

Effectiveness of rituximab in neuromyelitis optica: A meta-analysis

Fulin Gao

Department of Neurology, Gansu Provincial Hospital and School of Clinical Medicine, Gansu university of Traditional Chinese medicine <https://orcid.org/0000-0002-6865-3724>

Bingyan Chai

School of Clinical Medicine, Gansu university of Traditional Chinese medicine

Cheng Gu

Department of Neurology, Gansu Provincial Hospital

Ruipeng Wu

Department of Neurology, Gansu Provincial Hospital

Tong Dong

Department of Neurology, Gansu Provincial Hospital

Yuping Yao

Department of Neurology, Gansu Provincial Hospital

Yi Zhang

Department of Neurology, Gansu Provincial Hospital

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Abstract

Background: Neuromyelitis optica (NMO) is a severe autoimmune disorder of inflammatory central nervous system, which often resulting in paralysis or blindness. Rituximab (RTX) is a mouse-human chimeric monoclonal antibody specific for the CD20 antigen on B lymphocytes used to treat many autoimmune diseases. To evaluate the effectiveness of RTX, Disability and relapses were measured by the Expanded Disability Status Scale (EDSS) and annualized relapse rate (ARR) ratio. This review performed a meta-analysis of the efficacy of rituximab use in NMO.

Methods: We searched through the databases of PubMed, Embase, and Cochrane Library. We compiled 27 studies in this meta-analysis: 19 used ARR ratio, 23 used EDSS score, and there are 15 studies in the two main variables. Differences in the ARR ratio and EDSS score before and after rituximab therapy were the main efficacy measures. After a consistency test, the publication bias was evaluated and a sensitivity analysis was performed with mean difference (MD) of the efficacy of rituximab.

Results: A meta-analysis of 27 studies with 607 participants total was conducted. NMO patients have antibodies against aquaporin 4 autoantibody (AQP4-Ab) were recorded in 456 of 607 (75.12%). Rituximab therapy resulted in a mean (WMD) -1.58 (95%CI, -1.85 to -1.32) reduction in the mean ARR ratio and a mean (WMD) -1.17 (95%CI, -1.37 to -0.97) reduction in the mean EDSS score. 351 of 558 patients (62.9%) reached a relapse-free state. 107 of 607 (17.63%) patients had adverse reactions.

Conclusions: RTX has acceptable tolerance, reduces the frequency of relapse, and improves disability in most patients. However, treatment with RTX in reducing health-care costs, improving functional outcome and reducing adverse effects should be carefully addressed in future studies.

Background

Neuromyelitis optica (NMO) is a severe demyelinating disease, predominantly affecting the optic nerve and the spinal cord. The pathogenesis of NMO is related to the aquaporin-4 autoantibody (AQP4-Ab) [1-3]. Serum antibodies targeting AQP4-Ab have become sensitive and specific biomarker that enable early diagnosis of NMO and are found in most patients. Because the progression of NMO disability is related to the severity of the attacks, prophylactic treatment of NMO recurrence must be performed as soon as NMO is identified. Since studies have found that NMO patients have antibodies against AQP4-Ab, several studies have proposed treatment for B cells in NMO[4].

Rituximab (RTX) is a chimeric monoclonal antibody directed against CD20 epitope expressed on pre-B and mature B cells, and is used to treat B-cell-derived lymphoid neoplasms and antibody-mediated autoimmune diseases [5, 6]. The depletion of CD20 provides a theoretical basis for the treatment of autoimmune diseases in which B cells and autoantibodies play a key role, such as NMO, in which AQP4-Ab have been associated with the disease[7]. Here, we perform a meta-analysis to test rituximab efficacy is both well safe and tolerated, and examined the treatment efficacies using relapse rates and disability in NMO.

Methods

Literature search

This search was restricted only to articles published in English language. We searched for publications on the PubMed, Embase, Cochrane Library, without any temporal restriction. We did keyword and Medical Subject Heading (MeSH) searches for our theme, and MeSH terms, key words and their synonyms related to “rituximab” and “neuromyelitis optica”. A flowchart of the search strategy is shown in Fig. 1. One of us used a standardized form of data extraction to extract data, another person checks it, and revisits the data that does not match, and resolves the differences through discussion and consensus.

