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Research article

# Efficacy of rituximab as second-line therapy for autoimmune encephalitis: A systematic review and meta-analysis

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ABSTRACT

*Background:* Approximately 20%–50 % of individuals with autoimmune encephalitis (AE) demonstrate suboptimal responses to first-line therapies, leading to persistent neurological deficits and the need for second-line interventions. Although rituximab has shown potential as an alternative treatment in AE, the existing evidence remains insufficient. This study systematically evaluated and meta-analyzed the efficacy of rituximab in AE patients who either failed or exhibited inadequate responses to first-line treatments, aiming to refine and optimize therapeutic strategies for AE.

*Methods:* A comprehensive search of PubMed, Embase, and the Cochrane Library databases was conducted, covering studies published up to June 10, 2024. In addition, manual cross-referencing of relevant studies was performed using both subject-specific and free-text terms such as "Rituximab," "Rituxan," "Mabthera," "RTX," "Mab," "Ma," "AE," "encephalitis," "Anti-NMDAR encephalitis," and "autoimmune encephalitis." Data on rituximab's efficacy as a second-line therapy in AE were independently screened and extracted by two researchers. Statistical analyses were conducted using R4.2.1 software to assess the pooled outcomes of the included studies.

*Results:* Analysis of 14 studies involving 277 AE cases revealed an 80 % favorable prognosis rate (0.72–0.89) for rituximab, with superior efficacy in patients under 18 years compared to those over 18 ($I^2 = 65.9$ %, 38.7%–81.0 %; $p < 0.01$). The prognosis rate for patients under 18 was 0.85 (0.76–0.93), while for those over 18, it was 0.72 (0.56–0.88). Furthermore, a disease duration of ≤180 days correlated with a better prognosis than durations exceeding 180 days, with rates of 0.82 (0.69–0.94) and 0.74 (0.61–0.87), respectively.

*Conclusion:* Rituximab demonstrates an 80 % favorable prognosis rate in AE cases unresponsive to first-line treatments, particularly in patients under 18 or those with disease duration ≤180 days.

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## 1. Introduction

Autoimmune encephalitis (AE) is a rare inflammatory disorder characterized by diffuse or multifocal brain parenchymal damage resulting from immune-mediated attacks on central nervous system autoantigens. Clinically, AE presents with a broad spectrum of neuropsychiatric manifestations, including cognitive impairments, seizures, movement disorders, mental and behavioral alterations, autonomic dysfunctions, sleep disturbances, and varying levels of consciousness. In certain cases, prodromal symptoms such as fever, headache, and gastrointestinal disturbances precede the neurological onset [1,2].

Antibodies in AE are classified according to the localization of their target antigens into intracellular neuronal antigens (InAbs), synaptic antigens (SyAbs), and neural surface antigens (NSAbs) [3,4]. AE associated with InAbs and SyAbs tends to progress more gradually, exhibit lower recurrence rates, and often shows improvement in neurological symptoms following tumor resection [5]. In contrast, AE linked to neuronal surface antibodies (NSAE) is less frequent, with annual incidence rates ranging from 1 to 5 cases per million, depending on antibody subtype, ethnicity, and geographic region [6]. Among NSAEs, N-methyl-D-aspartate receptor (NMDAR) encephalitis is the most common, followed by cases associated with leucine-rich glioma-inactivated protein 1 (LGI1), contactin-associated protein-like 2 (CASPR2), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), and gamma-aminobutyric acid-A and B (GABA-A/B) receptors. NSAE is frequently not associated with tumors, as NSAbs predominantly induce reversible neuronal dysfunction via humoral immune mechanisms, leading to favorable responses to immunotherapy and generally positive clinical outcomes [6]. In contrast, other subtypes of AE tend to have more aggressive disease courses and higher recurrence rates. Variations in onset age, coexisting conditions, and immune regulatory mechanisms further differentiate the clinical presentations of AE based on antibody specificity [6].

The treatment paradigm for AE has undergone a significant shift, moving from broad immunosuppressive approaches to more targeted antibody-based therapies [7]. While glucocorticoids (GC) are effective in reducing inflammation in AE, their nonspecific inhibition of antibody-mediated immune responses limits their therapeutic utility [8]. In contrast, antibody-targeted therapies directly address key pathogenic mechanisms, including autoantibody production, immune mediator activity, and the involvement of B cells and transient plasma cells. Agents such as cyclophosphamide, azathioprine, and mycophenolate mofetil play a critical role in managing refractory AE and maintaining remission. Moreover, cytokine modulators like tocilizumab and low-dose IL-2 offer potential in regulating autoimmune and inflammatory pathways in AE. Current data suggest that 20%–50 % of AE patients do not achieve adequate responses to first-line treatments, leading to persistent neurological deficits and the need for second-line therapies [9]. Second-line options have shown benefits in terms of neurological improvement, reduced relapse rates, and favorable safety profiles [10,11]. However, the optimal timing for initiating second-line immunotherapy remains controversial, with some experts recommending early intervention based on disease severity, initial treatment response, and relapse risk. Although rituximab has proven effective in treating AE, its widespread use is hindered by a lack of comprehensive clinical evidence, primarily derived from isolated case reports. The absence of large-scale, multicenter, double-blind, randomized controlled trials further limits its broader application. This study, through a systematic review and meta-analysis, evaluates rituximab's effectiveness in AE patients who do not respond to first-line therapies, offering valuable insights for neurocritical care specialists and neurologists.

