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Safety and Efficacy of Mycophenolate Mofetil in Treating NMOSD : a protocol for systematic review and meta-analysis.

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4 Safety and Efficacy of Mycophenolate Mofetil in Treating NMOSD : a protocol
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6 for systematic review and meta-analysis.

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26

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32

33 **Abstract**

34
35 **Introduction** Neuromyelitis optica spectrum disorders (NMOSD) is an inflammatory
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37 and heterogeneous astrocyte disorder of the central nervous system (CNS) with the
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39 characteristic of higher incidence in women and Asian. Most patients with NMOSD
40
41 have a course of recurrence and remission, which are prone to cause paralysis and
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43 blindness. A number of studies have confirmed the efficacy and promising prospect of
44
45 mycophenolate mofetil (MMF) in the treatment of NMOSD. However, there are
46
47 controversial about its therapeutic effect and safety. The purpose of this study is to
48
49 conduct a systematic review and meta-analysis to assess the efficacy and safety of MMF
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51 in treating NMOSD.
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53 **Methods and analysis** This systematic review will include all comparative researches,
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55 from randomized controlled trials (RCTs) to cohort studies, and case-control study. A
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57 relevant literature search will be conducted in PubMed, Web of Science, EMBASE, the
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59 Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang
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4 Database, China Science and Technology Journal database (VIP) and CBM. We will
5 also search registers of clinical trials, potential gray literature, and conference abstracts.
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7 There are no limits on language and publication status. The reporting quality and risk
8 of bias will be assessed by two researchers independently. Expanded disability status
9 scales (EDSS), annualized relapse rate (ARR) will be evaluated as the primary outcome.
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11 The secondary outcomes will include the frequency and extent of adverse events (AEs),
12 best-corrected visual acuity (BCVA), relapse-free rate and time to the next attack.
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14 Meta-analysis will be performed using RevMan5.3 software provided by the Cochrane
15 Collaboration and Stata 12.0.
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21 **Ethics and dissemination** Because the data used for this systematic review will be
22 exclusively extracted from published studies, ethical approval and informed consent of
23 patients will not be required. The systematic review will be published in a peer-
24 reviewed journal, presented at conferences and will be shared on social media platforms.
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29 **PROSPERO registration number:** PROSPERO CRD42020164179.

30 **Strengths and limitations of this study:**

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33 ► This study is the first to conduct an exhaustive literature search to identify studies
34 aimed to assess the effectiveness and safety of MMF in treating NMOSD.
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37 ► One limitation of this study is that differences in patients, interventions and primary
38 outcomes may mean that meta-analysis cannot be conducted, and narrative and meta-
39 analytical syntheses are planned.
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42 ► Although we will include studies published in any language, translation difficulties
43 may arise, which will result in the exclusion of these studies.
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47 ► The analysis of different sources of heterogeneity and the assessment of risk of bias
48 of the included studies is a key point for extracting and synthesising evidence-based
49 conclusions.
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52 **Keywords:** mycophenolate mofetil, neuromyelitis optica spectrum disorders, protocol,
53 systematic review, meta-analysis.
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56 **1. Introduction**

