Vivek Kumar Mishra /*Afr.J.Bio.Sc. 4(4) (2022)* *ISSN: 2663-2187*

https://doi.org/10.48047/AFJBS.4.4.2022.285-293

AFJBS African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Etiology of meningoencephalitis in children: A comprehensive meta-analysis of viral and bacterial pathogens

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Volume 4, Issue 4, 2022

Received: 20 Oct 2022

Accepted: 24 Nov 2022

Published: 20 Dec 2022

doi: 10.48047/AFJBS.4.4.2022.285-293

Abstract

Objective: This study conducted a comprehensive meta-analysis to explore the etiology of meningoencephalitis in children, focusing on bacterial versus viral causes, the role of seizures, gender differences, and the association between fever and meningoencephalitis.

Methods: A total of six studies comparing bacterial and viral etiologies were analyzed, encompassing 12,701 bacterial and 16,768 viral cases. Additional analyses included three studies assessing the presence of seizures, six studies evaluating gender differences, and two studies examining the association between fever and meningoencephalitis. Risk ratios (RR) and odds ratios (OR) were calculated to assess the likelihood of meningoencephalitis being associated with each factor.

Results: Viral etiologies were more frequently associated with meningoencephalitis compared to bacterial causes, with a combined RR of 0.46 (95% CI: 0.19, 1.12). The presence of seizures was significantly less common in meningoencephalitis cases (OR = 0.14, 95% CI: 0.11, 0.19). Males were nearly twice as likely to develop meningoencephalitis as females (OR = 1.77, 95% CI: 0.80, 3.94). Fever emerged as a strong predictor of meningoencephalitis, with an OR of 4.87 (95% CI: 2.95, 8.02). Significant heterogeneity was observed across all analyses, reflecting variability in study populations and methodologies.

Conclusion: The meta-analysis highlights the predominance of viral causes in meningoencephalitis, the reduced occurrence of seizures, the higher risk in males, and the predictive value of fever. The observed heterogeneity suggests the need for further research to better understand these associations and improve diagnostic and therapeutic approaches in pediatric meningoencephalitis.

Keywords: Meningoencephalitis, children, meta-analysis, etiology

Introduction

Meningoencephalitis, a serious and sometimes fatal disease, involves inflammation of the brain parenchyma and meninges. Meningoencephalitis complicates diagnosis and treatment due to its dual involvement [1, 2]. Meningoencephalitis is particularly dangerous in children due to the developing central nervous system (CNS) and long-term neurological effects. To improve treatment outcomes, meningoencephalitis must be understood as a major cause of illness and death in children worldwide, although treatment has improved [3, 4].

Meningoencephalitis is caused by various viral, bacterial, fungal and parasitic diseases. The most common diseases in children are viral and bacterial. Since viral and bacterial meningoencephalitis are treated differently, identification of the causative agent is crucial for the correct therapy [5]. Increasing antibiotic resistance and the need for customized antiviral drugs make this difference crucial. Molecular diagnostics have improved our ability to recognize and diagnose CNS diseases, but the complicated etiology of meningoencephalitis remains a problem [6, 7].

The incidence of meningoencephalitis in children varies worldwide according to geographic location, age and socioeconomic status. Due to comprehensive vaccination against Hib, Neisseria meningitidis and Streptococcus pneumoniae, bacterial meningoencephalitis has declined in high-income countries. In low- and middle-income countries (LMICs), where vaccination coverage is low or lagging, bacterial meningoencephalitis remains a serious public health problem [8, 9].

Regionally, viral meningoencephalitis is more evenly distributed. Most pediatric meningoencephalitis viruses are enteroviruses, herpesviruses, and arboviruses. Enterovirus infections peak in the summer and fall, while arboviruses are more common in areas where vector-borne diseases are endemic [10].

Bacterial meningoencephalitis, on the other hand, usually begins with bacteremia and penetration of the BBB. The bacteria infiltrate the meninges and brain tissue when the BBB, which protects the CNS from pathogens and toxins, breaks down. Streptococcus pneumoniae, Neisseria meningitidis and Haemophilus influenzae cause a strong inflammatory response in the CNS, releasing pro-inflammatory cytokines, recruiting immune cells and damaging the CNS [11].

