]	Thailand	Cohort	Children hospitalized for illnesses suggestive of encephalitis or meningoencephalitis	Fair
Bodilsen et al[19]	Denmark	Cohort	Adults patients clinically diagnosed with meningitis or encephalitis	Good
Bernard et al[17]	France	Cohort	–	Good
Beig et al[16]	India	Cohort	Children with acute viral encephalitis	Good



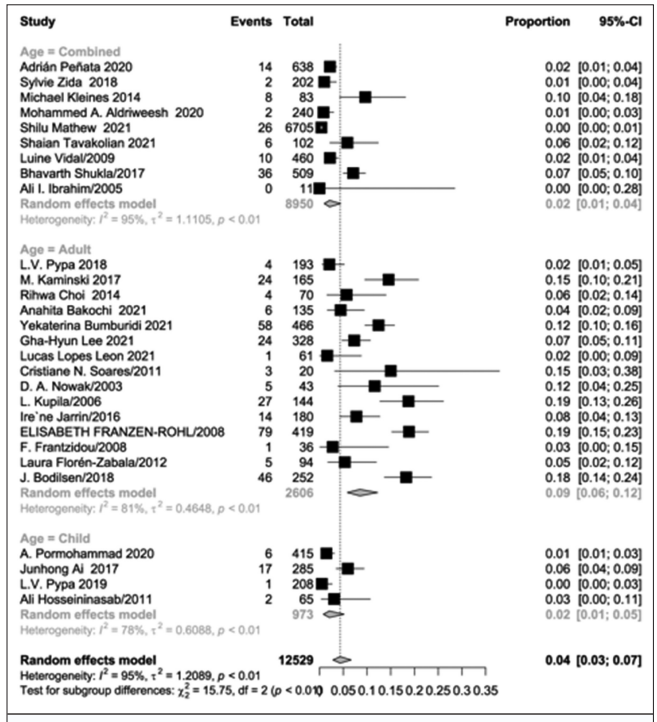
Supplementary Figure 1. Prevalence of HSV encephalitis among patients with virus-positive encephalitis.



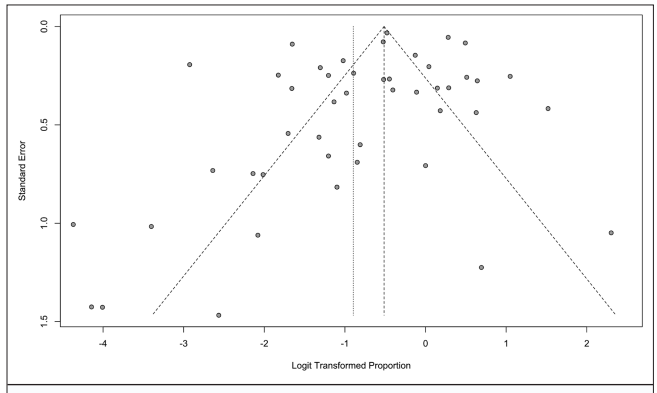
Supplementary Figure 2. Prevalence of HSV meningitis among patients with virus-positive meningitis.



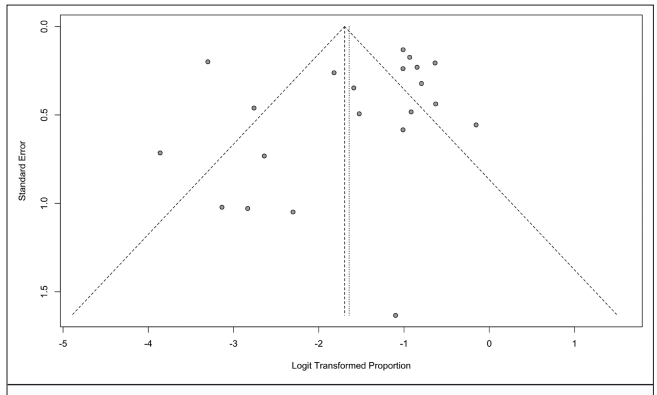
Supplementary Figure 3. Subgroup analysis for the prevalence of HSV encephalitis in different age groups.