Inclusion and exclusion criteria for the literature

Studies were included if they fulfilled the following criteria: 1) Published English articles in various journals; 2) Patients with NMO do not limit their age, gender, ethnicity, and whether they have received treatment before; 3) Main variables include ARR and/or EDSS; Exclusion criterion: 1) Case reports and studies that included fewer than 2 patients, review, meta-analysis; 2) studies without main variables.

Main variables

Among the 27 articles selected, we extracted the values (means and standard deviations) of EDSS and ARR directly available. Disability was measured by the EDSS. The ARR were calculated using the total number of relapses per patient-year.

Statistical Analysis

Data analysis was performed using statistical software provided by State 12.0. The heterogeneity across each effect size was evaluated with the I² index, in which I² value close to 0% indicates no heterogeneity between studies, close to 25% indicates low heterogeneity, close to 50% indicates moderate heterogeneity and close to 75% indicates high heterogeneity between studies. If $P > 0.1$, $I^2 < 50\%$, a fixed-effect model was used for meta-analysis. When $P < 0.1$, $I^2 > 50\%$, a random-effect model was used instead and meta-regression analyzed the causes of heterogeneity, such as age of onset, duration of disease, follow-up time, dose of infusion and AQP4-IgG serostatus. A P value < 0.05 was considered as clinical significance.

Results

Study identification and selection

By searching PubMed, Embase, and Cochrane library database dated until August 2018. The database search identified 1075 records. After removing duplicates, 990 titles were initially screened and 146 theme-related abstracts were selected for further screening. Finally, 27 studies were included in this systematic review. 19 used ARR ratio, 23 used EDSS score, and there are 15 studies in the two main variables.

Demographic and clinical characteristics

Table 1 lists detailed information from 27 included studies. The included studies were published between 2008 and 2018. The number of participants per study ranged from 3 to 100, with a total number of 607 (530 females and 70 males, with sex not specified in 7 patients). NMO patients have antibodies against AQP4-Ab were recorded in 456 of 607 (75.12%).

Efficacy on the ARR Ratio

Fig. 2 shows a forest plot of the mean difference in the ARR ratio before and after rituximab therapy. This finding suggested that the mean difference of ARR ratio after rituximab therapy was -1.58 (95%CI, -1.85 to -1.32). A random-effect model was used with I^2 of 80.8%. Sensitivity analyses were performed by removing each study in turn and re-analyzed. No studies found to significantly affect heterogeneity. To evaluate the effect of the different covariates on the ARR ratio reduction, a meta-regression was performed. No significant correlation was detected between the outcome (ARR ratio change) and the following variables: age of onset ($P = 0.83$; 95% CI, -0.22 to 0.18), duration of disease ($P = 0.72$; 95% CI, -0.01 to 0.02), follow-up time ($P = 0.73$; 95% CI, -0.05 to 0.04), dose of infusion ($P = 0.77$; 95% CI, -0.44 to 0.57) and AQP4-IgG serostatus ($P = 0.72$; 95% CI, -2.45 to 3.40).

Efficacy on the EDSS Score

Fig. 3 shows a forest plot of the mean difference in the EDSS score before and after rituximab therapy. This finding suggested that the mean difference of EDSS score after rituximab therapy was -1.17 (95%CI, -1.37 to -0.97). The heterogeneity was moderate ($I^2=12.2\%$, $P=0.294$). No significant correlation was detected between the outcome (ARR ratio change) and the following variables: age of onset ($P = 0.58$; 95% CI, -0.08 to 0.04), duration of disease ($P = 0.78$; 95% CI, -0.01 to 0.01), follow-up time ($P = 0.28$; 95% CI, -0.01 to 0.02), dose of infusion ($P = 0.99$; 95% CI, -0.22 to 0.21) and AQP4-IgG serostatus ($P = 0.26$; 95% CI, -2.51 to 0.75).