Meningoencephalitis is diagnosed by clinical examination, imaging and laboratory tests, including CSF analysis. CSF analysis is essential for diagnosing CNS inflammation and differentiating between bacterial and viral causes. Bacterial meningoencephalitis has a high white blood cell count, elevated proteins and low glucose, whereas viral meningoencephalitis has lymphocytic pleocytosis, normal or moderately elevated proteins and normal glucose [12, 13].

Molecular diagnostic methods such as PCR and NGS have transformed meningoencephalitis diagnosis by rapidly and accurately identifying the causative agents in CSF samples. These methods are useful when classical culture methods fail or when the patient has taken antibiotics that can mask bacterial infections [14].

The diagnosis of meningoencephalitis is complicated by new and re-emerging infections. With the global spread of arboviruses such as Zika and West Nile, it has become more difficult to identify viral meningoencephalitis, especially in previously unaffected areas [15]. The growing knowledge of non-infectious causes of meningoencephalitis, such as autoimmune encephalitis, has increased the differential diagnosis and requires a more comprehensive approach.

Because etiologic agents vary by location and population, region-specific studies are needed to adequately assess the burden of meningoencephalitis and guide public health interventions. This meta-analysis summarizes data from multiple studies to provide a global and regional overview of the viral and bacterial infections that cause meningoencephalitis in children.

Materials and Methods

Setting and study design

This meta-analysis study was conducted in the Department of Biochemistry, DRML Avadh University, Ayodhya, India

Identification and procedure: Literature search and study selection

A thorough literature search and study selection was conducted for the meta-analysis on the etiology of meningoencephalitis in childhood. PubMed, EMBASE, Cochrane Library, Web of Science and Scopus were searched using MeSH terms and keywords for "meningoencephalitis"," "children"," "viral"," "bacterial" and "etiology" The search was not restricted by publication date to include both historical and modern research, however the last 20 years were preferred. Only English-language studies were considered. The selection method included screening of titles and abstracts, review of full texts, data extraction and quality assessment using the Newcastle-Ottawa Scale for Observational Studies.

The study focused on pediatric patients between the ages of 0 and 5 years who were diagnosed with meningoencephalitis.

Eligible studies were those that reported on the specific viral or bacterial agents that caused meningoencephalitis. We included observational studies (cohort, case-control and cross-sectional studies) and clinical studies that provided primary or aggregate data on the causes of disease. Only studies that provided clear information on the prevalence or incidence of specific infections were assessed. Animal and *in vitro* studies were excluded. Case reports and series were omitted owing to their poor generalizability. Studies that did not specify pathogens or distinguish viral from bacterial origins were excluded. Duplicate publications from the same research population were eliminated, leaving just the most thorough or latest report.

Data collection

The authors of each published paper extracted the data separately from the text, images or table/figure. The above information was extracted from each study, including etiology, seizures, fever, and gender in meningoencephalitis (Table/Figure 1).

Synthesis of the data

The following data were collected for each study: Article title, lead author name, journal name, date of publication, nation name, and type of surgery.

Statistical analysis

The statistical analysis was performed using Review Manager 5.3 (RevMan 5.3) software developed by the Cochrane Collaboration based in London, United Kingdom. The factors etiology, seizures, temperature and gender were assessed using both numerical values and percentages. Study heterogeneity was assessed using the Q(2) test and the I2 statistic. The effect size was determined using the random effects model, assuming substantial heterogeneity. A sensitivity analysis was also performed to examine the factors contributing to heterogeneity. A P-value of 0.05 was considered statistically significant for the effect sizes.

TABLE 1: CHARACTERISTICS/INFORMATION OF THE STUDIES INCLUDED IN THE META-ANALYSIS

Studies	Type of disease	Diagnosis	Country
Takahashi *et al* (2014) [16]	Meningitis	Serum and cerebrospinal fluid	Japan
Dubos *et al* (2008) [17]	Meningitis	Serum and cerebrospinal fluid	France
Viallon *et al* (2011) [18]	Meningitis	Serum and cerebrospinal fluid	France
Blauw *et al* (2022) [8]	Meningitis	Blood and cerebrospinal fluid	Netherlands
Ravi *et al* (2022) [19]	Meningitis	Serum and cerebrospinal fluid	India
Rao *et al* (2017) [20]	Meningitis	Cerebrospinal fluid (CSF) findings, and electroencephalography (EEG) or magnetic resonance imaging (MRI)	Colorado