## 2. Methods

The systematic reviews and meta-analyses followed established methodological guidelines, ensuring strict compliance with protocol standards. The study protocol was pre-registered on https://inplasy.com/under registration number INPLASY202490012.

### 2.1. Literature search

Two authors independently conducted searches across six databases—PubMed, Google Scholar, Web of Science, EBSCO, CNKI, and Wanfang—covering all available records through June 10, 2024. Additionally, unpublished studies were sourced from preprint servers and other pertinent repositories. Studies that met predefined inclusion and exclusion criteria from both search strategies were included in the analysis. The search utilized two primary sets of keywords: "Rituximab," "Rituxan," "Mabthera," "RTX," "Mab," "Ma," "AE," "encephalitis," "Anti-NMDAR encephalitis," and "autoimmune encephalitis." Boolean operators "OR" connected terms within each keyword group, while "AND" merged the two groups, as further outlined in the supplementary material "Search Strategy.".

### 2.2. Inclusion and exclusion criteria

Inclusion criteria comprised: (1) documented AE cases receiving rituximab therapy; (2) administration of intravenous rituximab, irrespective of dosage, regimen, or duration; (3) prospective or retrospective studies published in English or Chinese; and (4) outcome assessments measuring rituximab's efficacy in AE patients refractory to first-line treatments. Exclusion criteria included: (1) review articles; (2) studies without primary outcome data; (3) publications in languages other than English or Chinese; and (4) studies reporting fewer than three cases.

### 2.3. Data extraction

Data extraction was performed independently by two researchers, with discrepancies resolved through team consensus. The screening process commenced with a review of titles and abstracts, adhering to predefined inclusion and exclusion criteria. Full-text

reviews were subsequently conducted for studies meeting initial eligibility. A standardized data collection format was utilized, followed by cross-verification by both assessors to ensure consistency and accuracy. The extracted data included the first author, publication year, study location, interventions, and other pertinent variables. The primary analysis focused on evaluating the efficacy of rituximab as a second-line treatment for autoimmune encephalitis, considering factors such as patient age and disease duration.

### 2.4. Study quality assessment

The quality of cohort studies was assessed using the Newcastle-Ottawa Scale (NOS), based on criteria such as population selection, group comparability, and outcome measurement. Studies were rated on a 0–9 star scale, with scores of 7 or higher indicating high quality, 4–6 representing moderate quality, and scores below 4 reflecting low quality.

### 2.5. Statistical analysis

Statistical analyses were performed using R 4.3.3, with the favorable prognosis rate as the primary outcome measure. A 95 % confidence interval (95%-CI) was applied for interval estimation. Heterogeneity was assessed using the $I^2$ statistic, where $P \geq 0.10$ and $I^2 \leq 50$ % supported the application of a fixed-effects model, while $P < 0.10$ or $I^2 > 50$ % indicated substantial heterogeneity, necessitating a random-effects model. Data from more than 10 meta-analyses were included for each outcome, with publication bias evaluated via the Begg test and funnel plots. Statistical significance was set at $\alpha = 0.05$.

## 3. Results

### 3.1. Literature search results

A comprehensive database search identified 5128 articles, from which 2741 duplicates and irrelevant titles or abstracts were removed. Following this, 118 full-text articles were reviewed, with additional exclusions for studies involving non-rituximab treatments (n = 36), non-AE cases (n = 10), studies reporting fewer than three cases (n = 18), and those with incomplete data (n = 26). Ultimately, 14 studies, encompassing 277 AE cases, were included in the meta-analysis [12–25]. The full selection process was illustrated in Fig. 1.

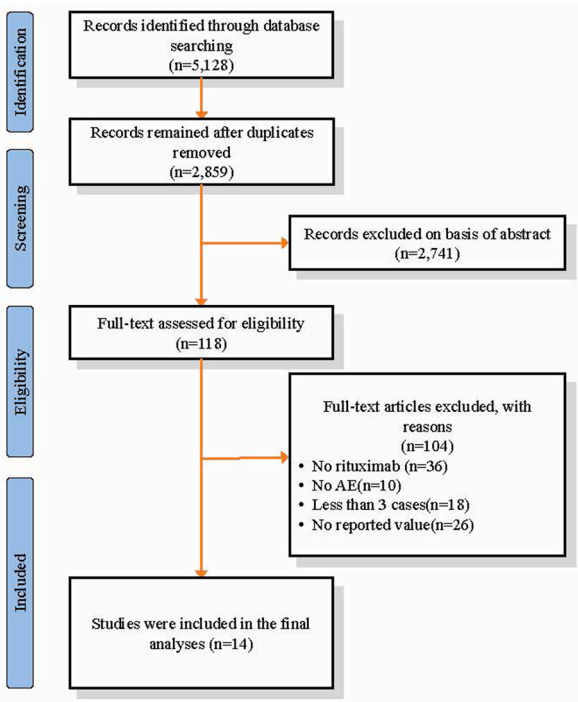


**Fig. 1.** Flowchart of literature search and screening. AE: autoimmune encephalitis.

### 3.2. Primary results

#### 3.2.1. Basic information

The studies reviewed were conducted across multiple countries, including six from China, three from France, two from South Korea, and one each from Brazil, Japan, Australia, the United States, Canada, the United Kingdom, and Turkey. A detailed overview of study characteristics was presented in Table 1.