Safety

351 of 558 patients (62.9%) reached a relapse-free state. Adverse effects were recorded in 107 of 607 (17.63%) patients treated with rituximab. Twelve of the patients experienced severe adverse reactions, five patients developed severe pneumonia, two patients developed transit hyperpyrexia, two patients developed septicemia, one patient developed a severe allergic reaction, one patient had a urogenital infection, and one patient developed seborrheic dermatitis. Five patients died. Two patients died of pneumonia, one patient died of urogenital infection and thrombosis, one patient died of bone marrow transplantation, and one patient died of cardiac and respiratory failure due to very extensive myelitis reaching the medulla oblongata.

Publication bias

The funnel plot for studies on the incidence of ARR and EDSS were symmetrical. The funnel plots indicated an absence of publication bias. (Fig. 4)

Discussion

NMO is a relapsing disease with a high early mortality rate. Without employing appropriate immunosuppressant treatment, more than 50% of patients with NMO will be functionally blind, or will progress to wheelchair dependence, within 5 years [8, 9]. Its treatment options are based on case series and expert opinion, and immunosuppressive therapy is the main method to prevent recurrence and prevent disability. The successful use of RTX has been widely reported in NMO. However, Randomized controlled trials in NMO are relatively few and there are currently no established guidelines for the treatment of RTX. Although rituximab is expensive in the past, it can offset the cost of recurrence and plasma exchange with its good therapeutic effect [10, 11]. At present, RTX has been biosimilarized, and its price has gradually been accepted by patients.

The therapeutic effect of RTX varies among patients with different outcomes. We did a meta-regression and analyzed the causes of heterogeneity. We found no significant correlation between the age of onset, duration of disease, follow-up time, dose of infusion, AQP4-IgG serostatus and major variables (ARR and EDSS). We speculated that the causes of heterogeneity may be related to differences in ethnicity, differences in study design, differences in the criteria for inclusion in patients, and whether other treatments are received prior to treatment.

With the increasing number of treatment options, the choice of the right therapeutic agent for the right patient becomes more important. Monoclonal antibody therapies are perspective options for NMO patients to prevent relapses compared with traditional immunosuppressants, especially in refractory patients. Some studies have used RTX as a first-line treatment for prophylactic treatment, which can reduce the severity of disease recurrence [13, 14]. Quan et al. has reported that rituximab treatment is well tolerated and resulted in a gradual recovery of neurological function. Rituximab mainly exerted its function through two stages. It not only eliminates or inhibits the pathogenic effector B cells to achieve early effects, but also regulates the proportion of functional B cells to make a more lasting improvement in efficacy [15].

Although AQP4-Ab is critical in the diagnosis of NMO, its involvement in the pathogenesis of the disease remains controversial[9]. Some studies suggest that AQP4-Ab is generally used as a marker of disease activity in an individual patient, and AQP4-IgG titers increase significantly during NMO recurrence period, but these indices decline during remission period [16, 17]. Therefore, there is a correlation between rises in antibody levels and clinical attacks, and treatment with RTX resulted in the most pronounced decline in AQP4-Ab levels. However, many studies have shown that AQP4-Ab is only a diagnostic marker for NMO, which can be detectable in serum during relapse as well as during remission. RTX can effectively reduce CD20 B cells in blood and cerebrospinal fluid, but it does not eliminate plasma cells in the bone marrow. This may be other mechanisms beyond AQP4-Ab to maintain disease stabilization, including inhibition of B cell/T cell interactions, increased regulatory T cells, and decrease of CD20 cells with reduction of proinflammatory cytokines, as well as modulation of the T cell compartment [18, 19]. Therefore, there is a lack of correlation between AQP4-Ab titers and clinical disease activity. Partial AQP4-Ab negative NMO patients still have a good response to the treatment of RTX [20].