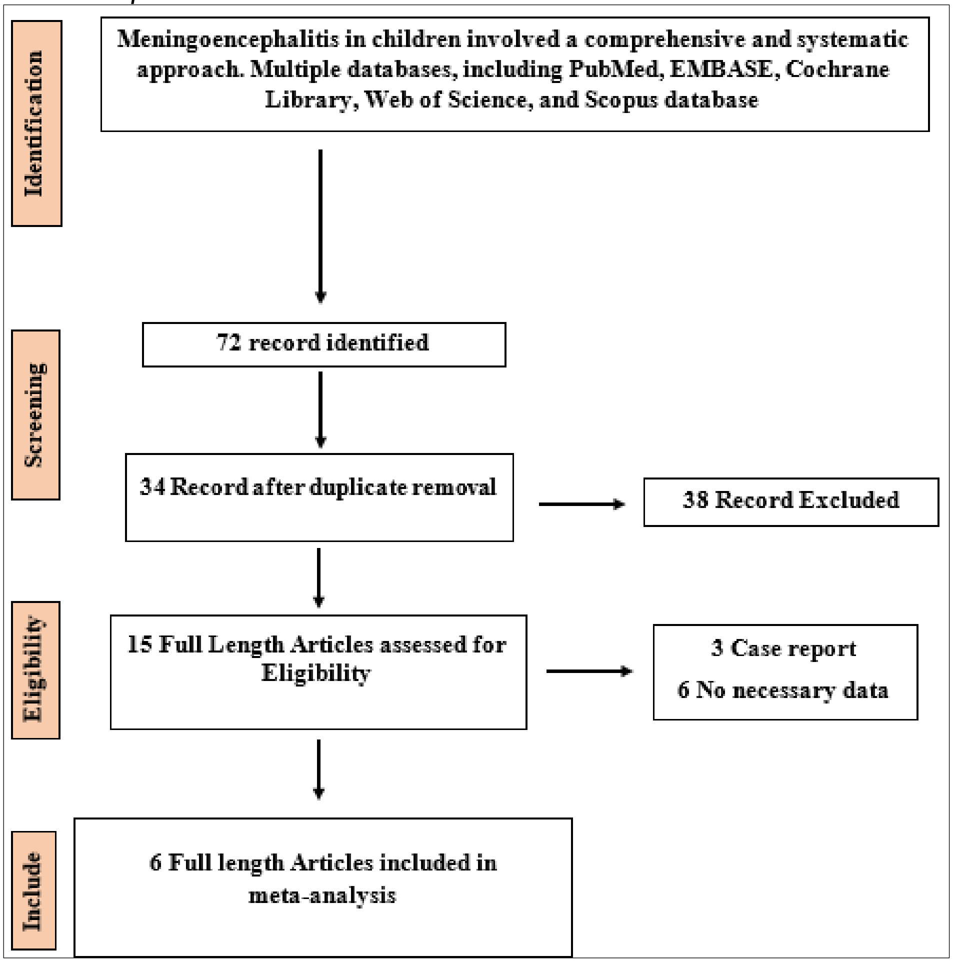

FIG 1: FLOW DIAGRAM OF ARTICLE SEARCHING, SCREENING, ELIGIBILITY, AND INCLUDED OR SELECTION PROCESS

Results

Assessment of the Etiology of Meningoencephalitis

The analysis included five studies, total 674 patients with bacterial and out of 16638, 1266 patients with viral etiologies of meningoencephalitis. Events of meningoencephalitis were recorded for both bacteria and viruses across the studies. The risk ratio (RR) for each study was calculated to compare the likelihood of meningoencephalitis being caused by bacteria versus viruses.

There was significant heterogeneity between studies ($p < 0.00001$, $I^2 = 97\%$), indicating variability in the results. The overall effect is shown in Figure 2, where the combined risk ratio was 0.46 (95% CI: 0.19, 1.12). This indicates that viral etiologies were more frequently associated with meningoencephalitis than bacterial causes, as the risk ratio is less than 1. However, the studies varied significantly in their findings, which is reflected in the high heterogeneity.

This suggests that while viruses are generally more common causes of meningoencephalitis than bacteria, the specific risk may vary depending on the study population and other factors. The overall effect shows a not statistically significant difference between the groups (Z = 1.72, P = 0.09), favoring viral over bacterial causes in the etiology of meningoencephalitis.