#### 3.2.2. Quality assessment of included studies

The NOS scores for case-control and cohort studies ranged from 5 to 7, with two studies scoring 5, five scoring 6, and seven scoring 7, resulting in an average score of 6.4. Most studies were retrospective in design and lacked sufficiently matched cases and controls. A comprehensive summary of the quality assessment was provided in Table 2.

### 3.3. Meta-analysis results

A meta-analysis of 14 studies evaluated the efficacy of rituximab as a second-line therapy in AE, showing significant therapeutic benefits. Heterogeneity analysis revealed $I^2 = 64.1\ \%$ (36.4%–79.7 %), $p < 0.01$, justifying the use of a random effects model for effect size estimation. The estimated favorable prognosis rate was 0.80 (0.72–0.89) (Fig. 2). Funnel plot analysis indicated potential publication bias ($t = 2.29$, $p = 0.0408$) (Fig. 3).

### 3.4. Subgroup analysis

#### 3.4.1. Age subgroup

The analysis demonstrated that rituximab was more effective in patients under 18 years compared to those aged 18 and older, with considerable heterogeneity observed ($I^2 = 65.9\ \%$, 38.7%–81.0 %; $P < 0.01$). A random-effects model was applied to estimate the effect size, revealing a favorable prognosis rate of 0.85 (0.76–0.93) for the younger group and 0.72 (0.56–0.88) for the older cohort (Fig. 4). Funnel plot analysis revealed no significant publication bias in the assessment of age-related treatment effects ($t = 2.08$, $p = 0.0615$) (Fig. 5).

**Table 1**
Basic characteristics of the included studies.

| Author | Year | Country | Dose of Rituximab | Total number of cases | Number of cases with good prognosis | Immunotherapy before Rituximab treatment |
|---|---|---|---|---|---|---|
| Dale R.C et al. [12], | 2014 | Australia USA Canada France UK Turkey | 375 mg/m2 weekly for 4 weeks | 39 | 31 | Steroid, IVIG, Plasma exchange, Cyclophosphamide, Mycophenolate mofetil, azathioprine |
| Zekeridou A et al. [13] | 2015 | France | 375 mg/m2 | 26 | 22 | First-line immunotherapy |
| Byun J et al. [14] | 2016 | South Korea | 375 mg/m2 weekly for 4 weeks | 12 | 6 | Steroid, IVIG, Plasma exchange |
| Lee W.J et al. [15], | 2016 | South Korea | 375 mg/m2 weekly for 4 weeks | 80 | 55 | Steroid, IVIG, Plasma exchange |
| Etienne de Montmollin E [16]. | 2017 | France | 375 mg/m2 weekly for 4 weeks | 22 | 12 | First-line immunotherapy |
| Wada T et al. [17] | 2017 | Japan | – | 5 | 4 | First-line immunotherapy |
| Xie W et al. [18] | 2017 | China | 375 mg/m2 weekly for 4 weeks | 7 | 7 | combine steroid, intravenous immunoglobulin |
| Wang B.J et al. [19] | 2017 | China | 100 mg IV infusion, once per week for 4 consecutive weeks | 10 | 9 | Corticosteroids, IVIG, Corticosteroids |
| Fu Z et al. [20] | 2017 | China | 375 mg/m2 weekly for 4 weeks | 14 | 10 | Steroi, IVIG, Cyclosporine, Cyclophosphamid, Azathioprine |
| Ho A.C et al. [21] | 2018 | China | 375 mg/m2 weekly for 4 weeks | 3 | 3 | IVIG, steroid, plasmapheresis |
| Kong S.S et al. [22] | 2019 | China | 375 mg/m2 weekly for 4 weeks | 14 | 10 | Steroids, IVIG |
| Valle D et al. [23] | 2019 | Brazil | 375 mg/m2 weekly for 4 weeks | 3 | 3 | Steroid, IVIG, Cyclosporine, Cyclophosphamide |
| Deng B et al. [24] | 2019 | China | Two doses of rituximab (100 mg and 500 mg) were given in 2 consecutive days. | 10 | 10 | Steroid, IVIG, Plasmapheresis |
| Zhang J et al. [25] | 2019 | China | 375 mg/m2 weekly for 4 weeks | 32 | 24 | First-line immunotherapy |