Maintaining the consumption of memory B cells by repeated treatment may be the pivotal to the clinical effects of RTX in NMO patients [21]. Some studies have developed a personalized maintenance treatment program for CD19 + CD27 + memory B cell detection, and achieved good results. However, the increase in the relapses rate of NMO also occurs in the case of low levels of CD19+ B cells, which makes it difficult to control the disease [12, 14, 22-24]. Therefore, CD27+ memory B cells can better detect the therapeutic effect of RTX relative to CD19 + B cells. Yang et al. found that in Asian NMO, lower doses of RTX can achieve better reactivity with cost and availability advantages[25]. Low doses of RTX can effectively reduce the recurrence rate and improve the prognosis in most NMOs cases. Repeated RTX treatments are superior to single RTX doses for NMO therapy. Some patients required an increased frequency of RTX infusion to maintain low levels of CD19+ cells, and long-term use of lower dose RTX may lead to cost savings [19, 26].

Due to ethical issues, there are currently relatively few placebo-controlled studies of rituximab [12]. Zhang et al. has investigated the NMO patients treated with RTX and acetazolamide (AZA), study has found that RTX is more effective in preventing NMO recurrence than patients treated with AZA and can improve symptoms [27]. The most common reported adverse drug reactions are infections. A decrease in immunoglobulin levels was

observed in some patients following rituximab treatment, which may increase the probability of infection in patients [28, 29]. Relatively few reports of serious adverse reactions leading to death. In our meta-analysis, 5 patients died due to serious illness and related complications. Only 2 of these deaths were associated with adverse reactions to RTX. One patient died of pneumonia, one patient died of urogenital infection and thrombosis.

Our meta-analysis was not only to present efficacy data, but also to expand the knowledge about the safety of RTX treatments. Although RTX has significant benefits for the treatment of NMO, long-term benefits and risks remain to be determined. Moreover, most patients receive other immunotherapies before and after RTX treatment, so the benefits and risks of treatment are inaccurate due to a single drug [5, 20, 30, 31]. And it is unclear whether patients have the appropriate time to discontinue RTX treatment without the risk of further relapse. In the previous meta-analysis, there was no mention of publication bias. And found that the disease duration and the efficacy measures showed a significant correlation. However, we did not find a correlation between the disease duration and the efficacy measures in our meta-analysis. This may be related to the differences in our inclusion in the literature. Limitations of this study: 1) Although the search strategy is relatively complete, it does not rule out that eligible articles are not included. 2) A large sample of multicenter studies was lacking in the included studies.

Conclusions

RTX has acceptable tolerance, reduces the frequency of relapse, and improves disability in most patients. However, treatment with RTX in reducing health-care costs, improving functional outcome and reducing adverse effects should be carefully addressed in future studies.

Abbreviations

NMO: Neuromyelitis optica; RTX: Rituximab; ARR: annualized relapse rate; EDSS: Expanded Disability Status Scale; MD: mean difference; AQP4-Ab: aquaporin-4 autoantibody; MeSH: Medical Subject Heading; AZA: acetazolamide; RCT: randomized clinical trial.

Declarations

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Availability of data and materials

All data analyzed during this study are included in this article.

Authors' contributions

FLG, BYC: search and screen the literature, extract the data, drafting the manuscript. CG, RPW, TD, YPY: collate the data. YZ: revising the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

1 Department of Neurology, Gansu Provincial Hospital, No. 204 of Donggang West Road, Lanzhou City, Gansu province 730000, PR China. 2 School of Clinical Medicine, Gansu university of Traditional Chinese medicine, No. 35 of Dingxi East Road, Lanzhou City, Gansu province 730000, PR China.