57 Neuromyelitis optica (NMO), also known as Devic disease, is currently considered to
58 be a rare autoimmune astrocyte disease of the central nervous system mediated by
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4 autoantibodies, dominated by humoral immunity and involving multiple immune cells
5 and factors, with optic neuritis(ON) and acute transverse myelitis as typical clinical
6 manifestations.¹ NMO has been recognized as a subtype of multiple sclerosis (MS) for
7 more than 100 years since it was first described and reported.² Until 2004, the discovery
8 and confirmation of anti-aquaporin-4 immunoglobulin G (AQP4-IgG) made significant
9 progress in pathogenesis, diagnosis and treatment of NMO.³ ⁴ The concept of
10 neuromyelitis optica spectrum disorders (NMOSD) was first proposed based on the
11 widespread clinical use of specific AQP4-IgG,⁴ which mainly referred to the limited
12 NMO of positive AQP4-IgG. However, with the gradual improvement of the specificity
13 of AQP4-IgG clinical testing, the shortcomings of the diagnostic criteria of NMO in
14 2006 and NMOSD in 2007 became prominent. In 2015, the international NMO
15 diagnostic team proposed a new international diagnostic standard for NMOSD.⁵
16 NMOSD includes NMO, ON, longitudinally extensive transverse myelitis and other
17 typical demyelinating brain syndrome.⁵ Up to now, there is no solid data on the
18 incidence and prevalence of NMOSD in the world. According to the existing
19 epidemiological data of small samples, middle-aged and young women are the high
20 incidence of this disease, with the onset age ranging from 32 to 41 years old, and the
21 incidence of female is about 10 times that of male.⁵ The incidence and prevalence vary
22 from region to region, with the incidence and prevalence being about 0.05-0.40 and
23 0.52-4.40/100,000, respectively.⁶ The areas with a large Asian population are the region
24 with high incidence of NMOSD.⁷⁻⁹ Most patients with NMOSD have a course of
25 recurrence and remission, including ON, myelitis and lesions in special parts of the
26 brain, which are prone to cause paralysis and blindness.⁵ NMOSD has become one of
27 the most common causes of non-traumatic disability and blindness in young and
28 middle-aged people, bringing heavy burdens on the life, work and study of patients, as
29 well as the society and economy of various countries.¹⁰ Relevant clinical data show that
30 after an average of 5 years of NMO, about 1/4 of the patients will be unable to walk
31 independently, about 10% will be wheelchair-dependent, and more than half of the
32 patients will develop severe visual impairment in at least one eye.¹¹ In particular, ON
33 associated with NMO (NMO-ON) has poor recovery of visual impairment even after
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4 conventional treatment. They often develop into severe bilateral visual impairment in
5 the long term, leaving behind varying degrees of optic atrophy, which is different from
6 MS.^{12 13}
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9 Currently, there are no uniform guidelines for the clinical management of NMOSD.
10 The class of drugs in treating NMOSD is collectively referred to as disease modifying
11 drugs,¹⁴ and the treatment is divided into two stages: acute phase and remission phase.
12 The former is based on corticosteroids to reduce the severity of acute attacks. Treatment
13 options include intravenous corticosteroids (IVCSs), plasma exchange (PLEX) and
14 immunoglobulin. Immunosuppressive agents are often used in the latter to prevent
15 recurrence and reduce the progression of neurological disability.¹⁵ Common drugs
16 include mycophenolate mofetil (MMF), azathioprine (AZA), tacrolimus, cyclosporine,
17 and monoclonal antibodies, etc.¹⁵ Although AZA and rituximab are suggested as first-
18 line treatments based on observational studies and expert opinion from the published
19 guidelines for NMOSD recommending,¹⁶ there are still AEs such as disease recurrence
20 and myelosuppression, which lead to drug withdrawal in patients with MMF.¹⁷ In recent
21 years, rituximab has also been reports of infusion reactions, infection, and even death,<sup>18-
22 20</sup> and its clinical application has been limited by factors such as high price.^{18 21}
23 Therefore, we urgently need to find new immunoregulatory drugs for the treatment of
24 NMOSD. The application of MMF in NMOSD is still in the exploration stage and is
25 recommended as second-line treatments,¹⁶ but a number of studies have confirmed the
26 efficacy and promising prospect of MMF in the treatment of NMOSD,²¹⁻²⁴ and only a
27 few adverse events (AEs) have been reported.^{21 22} Further studies also suggested that
28 MMF was more effective and caused fewer AEs than AZA.^{25 26}
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31 Although MMF is increasingly used in NMOSD, its therapeutic effect and safety are
32 still controversial. There are no systematic reviews and meta-analysis yet that evaluated
33 the effects of MMF against other therapies in patients with NMOSD. It is therefore
34 timely to perform a systematic review and meta-analysis to assess the efficacy and
35 safety of MMF on current research for its potential use in clinical practice in treating
36 NMOSD.
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38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 **2. Methods**

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4 This protocol has been registered on PROSPERO (registration number: CRD
5 42020164179). Our protocol will follow the Meta-analysis of Observational Studies in
6 Epidemiology (MOOSE),²⁷ the Cochrane Handbook for Systematic Reviews of
7 Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-
8 Analysis Protocol (PRISMA-P) statement guidelines.^{28 29}

13 **2.1 Inclusion criteria for study selection**

15 **2.1.1 Types of studies**

17 All comparative researches, from randomized controlled trials (RCTs) to cohort studies,
18 and case-control study, covering at least two interventions, will be included. The current
19 clinical trial results will be objectively integrated, which is conducive to the evaluation
20 of the efficacy and safety of MMF for NMOSD. We will exclude reviews, qualitative
21 studies, animal trials, laboratory studies and studies only involving one intervention.