**Table 2**
NOS scores of the included studies.

| Author | Year | Selection of research population | Comparability between groups | Outcome measure | NOS scores |
|---|---|---|---|---|---|
| Dale R.C et al. [12], | 2014 | 3 | 1 | 2 | 6 |
| Zekeridou A et al. [13]. | 2015 | 4 | 1 | 2 | 7 |
| Byun J et al. [14] | 2016 | 3 | 2 | 2 | 7 |
| Lee W.J et al. [15], | 2016 | 4 | 2 | 1 | 7 |
| Montmollin E [16]. | 2017 | 4 | 1 | 1 | 6 |
| Wada T et al. [17]. | 2017 | 3 | 2 | 2 | 7 |
| Xie W et al. [18] | 2017 | 3 | 2 | 1 | 6 |
| Wang B.J et al. [19] | 2017 | 3 | 1 | 1 | 5 |
| Fu Z et al. [20] | 2017 | 4 | 1 | 2 | 7 |
| Ho A.C et al. [21] | 2018 | 3 | 1 | 2 | 6 |
| Kong S.S et al. [22] | 2019 | 4 | 2 | 1 | 7 |
| Valle D et al. [23] | 2019 | 3 | 1 | 2 | 6 |
| Deng B et al. [24] | 2019 | 4 | 1 | 2 | 7 |
| Zhang J et al. [25] | 2019 | 3 | 1 | 1 | 5 |

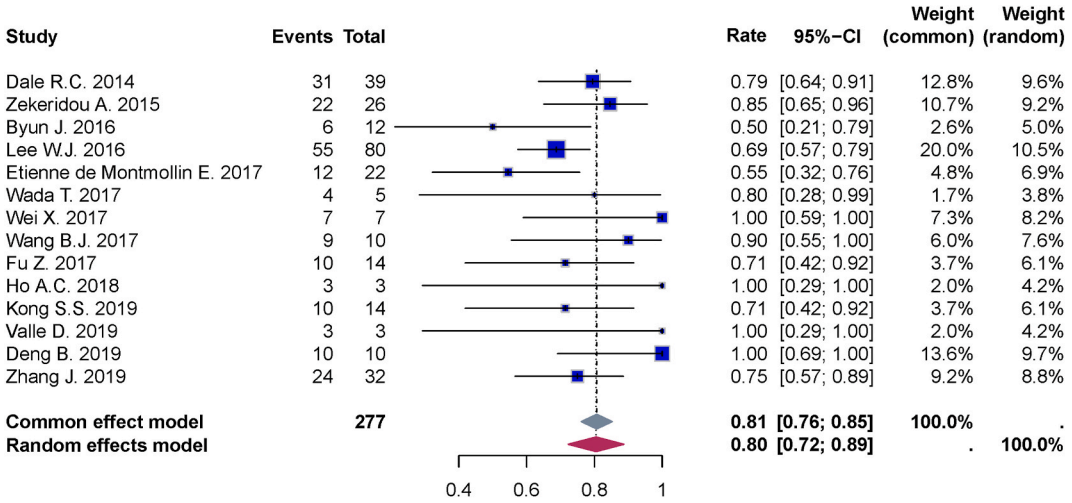


**Fig. 2.** Forest plot of efficacy of rituximab as second-line therapy for autoimmune encephalitis patients. CI: confidence intervals.

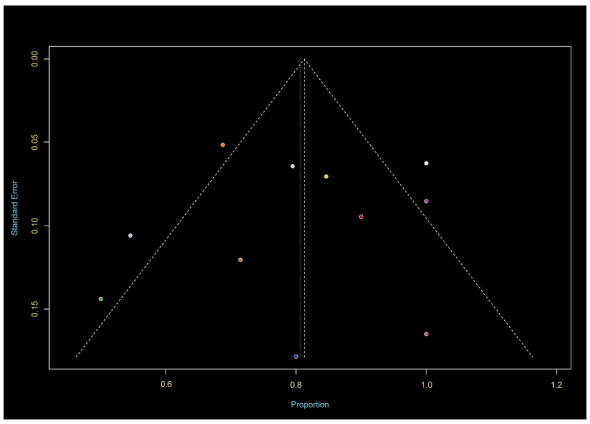


**Fig. 3.** Funnel plot of efficacy of rituximab for autoimmune encephalitis patients.

### *3.4.2. Disease duration subgroup*

The analysis revealed that patients with a disease duration of ≤180 days showed significantly better prognoses following rituximab treatment compared to those with a duration exceeding 180 days. Substantial heterogeneity was observed ($I^2 = 70.3\,\%$, 44.8%–84.0 %, $p < 0.01$), requiring the application of a random-effects model for effect size estimation. The favorable prognosis rate for the ≤180-day