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Table

Table 1 Clinical and demographic characteristics of 607 patients from 27 studies included in the systematic review

Reference (study)	Research type	Patient No.	Sex (F/M)	Age (year)	AQP4-Ab(+) (case)	Duration of disease (years/month)	Follow-up (years/month)
Jacob [11] 2008	Retrospective	25	22/3	38(7-65)	11	4.5(0.8-17)y	19(6-40)m
Jarius [16] 2008	Retrospective	4	NC	45(19-59)	4	NC	62(33-144)m
Pellkofer [18] 2011	Prospective	9	8/1	36.1(11.5)	9	11(7.7)y	29.6(14.5)m
Gurdesh [2] 2011	Retrospective	23	21/2	37.1(14.6)	15	114(13-266)m	32.5(7-63)m
Lindsey [32] 2012	Retrospective	8	7/1	37.6(14.4)	4	65.1(53.7)m	39.9(40.7)m
Yang [25] 2013	Retrospective	3	NC	34.3(8.5)	2	9.3(4)y	12.7(0.6)m
Ip [5] 2013	Retrospective	7	6/1	52(22-62)	4	57(40-272)m	24(1-42)m
Ayzenberg [33] 2013	Retrospective	3	3/0	35(7.8)	3	6.7(3.7)y	14.7(15.1)m
Gredler [34] 2013	observational	4	4/0	42.5(15.4)	4	6.2(4.2)y	3.1(2.1)y
Chay [10] 2013	Retrospective	6	4/2	37.8(20.6)	3	NC	NC
Kim [35] 2013	Retrospective	30	27/3	38(23-58)	23	4.5(0.5-12.9)y	60(9-82)m
Longoni [31] 2014	Retrospective	5	4/1	13.7(2.7)	5	3.2(0.3)y	21.5(6.9)m
Kim [29] 2015	Retrospective	100	92/8	43(11)	94	11(5)y	67(9-108)m
Zephir [28] 2015	Retrospective	32	27/5	45(12.1)	28	6.5(1-410)m	28.7(21)m
Weinfurtnr [20] 2015	Retrospective	4	3/1	26.5(22.3)	3	6.5(3.1)y	6(1.2)y
Valentino [7] 2016	Retrospective	7	6/1	38.3(16.6)	7	NC	59.4(29.7)m
Jeong [36] 2016	Retrospective	55	50/5	42(15-68)	52	41.7(2.1-231.5)m	64.7(6.2-99.8)m
Annovazzi [1] 2016	Retrospective	76	64/9	46.5(12.5)	53	6(7.2)y	35.6(27)m
Collongues [24] 2016	Retrospective	21	19/2	37.8(15.5)	19	46.9(51.2)m	31(18)m
Zhang [27] 2017	Case-control	31	23/8	42.2(16.9)	15	4.05(2.11)y	27.45(11.68)m

Nikoo[37] 2017	RCT	33	29/4	35.33(8.98)	13	6.23(4.29)y	>12m
Evange. [19] 2017	Retrospective	5	5/0	54(10.21)	5	6.8(1.3)y	6.6(0.9)y
Cohen [23] 2017	Prospective	40	33/7	40.2(22-62)	20	40(2-165)m	2y
Tallantyre [22] 2018	Retrospective	5	5/0	36.6(14.5)	5	11.5(9.4)y	3.5(0.2-8.9)y
Yang [17] 2018	Prospective	20	19/1	40.7(11.4)	10	11(0.2-240)m	29(18-40)m
Cabre [12] 2018	Prospective	32	30/2	39.9(12.1)	20	NC	2y
Li [26] 2018	Retrospective	19	16/3	34.8(13.7)	17	3.4(3.4)y	2.5(1.7)y

RCT=randomized clinical trial, AQP4-Ab=aquaporin 4 autoantibody, NC=no clear

Figures

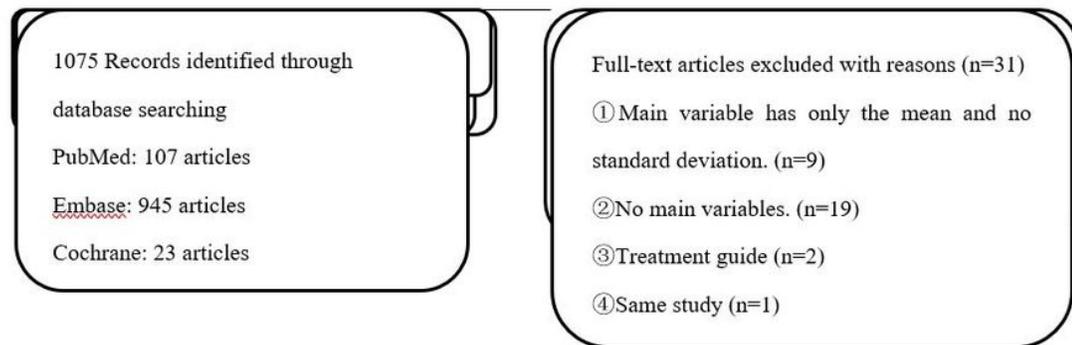


Figure 1

Flow chart presenting the process of the study selection for NMO meta-analysis.