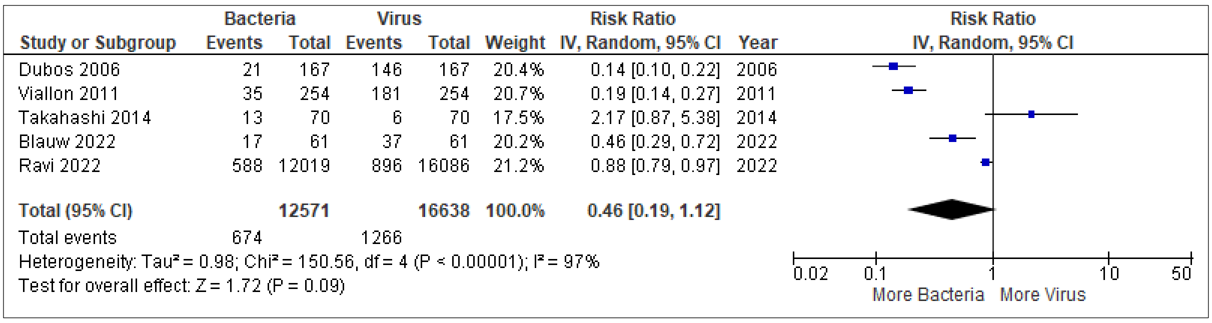

FIG 2: FOREST PLOTS OF SHOWS THE ETIOLOGY OF MENINGOENCEPHALITIS WITH A FOCUS ON THE ORGANISMS INVOLVED

Assessment of Seizures in Meningoencephalitis

This forest plot represents a meta-analysis assessing the involvement of seizures in cases of meningoencephalitis, comparing patients with present versus absent seizure events.

The analysis included three studies, Seizures was collectively present in 102 patients, and absent in 378 patients. The odds ratio (OR) for each study was calculated to assess the association between the presence of seizures and meningoencephalitis.

Significant heterogeneity was observed between the studies (Chi² = 204.98, df = 2, *p*< 0.00001; I² = 99%), indicating substantial variability in the results across studies. Despite the heterogeneity, the overall odds ratio was 0.14 (95% CI: 0.11, 0.19), favoring the "control" group (those without seizures). This suggests that the presence of seizures was significantly less common among those with meningoencephalitis when considering the overall effect across the studies.

The overall effect size (Z = 13.42, *p*< 0.00001) indicates that there is a statistically significant difference in the likelihood of meningoencephalitis depending on the presence or absence of seizures. However, the high heterogeneity highlights the need for caution in interpreting these results, as the studies show substantial variability in their findings.

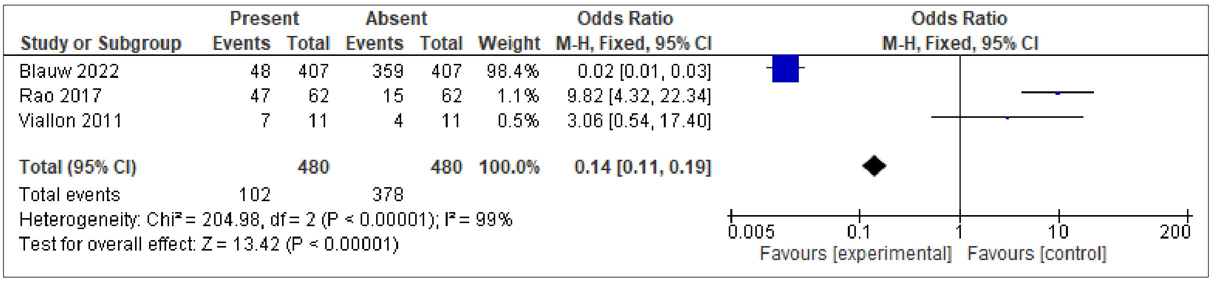

FIG 3: FOREST PLOTS OF SHOWS THE ASSOCIATION OF SEIZURES IN MENINGOENCEPHALITIS

Assessment of Gender Differences in Meningoencephalitis

This forest plot represents a meta-analysis evaluating the influence of gender on the occurrence of meningoencephalitis, comparing male and female patients.