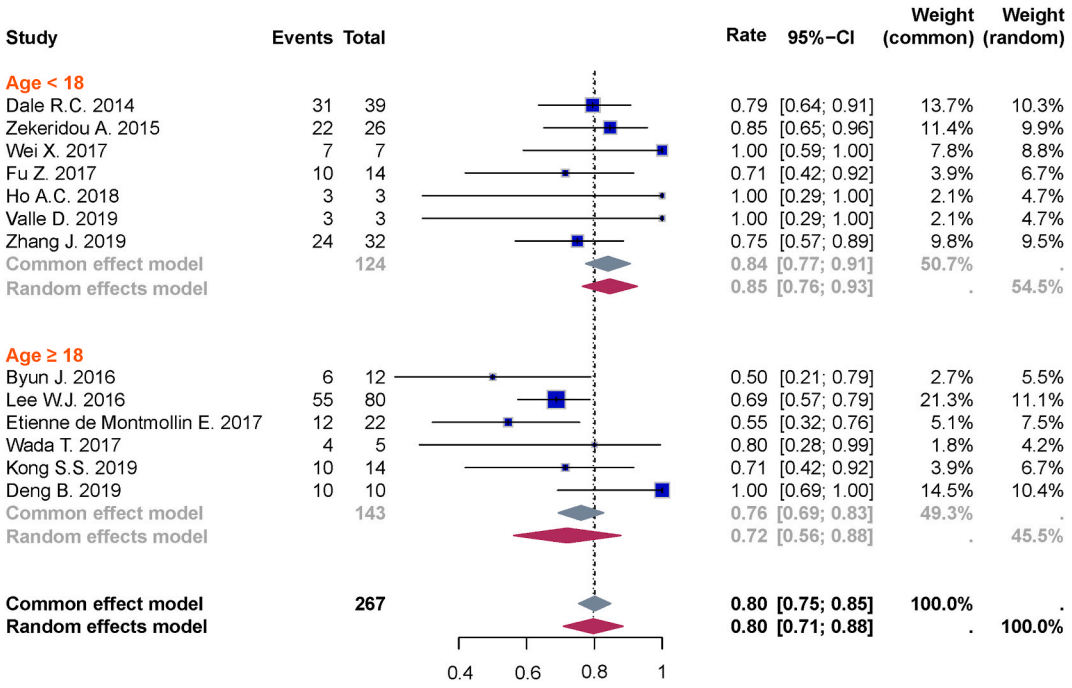


**Fig. 4.** Forest plot of efficacy of rituximab in different age groups of autoimmune encephalitis patients. CI: confidence intervals.

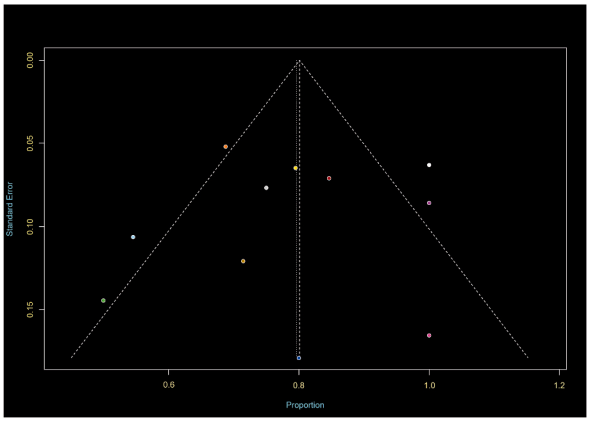


**Fig. 5.** Funnel plot of efficacy of rituximab in different age groups of autoimmune encephalitis patients.

group was 0.82 (95 % CI: 0.69–0.94), compared to 0.74 (95 % CI: 0.61–0.87) for those with a longer disease duration (Fig. 6). Funnel plot analysis of rituximab's effectiveness across different disease durations showed no significant publication bias (t = 1.82, $p$ = 0.1022) (Fig. 7).

### *3.4.3. Sensitivity analysis*

A sensitivity analysis, conducted by excluding individual studies to evaluate the robustness of the results, produced consistent outcomes, thereby validating the reliability of the meta-analytic findings (Fig. 8).

## 4. Discussion

Treatment strategies for AE encompass immunotherapy, symptomatic management, supportive care, and rehabilitation, addressing both epileptic seizures and psychiatric symptoms. In tumor-related cases, anti-tumor therapies, including surgical resection, are essential components. Immunotherapy is divided into first-line, second-line, and maintenance approaches. First-line therapies primarily consist of corticosteroids, intravenous immunoglobulin, plasma exchange, and immunoadsorption [26,27]. However, 20%–50 % of patients fail to respond adequately to first-line immunotherapy [28–32]. In cases where no clinical improvement occurs within