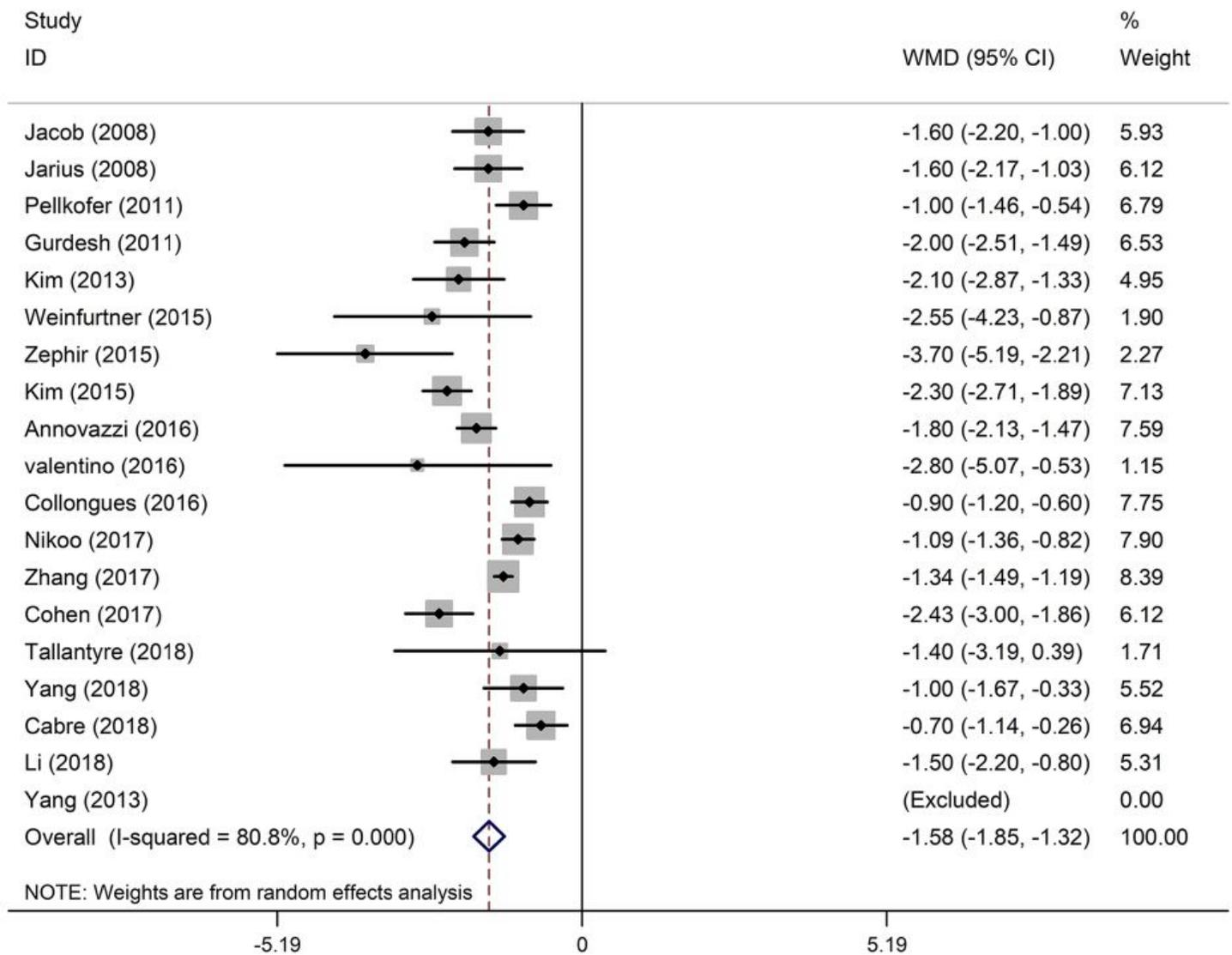


Figure 2

Forest plot of the mean difference in the ARR ratio before and after rituximab therapy. The three patients of Yang2013 had no relapse after treatment and could not be estimated in the forest plot. The estimated pooled weighted mean difference was -1.58 was highly significant ($p < 0.0001$), however, there was a large heterogeneity of study results ($I^2 = 80.8\%$).