27 **2.1.2 Types of patients**

29 Patients diagnosed as having NMOSD will be included in the study.^{5 30} There will be
30 no restrictions based on other conditions, such as age at onset, sex, ethnicity,
31 educational or economic status, number of relapses prior to treatment, previous
32 treatment, duration of illness, disease severity, and baseline expanded disability status
33 scales (EDSS), AQP4-IgG serological status.

39 **2.1.3 Types of interventions**

41 Trials comparing MMF to placebo or to any other active drugs will be considered.
42 Besides, the types, dosage, and frequency of MMF were not limited. Studies that MMF
43 with combination therapy fail to objectively evaluate the efficacy and safety of MMF
44 will be excluded. The control interventions will include AZA, tacrolimus, cyclosporine,
45 and monoclonal antibody drugs, placebo, etc.

50 **2.1.4 Types of outcome measures**

52 **2.1.4.1 Primary outcomes**

54 (1) EDSS: Disability progression was defined as an increase of at least 1 point above
55 the pre-treatment score if baseline score < 5.5, and of at least a half point if baseline
56 score > 5.5, of the Kurtzke EDSS. Outcome measured was the mean change in the
57 EDSS from before and after MMF treatment.^{31 32}

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4 (2) Annualized relapse rate (ARR): A relapse is defined as neurologic symptoms
5 lasting for > 24 h, which occur at least 30 days after the onset of a preceding event.
6 ARR is computed as a function of the number of relapse over the number of days
7 (years) in observation. Post-treatment ARR were compared to pre-treatment ARR.
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13 **2.1.4.2 Secondary outcomes**

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15 (1) The frequency and extent of Adverse events (AEs): Any symptomatic events which
16 had a possible, probable or definite causal relationship with MMF treatment were
17 defined as AEs during the treatment and follow-up periods.
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19 (2) Relapse-free rate: the absence of relapse during the observation period of the study
20 reported as percentage per study.³²
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22 (3) Best-corrected visual acuity (BCVA): measured according to a validated measure
23 such as the ETDRS chart, Snellen chart or a similar tool, other measures of visual
24 acuity would be considered if outcomes could be justified and validated in relation
25 to accepted relevant standard measures. Outcome measured was the mean change
26 in the BCVA from before and after MMF treatment.³⁴
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- 33 (4) Time to the next attack.
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- 36 (5) Relapse-free rates.
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39 **2.1.4.3 Security index**

40 The safety was assessed by the occurrence of AEs. Any unexpected events that occurred
41 during the studies will be recorded on an adverse event report form, including:³⁵
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- 43 (1) General physical examination (temperature, pulse, respiration, blood pressure).
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45 (2) Routine examination of blood, urine and stool.
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47 (3) Liver and kidney function examination.
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49 (4) Gastrointestinal discomfort.
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51 (5) Hair loss or Alopecia.
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53 (6) Allergic or Anaphylactoid reactions.
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55 (7) Drug discontinued due to drug-related AEs.
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57 (8) Possible AEs and related detection indicators.
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60 **2.2 Search methods for the identification of studies**

2.2.1 Electronic searches

A relevant literature search by sensitive search strategies was conducted using the the following electronic databases from their inception to December 31, 2019: PubMed, Web of Science, EMBASE, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal database (VIP) and CBM. Search methods of MeSH terms with free words were applied in English databases. The related terms are as follows: Participants (neuromyelitis optica, neuromyelitis optica spectrum disorders, Devic Neuromyelitis Optica, Devic's Neuromyelitis Optica, Devic's Syndrome, NMO spectrum disorders), Intervention (mycophenolic acid, mycophenolate mofetil, "mofetil, mycophenolate", cellcept, myfortic, RS61443). The search strategy for PubMed is listed in Table 1, which including all search terms, and other searches will be conducted based on these results. This will be appropriately adapted for search in the other databases. There are no limits on language and publication status.