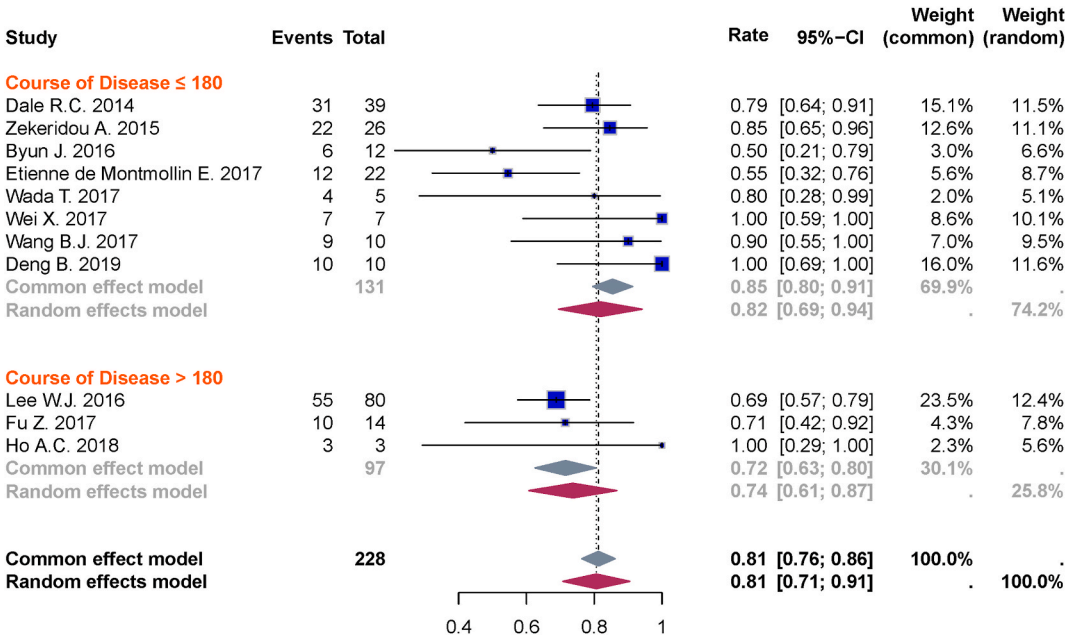


**Fig. 6.** Forest plot of efficacy of rituximab in autoimmune encephalitis patients with different disease durations. CI: confidence intervals.

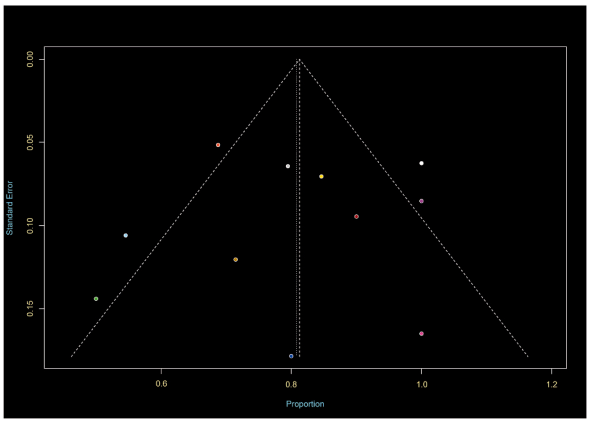


**Fig. 7.** Funnel plot of efficacy of rituximab in autoimmune encephalitis patients with different disease durations.

10–14 days, second-line treatment is recommended [28,33]. Dalmau et al. emphasized the need for prompt initiation of second-line immunotherapy, particularly for patients diagnosed later, when symptoms persist beyond 10 days of first-line treatment. In non-tumor cases, timely second-line intervention is linked to a lower risk of recurrence [28]. This study analyzed 14 articles detailing patients who initially received first-line immunotherapy—comprising glucocorticoids, IVIG, and plasma exchange—before transitioning to second-line rituximab, which ultimately proved ineffective.

Rituximab is the most commonly used second-line immunotherapy for anti-NMDAR encephalitis. This chimeric human-mouse monoclonal antibody is engineered via recombinant technology, combining the variable regions of a mouse-derived anti-CD20 monoclonal antibody with the constant regions of human light and heavy chains. This design enables precise antigen targeting while minimizing the variability typically observed in mouse monoclonal antibodies. Rituximab induces B cell apoptosis, preventing their differentiation into antibody-secreting plasma cells, thereby selectively inhibiting B cell function. Anti-NMDAR encephalitis is characterized by significant infiltration of B cells and plasma cells in the brain, primarily originating from B cells [34], which are essential for antibody production. This indicates that rituximab alleviates the disease by depleting B cells. For patients diagnosed late and without tumors, Dalmau recommended initiating second-line immunotherapy immediately to enhance treatment outcomes. Compared to first-line therapies, rituximab demonstrates greater specificity and effectively reduces B cell levels in both serum and cerebrospinal fluid.

In 2008, Ishiuraet al. [35] reported the first successful use of rituximab for treating anti-NMDAR encephalitis. The patient initially