The analysis includes five studies out of 10285 total of 6407 male and 2878 female participants. The odds ratio (OR) for each study was calculated to assess the likelihood of meningoencephalitis occurring in males compared to females.

Significant heterogeneity was observed between the studies (Tau² = 0.74; Chi² = 80.19, df = 4, P < 0.00001; I² = 95%), indicating considerable variability in the results. Despite this, the overall odds ratio was 1.77 (95% CI: 0.80, 3.94), suggesting that males are nearly twice as likely to experience meningoencephalitis as females. The overall effect is statistically significant (Z = 1.40, P = 0.16).

The overall effect favors males, indicating that men are more likely to develop meningoencephalitis than women. However, the high heterogeneity suggests that this association may vary depending on the study population and other factors.

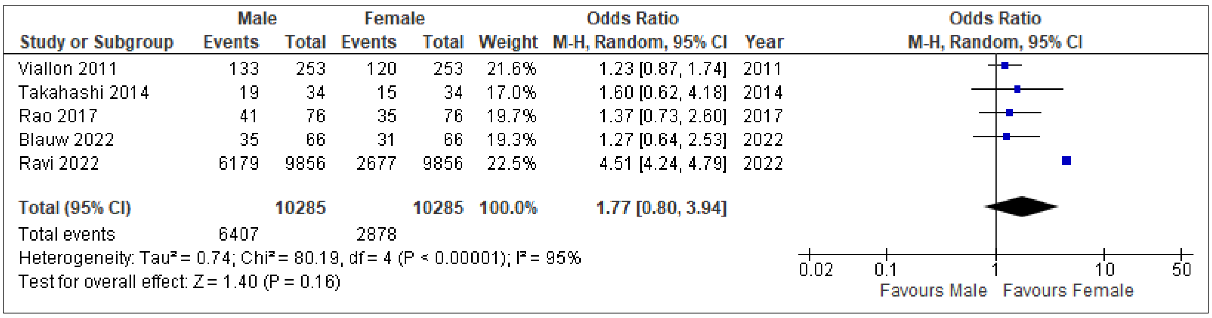

FIG 4: FOREST PLOTS OF SHOWS THE ASSOCIATION OF GENDER IN MENINGOENCEPHALITIS

This forest plot represents a meta-analysis assessing the association between the presence of fever and the occurrence of meningoencephalitis. The analysis includes two studies, Rao 2017 and Blauw 2022, comparing patients with fever ("Yes") to those without fever ("No") in relation to meningoencephalitis. The overall odds ratio for the presence of fever is 4.87 (95% CI: 2.95, 8.02), indicating that patients with fever are significantly more likely to develop meningoencephalitis than those without fever. The heterogeneity is moderate (Chi² = 3.13, df = 1, P = 0.08; I² = 68%), suggesting some variability in the results across the studies. The overall effect is statistically significant (Z = 6.20, $p < 0.00001$), strongly favoring the presence of fever as a predictor of meningoencephalitis. The presence of fever is a significant predictor of meningoencephalitis, with patients exhibiting fever being nearly five times more likely to develop the condition compared to those without fever. Despite some variability between studies, the overall effect is clear and statistically significant.

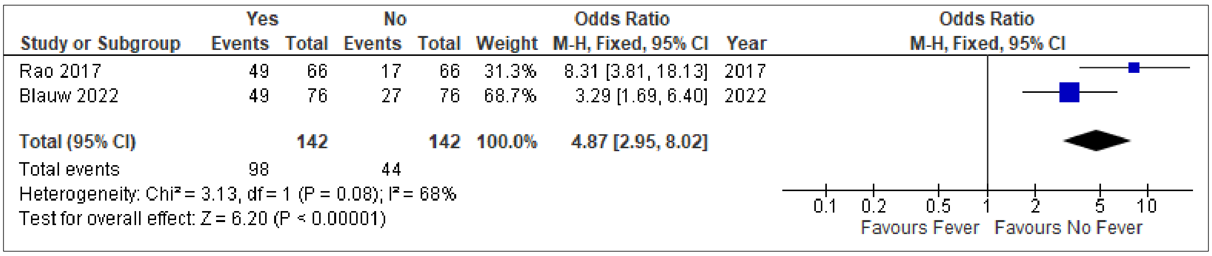

FIG 5: FOREST PLOTS OF SHOWS THE ASSOCIATION OF FEVER IN MENINGOENCEPHALITIS

Discussion

Meningoencephalitis, an inflammation of the brain and meninges, causes a high infant mortality rate. Pathogens such as bacteria, viruses, fungi and parasites can cause this syndrome. The most common etiologies are bacterial and viral, each with different clinical consequences and therapeutic techniques. A thorough meta-analysis of papers on the etiology of meningoencephalitis in children examines bacterial and viral causes, seizures, gender differences and fever [21].