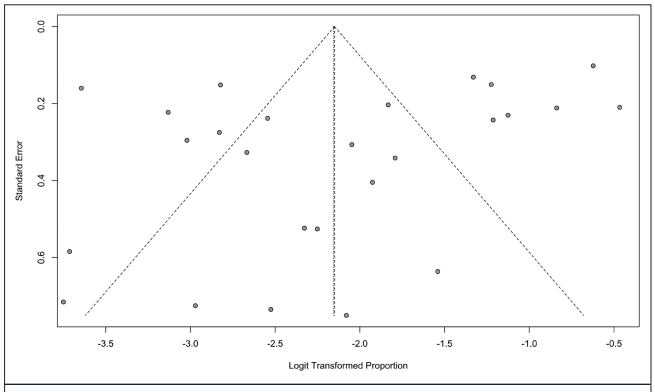
Supplementary Figure 4. Subgroup analysis for the prevalence of HSV meningitis in different age groups.



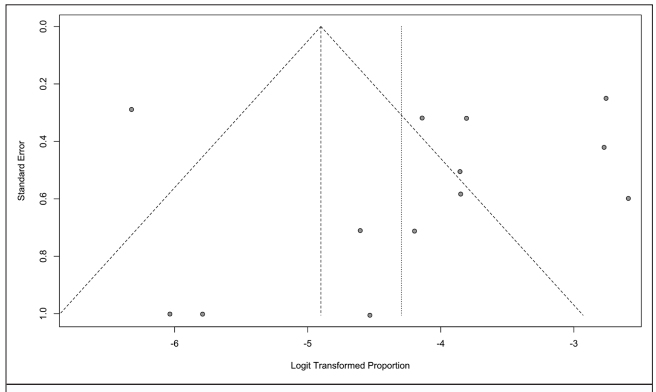
Supplementary Figure 5. Funnel plot for the prevalence of HSV encephalitis among patients with virus-positive encephalitis.



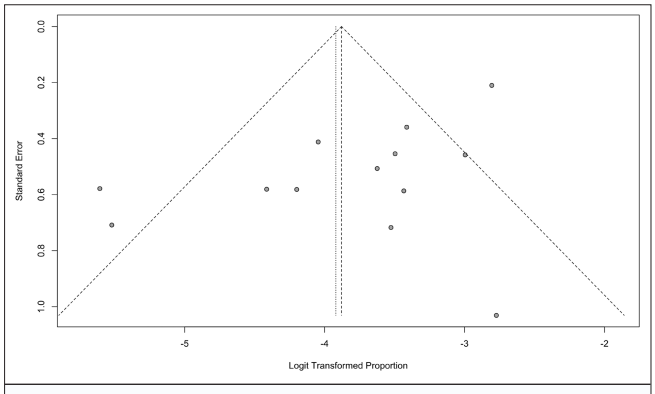
Supplementary Figure 6. Funnel plot for the prevalence of HSV meningitis among patients with virus-positive meningitis.



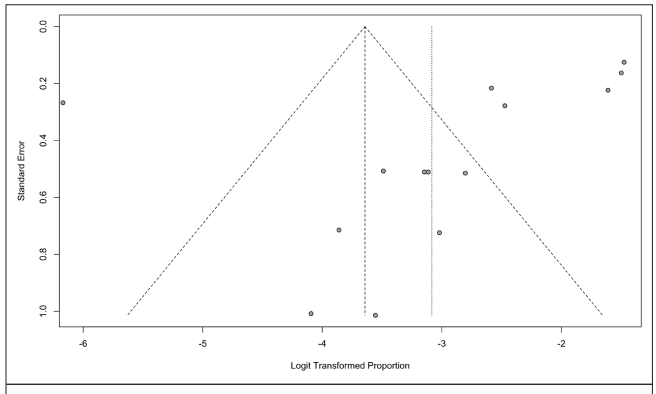
Supplementary Figure 7. Funnel plot for the prevalence of HSV-1 encephalitis.



Supplementary Figure 9. Funnel plot for the prevalence of HSV-1 meningitis.



Supplementary Figure 8. Funnel plot for the prevalence of HSV-2 encephalitis.



Supplementary Figure 10. Funnel plot for the prevalence of HSV-2 meningitis.