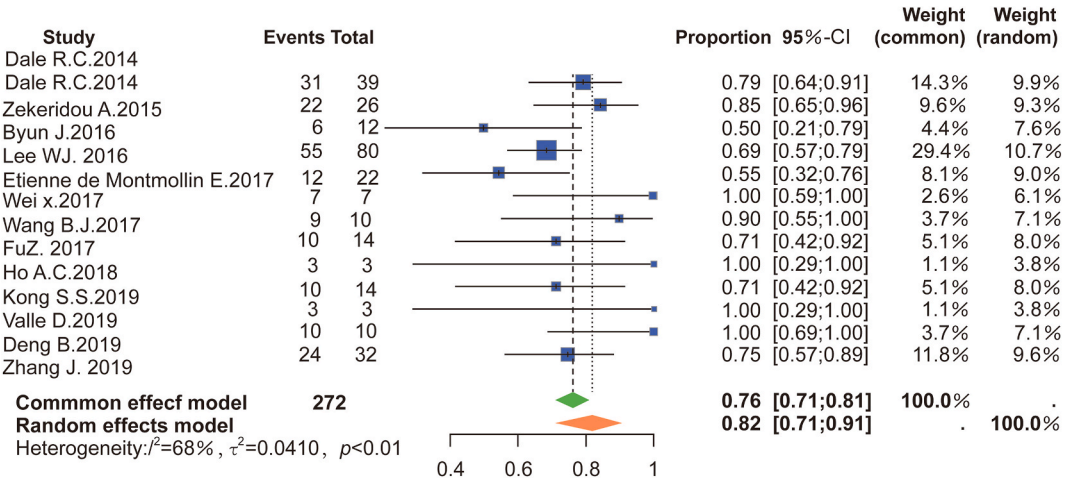


**Fig. 8.** Sensitivity analysis.

presented with headache, which progressed to generalized epilepsy, high fever, hallucinations, and oral numbness. Treatment with midazolam and methylprednisolone resulted in limited clinical improvement and minimal changes in MRI findings. Detection of anti-NR1/NR2 antibodies in the cerebrospinal fluid prompted the initiation of rituximab, leading to a rapid decrease in peripheral $CD20^+$ B lymphocytes from 8.0 % to 0. Complete recovery was achieved after over two months of treatment. Subsequent case reports and both prospective and retrospective studies have increasingly confirmed rituximab's efficacy in managing anti-NMDAR encephalitis [36–38]. Dale et al. [39] conducted a multicenter retrospective study to evaluate rituximab's efficacy in anti-NMDAR encephalitis, involving 39 patients (29 females, 10 males) with a median age of 8.7 years (range 1.6–17). At baseline, only 5.1 % of participants had a modified Rankin Scale (mRS) score of 0–2. All participants had previously received first-line immunotherapy, including steroids, intravenous immunoglobulin, and plasma exchange. Rituximab was administered at 375 mg/$m^2$ weekly for four weeks, with a median follow-up of 1.3 years (range 0.4–4.5). Following treatment, the proportion of patients achieving an mRS score of 0–2 increased substantially to 79.5 %, with one patient showing no improvement and no cases of clinical deterioration. Early rituximab administration (disease duration ≤0.1 year) resulted in 92.0 % of patients reaching an mRS score of 0–2, compared to 57.1 % in those treated later (disease duration >0.1 year). Among patients with inadequate responses to first-line therapies, the response rate was 0.80 (95 % CI, 0.72–0.89), confirming rituximab's significant therapeutic efficacy. These results are consistent with those from other studies [40–42], highlighting the advantages of early treatment initiation for improved outcomes.

Meta-analyses have established rituximab as an effective second-line treatment for autoimmune encephalitis, with a manageable toxicity profile. Patients receiving rituximab demonstrated improved functional outcomes (mRS< 2), characterized by significant reductions in mRS scores and lower recurrence rates. In both the anti-NMDAR AE and mixed AE subgroups, post-treatment functional outcomes and recurrence rates were comparable, though the anti-NMDAR AE subgroup exhibited a more pronounced decrease in average mRS scores [43]. Age has been identified as an independent prognostic factor in AE, with younger patients showing better outcomes, likely due to earlier disease onset, more robust immune responses, and a lower prevalence of comorbid infections or tumors [44]. Recovery following immune regulation therapy is also observed to occur more rapidly in younger individuals. Subgroup analysis assessing the influence of age and disease duration on rituximab efficacy revealed greater treatment effectiveness in patients under 18 compared to those older than 18 ($I^2$ = 65.9 %, 38.7%–81.0 %, $P$ < 0.01). The favorable prognosis rates were 0.85 (0.76–0.93) for patients under 18 and 0.72 (0.56–0.88) for those over 18, consistent with prior findings [44,45]. Severe consciousness disorders, serious infections, multiple organ dysfunction syndrome, limited response to immunotherapy, prolonged ICU stays, and refractory seizures are significant factors associated with prolonged hospitalization and poor outcomes [46]. In this study, patients with a disease duration of ≤180 days showed markedly better prognoses than those with longer durations, with an $I^2$ of 70.3 % (44.8%–84.0 %, $P$ < 0.01), based on analysis using a random effects model. The estimated favorable prognosis rate for patients with a disease duration of ≤180 days was 0.82 (0.69–0.94), compared to 0.74 (0.61–0.87) for those with a disease duration exceeding 180 days. Rituximab exhibited strong efficacy in patients refractory to first-line immunotherapy, particularly benefiting individuals younger than 18 years or with a disease duration of ≤180 days. These results are consistent with previously reported outcomes [47,48].

AE is categorized into intracellular and cell surface antigen antibody-associated encephalitis, based on the localization of autoimmune antigens [49]. Intracellular antigen-associated forms include antibodies such as anti-Hu, anti-Ri, anti-Yo, and anti-MA2 [49]. In contrast, cell surface antigen-associated encephalitis, more commonly encountered, targets extracellular domains of membrane proteins, including anti-NMDAR, anti-LGI1, anti-CASPR2, anti-GABABR, and anti-AMPA receptor antibodies [49]. Anti-NMDAR antibody-associated encephalitis has been extensively investigated [50]. A recent analysis of 220 cases found that 86.8 % of patients had a favorable prognosis after 12 months of follow-up [51]. While short-term outcomes for anti-NMDAR encephalitis are often suboptimal, significant improvements are seen with immunotherapy and extended follow-up beyond one year [51]. In patients with anti-LGI1 and anti-CASPR2 antibody encephalitis, favorable short-term outcomes have been reported, but no significant changes are noted after 12 months of follow-up [52,53]. Mortality rates for severe anti-NMDAR antibody encephalitis range from 2.9 % to 9.5 %,

with some cases requiring over two years for complete recovery [54]. GABAB antibody-positive AE is frequently linked to severe neurological complications, such as status epilepticus, and an increased incidence of malignant tumors, both contributing to higher mortality rates [55]. Patients with GABAB antibody-positive AE and concurrent tumors typically exhibit poor responses to immunotherapy and unfavorable outcomes [56,57]. The mortality rate for anti-LGI1 antibody encephalitis is reported to be 6 % [58]. Evidence highlights the importance of early immunotherapy, with timely intervention leading to improved outcomes in AE cases [59,60]. For patients with a high clinical suspicion of AE, immunotherapy should be initiated promptly, even before antibody confirmation, once infectious encephalitis has been ruled out. This study does not explore this aspect in detail, highlighting the need for further research.