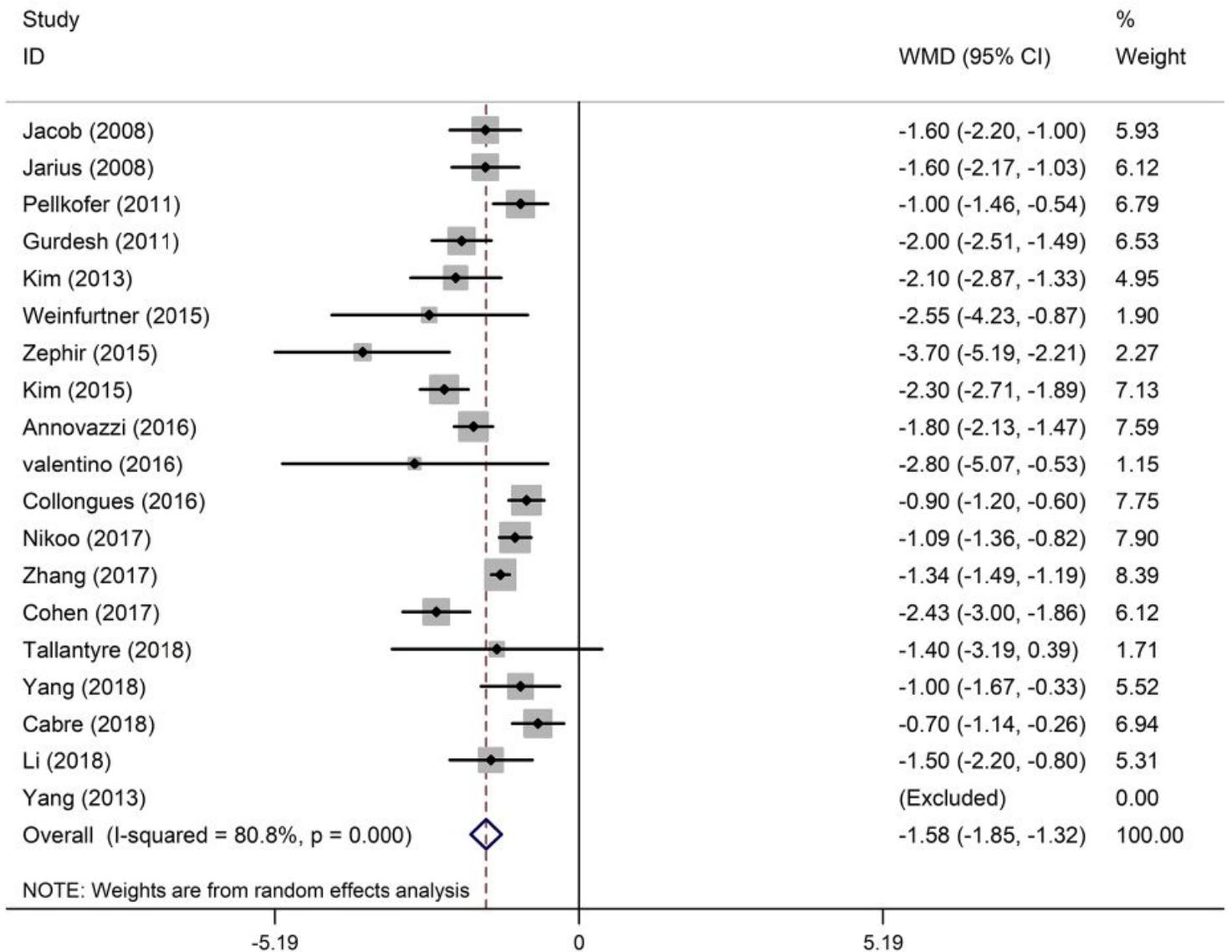


Figure 3

Forest Plot Showing the EDSS score of Patients with NMO after Rituximab Therapy. The estimated pooled weighted mean difference was -1.17 was highly significant ($p < 0.0001$), there was a moderate heterogeneity of study results ($I^2 = 12.2\%$).

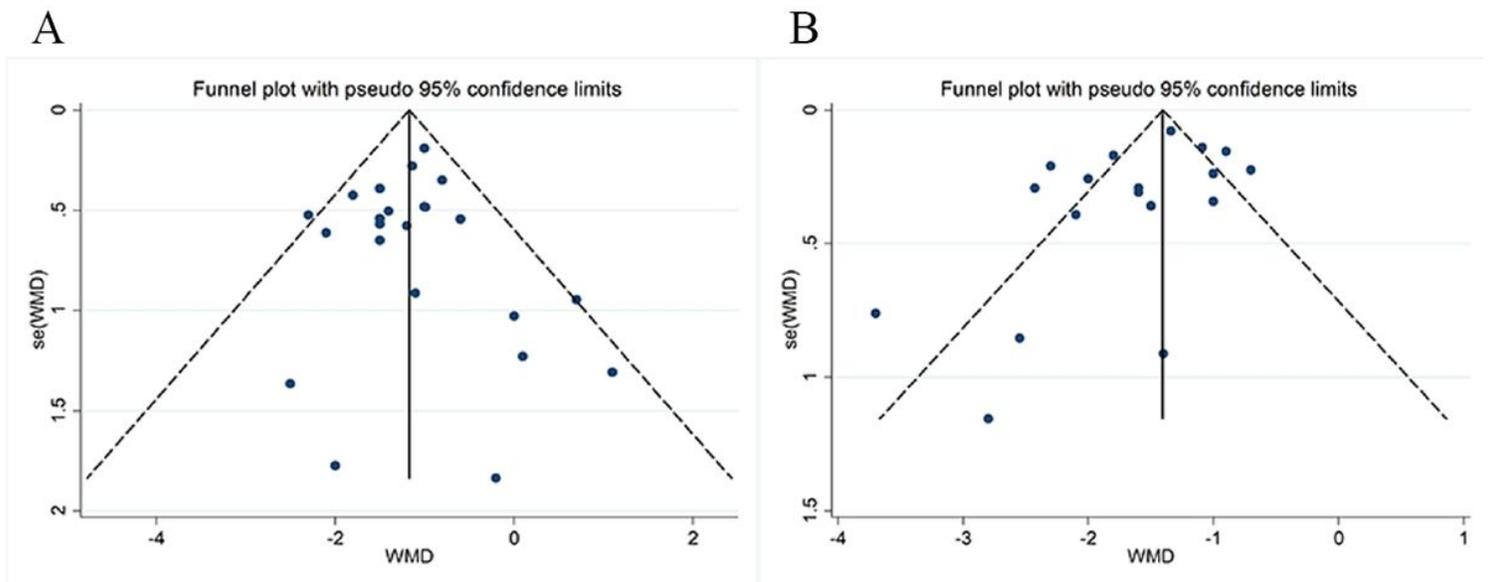


Figure 4

Funnel plot showing the incidence of ARR and EDSS of Patients with NMO after Rituximab Therapy. The funnel plot for studies on the incidence of ARR were generally symmetrical ($P=0.813$; 95% CI, -3.51 to 0.31) (A). The funnel plot for studies on the incidence of EDSS were symmetrical ($P=0.095$; 95% CI, -0.83 to 1.05) (B).