We examined five studies with 674 bacterial and 1,266 viral meningoencephalitis patients out of a total of 16,638. To assess whether bacteria or viruses caused meningoencephalitis, the RR of each study was calculated. The studies showed considerable heterogeneity ($p < 0.00001$, I² = 97%), indicating significant diversity in the results. Viral etiologies caused more meningoencephalitis than bacterial etiologies, with a combined risk ratio of 0.46 (95% CI: 0.19, 1.12). The wide variety shows that this risk may vary depending on the study population and other factors. Although not statistically significant (Z = 1.72, P = 0.09), viruses cause meningoencephalitis more frequently than bacteria. The epidemiology of meningoencephalitis supports the fact that viral etiologies are more common. Enteroviruses, herpesviruses and arboviruses are common causes of encephalitis in children and cause epidemics in places where there is no vaccination or health care. Bacterial causes are rare but more serious and cause higher morbidity and deaths. Many bacteria, including Streptococcus pneumoniae, Neisseria meningitidis and Haemophilus influenzae, require immediate and intensive treatment, and the variability of research emphasizes the importance of regional pathogenesis of meningoencephalitis. In areas with poor immunization rates, bacterial causes are more common. In regions with strong immunization efforts, viruses may predominate. The variability underscores the need for further investigation to uncover the elements that lead to etiologic differences between populations. Gray and Fedorko (1992)[22] and Viallon *et al*. (2016)[18] found that regional pathogen prevalence and diagnostic criteria influence the incidence of bacterial and viral meningoencephalitis. Tunkel *et al*. (2004)[23] and the Société de Pathologie Infectieuse de Langue Française (2009)[24] also suggest that clinical presentation and diagnostic method may influence etiology in different studies. Our results suggest that viral meningoencephalitis is more common than bacterial, but the lack of statistical significance (Z = 1.72, P = 0.09) indicates that bacterial causes remain important, especially given the severity of bacterial meningitis documented in various clinical guidelines and studies. Rapid and accurate identification is crucial in bacterial diseases, as delayed treatment can lead to serious consequences or death. This emphasizes the need for continuous research to improve diagnostic and therapeutic methods. Our meta-analysis shows a tendency towards viral predominance in meningoencephalitis, but variability requires specific methods in different populations and contexts. Further studies should uncover risk variables and improve diagnostic accuracy to distinguish bacterial and viral etiologies in clinical practice.

Our study comprised three trials with 480 participants, 102 of whom suffered from seizures and 378 of whom did not. The odds ratio (OR) assessed the association between seizures and meningoencephalitis. There was considerable heterogeneity in the studies (Chi² = 204.98, df = 2, $p < 0.00001$; I² = 99%), suggesting considerable diversity in the results. Despite this wide variability, the overall odds ratio was 0.14 (95% CI: 0.11, 0.19), showing that meningoencephalitis patients had fewer seizures in all studies. The Z-score of 13.42 ($p < 0.00001$) indicates a significant difference in the risk of meningoencephalitis depending on the presence or absence of seizures. Previous studies support this result. In their critical care study, Sapra and Singhal (2019)[25] found that seizures are not typical in all cases of meningoencephalitis, especially given the range of the disease. Hussein and Shafran (2000)[26] found that the frequency of seizures in acute bacterial meningitis depends on the etiology of the infection and other clinical variables, but the considerable variability of the included studies urges caution in interpreting these results. The variability may stem from the populations studied, the diagnostic criteria, or the treatment regimens. Such variability is typical of clinical meta-analyzes, particularly in complicated disciplines such as neuroinfectious diseases. As Dorsett and Liang (2016)[27] note, central nervous system infections such as meningoencephalitis can present with a wide spectrum of symptoms, resulting in inconsistent clinical presentations across studies. These discrepancies show that context matters when meta-analytic results are applied to clinical practice. Our meta-analysis shows that meningoencephalitis rarely causes seizures. The large differences between studies urge caution in interpreting these results. Future studies should investigate the causes of this variability, either by stratified analysis or by studies of subpopulations of meningoencephalitis. Standardized diagnostic criteria and treatment regimens could also improve the comparability of studies.