AE, an autoimmune disorder, typically follows a chronic and protracted course, which substantially heightens the risk of recurrence in anti-NMDAR encephalitis, although relapse rates reported in the literature exhibit considerable variability. Titulaeret al. documented a 12 % relapse rate over a two-year follow-up, with 4 % of patients experiencing more than two relapses. Among those who relapsed, 67 % had a single recurrence, while others experienced up to five episodes [29]. Relapsed cases generally present with milder symptoms compared to the initial episode, with approximately 10 % exhibiting more severe manifestations. Tumor-associated cases demonstrate lower relapse rates than tumor-free cases [61]. Additionally, approximately 30 % of patients experience relapse after discontinuing immunosuppressants, with intervals between episodes ranging from three months to six years [61]. Risk factors for AE recurrence remain controversial and may include the lack of initial immunosuppressive therapy, unidentified tumor-related factors, or inadequate immunosuppressant dosing [62–64]. The high relapse rate observed across most AE subtypes necessitates continuous monitoring of clinical symptoms and antibody titers. Long-term follow-up is essential for early detection and prompt intervention, both of which are vital for improving patient outcomes. Management of relapsed cases typically involves second-line therapy after first-line treatment, with extended durations often required for the second-line regimen. Post-relapse management should focus on tumor screening, reassessment of AE antibody titers, individualized immunosuppressant strategies, and optimized dosing schedules. However, the limited data on AE relapse highlights the need for further research to validate these findings.

Rituximab, a monoclonal antibody, primarily induces infusion-related reactions, including nausea, vomiting, headache, rash, and flu-like symptoms. Clinically, reducing the infusion rate alleviates these effects, which typically diminish with repeated administrations and rarely lead to discontinuation. The antibody is highly specific for CD20-positive cells, enabling rapid depletion; however, severe allergic reactions, such as urticaria, laryngeal spasm, bronchospasm, and dyspnea, occur in approximately 0.05 % of cases [65]. Management of these reactions involves immediate infusion cessation and symptomatic treatment with glucocorticoids and antihistamines. While rituximab monotherapy is not commonly associated with bone marrow suppression, periodic complete blood count monitoring is advised due to limited clinical data on hematologic safety. Recent studies demonstrate that high-dose rituximab significantly alleviates symptoms in pediatric patients with anti-NMDAR encephalitis but is associated with an increased risk of severe infections [66], limiting its use to high-risk patients. Joubert et al. [67] reported that rituximab appeared relatively safe for pregnant women with anti-NMDAR encephalitis (gestational age: 0–9 months), as follow-up evaluations showed generally healthy infants without malformations, hypogammaglobulinemia, or leukopenia. However, the small sample size ($n = 11$) underscores the need for further investigation. Among the 14 studies reviewed, no adverse reactions were reported, supporting rituximab's favorable safety profile in patients with anti-NMDAR encephalitis.

### *4.1. Limitation*

The study demonstrated significant efficacy of rituximab in patients who were unresponsive to first-line immunotherapy, especially in those under 18 years of age or with a disease duration of 180 days or less. However, the results are limited by small sample sizes and variability in study quality. Several factors, including treatment response variability, timing, patient age, disease duration, ICU stay length, comorbid tumors, and tolerability—particularly due to the predominance of pediatric cases—may introduce bias. To mitigate these limitations, large-scale, multicenter randomized controlled trials are necessary for further validation.

## 5. Conclusion

Rituximab yields an 80 % favorable prognosis rate in AE patients who are refractory to first-line therapy, with notably higher effectiveness in patients under 18 years of age or those with a disease duration of $\leq$180 days.

## CRediT authorship contribution statement

**Lin-ming Zhang:** Writing – review & editing, Visualization, Supervision, Resources, Methodology, Funding acquisition, Data curation, Conceptualization. **Xuan-lin Xing:** Software, Resources, Project administration, Methodology, Investigation. **Bing-ran Zhang:** Visualization, Validation, Software, Resources, Investigation, Formal analysis, Data curation. **Qiu-juan Zhang:** Visualization, Validation, Supervision, Software, Formal analysis, Conceptualization. **Yan-lin Zhu:** Software, Project administration, Investigation, Data curation. **Shu-ji Gao:** Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ming-wei Liu:** Writing – review & editing, Writing – original draft, Supervision, Software, Investigation, Funding acquisition, Formal analysis, Conceptualization.

## Ethics approval and consent to participate

Ethical approval was not required for this study.

## Data availability statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2025.e41747.

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