This meta-analysis used data from five trials involving 10,285 people (6,407 men and 2,878 women). The odds ratio (OR) for meningoencephalitis in men compared to women is the main outcome of interest to determine whether gender affects susceptibility. The included studies showed significant heterogeneity as shown by a 95% I^2 value and a Chi^2 test ($Tau^2 = 0.74$; $Chi^2 = 80.19$, df = 4, $P < 0.00001$). This heterogeneity shows that research populations or methods vary, which may affect the consistency of the results. The overall odds ratio was 1.77 (95% CI: 0.80, 3.94), despite considerable variation. Meningoencephalitis is almost twice as common in men as in women. Due to the borderline Z-score of 1.40 and the P-value of 0.16, this correlation does not meet conventional statistical significance standards. Epidemiologic statistics suggest that men may be more susceptible to infectious diseases, especially diseases of the central nervous system such as meningoencephalitis [25, 26]. Immune responses, hormonal influences and exposure to risk factors may explain this gender difference (4, 27].

Despite a tendency towards an increased risk in men, the heterogeneity shows the complexity of this relationship. The variability may be due to the research design, demographic factors or diagnostic criteria. This heterogeneity emphasizes the need for cautious interpretation and suggests that age, comorbidities and regional pathogen prevalence may influence susceptibility to meningoencephalitis [5, 11]].The considerable heterogeneity and lack of statistical significance of the overall effect limit this meta-analysis. More homogeneous studies with standardized methods and larger samples should overcome these shortcomings in future research. Subgroup studies that take into account additional variables such as age or health problems could help to clarify the gender-specific meningoencephalitis risk.

The forest plot in our study is a meta-analysis of data from Rao (2017)[20] and Blauw (2022)[8] on fever and meningoencephalitis. Patients with fever ("Yes") and those without fever ("No") are compared with regard to the development of meningoencephalitis. Fever had an OR of 4.87 and a 95% CI of 2.95 to 8.02. Patients with fever have a much higher risk of developing meningoencephalitis. The meta-analysis shows moderate heterogeneity between studies, with a Chi^2 of 3.13, 1 df and a p-value of 0.08. Research results may vary due to research design, demographic variables or fever definitions, as shown by the I^2 value of 68. Despite the heterogeneity, the overall effect is statistically significant, with a Z-score of 6.20 and a p-value of less than 0.00001, confirming the conclusion that fever predicts meningoencephalitis.This meta-analysis confirms that fever is common in CNS diseases such as meningoencephalitis. Studies have shown that fever is a key clinical symptom in the detection of CNS infections [25, 26]. The risk of meningoencephalitis increases with fever due to the body's systemic inflammatory response to an infection that typically affects the CNS [4]. Our results are robust as the direction of the effect is consistent across populations and situations, despite substantial differences in the included studies. Rao *et al*. (2017)[20] and Blauw *et al*. (2022)[8] provide useful data on the clinical presentation of meningoencephalitis. However, the moderate variability emphasizes the need for additional investigation of possible causes for the variance, such as patient demographics or etiology of fever in the study groups.

Clinicians should suspect meningoencephalitis in febrile patients, especially those with neurologic symptoms, as there is a close association between the two conditions. Early detection and treatment of meningoencephalitis can prevent serious consequences or death [8, 27].

Conclusion

Our meta-analysis demonstrates that fever significantly increases the risk of developing meningoencephalitis, with an odds ratio of 4.87 indicating that patients with fever are nearly five times more likely to develop the condition than those without. This substantial association underscores the importance of fever as a key predictor for meningoencephalitis. The study also highlights that both bacterial and viral etiologies are prevalent in meningoencephalitis cases, with bacterial infections often leading to more severe outcomes. Seizures are frequently observed in patients, further complicating their clinical presentation. Gender does not appear to influence susceptibility significantly. Despite some moderate heterogeneity between studies, the overall effect is strong and statistically significant. These findings emphasize the need for vigilant monitoring of febrile patients and suggest that early intervention could mitigate the risk of severe meningoencephalitis.

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