2.2.2 Searching other resources

we will also search PROSPERO, the International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov, dissertations, and gray literature to identify systematic reviews or clinical trials related to mycophenolate mofetil and neuromyelitis optica spectrum disorders. Relevant journals and conference processes will be manual searched. We will also review papers and bibliographies included in the trials.

2.3 Data collection and analysis

2.3.1 Selection of studies

Two reviewers (MYH and ZQL) will independently browse the titles and abstracts of all of the retrieved records to distinguish and exclude any obviously irrelevant articles. Studies only related to human subjects will be included. Any disagreements will be resolved by discussion between the 2 authors and an arbiter (MJ). The study selection procedure is presented in a PRISMA flow chart (Fig. 1).

2.3.2 Data extraction and management

Based on the inclusion criteria, a standard data collection form will be produced prior to data extraction. Search results will be entered into an EndNote X9 database and

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4 duplicate entries removed. Two authors (MYH and ZQL) will extract the data of
5 interest from the eligible study and enter the following information in the data
6 extraction sheet: The basic characteristics of each study (study design or methods ,
7 author, title, source/journal, time of publication, country, hospital setting); participants
8 characteristics (average age, gender, sample size, inclusion and exclusion criteria,
9 baseline situation); Interventions (type, duration, frequency and dosage of MMF,
10 randomization, allocation concealment, blinding methods); Comparators (AZA,
11 tacrolimus, cyclosporine, monoclonal antibodies, and placebo, etc); Outcomes
12 (measures, main outcomes, security indexes, and follow up); If funded, it will also be
13 recorded. When the consensus on data extraction is not available through discussion,
14 the third reviewer (MJ) will make a decision.

25 **2.3.3 Assessment of risk of bias**

26
27 Two authors (Yang Chen and LQN) will independently evaluate the risk and bias using
28 the Cochrane risk of bias (ROB) assessment tool for RCTs.³⁶ Methodological quality
29 assessment of the included observational studies will be performed using the
30 Newcastle–Ottawa Scale (NOS).³⁷ The RevMan software program (V.5.3) will record
31 the selected details of each study.³⁸

36 **2.3.4 Measures of treatment effect**

37
38 The risk ratio (RR) and 95% confidence interval (CI) will be used to analyze
39 dichotomous data and measure the treatment effect. A weighted mean difference
40 (WMD) or a standard mean difference (SMD) with 95% CIs will be used to analyze
41 continuous outcomes.

46 **2.3.5 Unit of analysis issue**

47
48 We will only extract the 1st experimental period data of crossover trials to avoid
49 carryover effects. Meanwhile, considering that there are multiple intervention groups
50 in trials, we will combine all analogous groups into a single pairwise comparison to
51 prevent a unit of analysis issue.

56 **2.3.6 Management of missing data**

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58 Reviewer (YLQ) will contact the appropriate author of the included trials for
59 clarification or more details via email and telephone if necessary. The missing data will
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4 be deleted, if there is no response from the author. In this case, this will be addressed
5 in the discussion. Qualitative analysis would be used if relevant data was not available.

7 **2.3.7 Assessment of heterogeneity and data synthesis**

9 We will use the complete case data as the analysis data. Heterogeneity will be tested
10 with a standard Chisquare test.³⁹ In order to quantify the impact of the statistical
11 heterogeneity on the systematic review, the I^2 value will be applied to calculate and
12 present the heterogeneity degree. When $P > 0.1$, $I^2 < 50\%$, it is considered that there is no
13 heterogeneity between the trials, and the fixed effect model will be used, otherwise, the
14 random effect model will be adopted. All statistical analyses will be performed using
15 RevMan5.3 software provided by the Cochrane Collaboration. Using the software to
16 obtain forest plots and test the heterogeneity between the included studies. The Grades
17 of Recommendation, Assessment, Development and Evaluation (GRADE) will be use
18 to assess the meta-analysis findings and determine the quality of evidence. Narrative
19 comprehensive synthesis will be adopted, if meta-analysis is not possible due to lack of
20 clinical studies or heterogeneity.

31 **2.3.8 Assessment of reporting biases**

32
33 When 10 or more studies are included in a meta-analysis, we will assess funnel plot
34 asymmetry for reporting biases and small study effects using Egger's method.⁴⁰ For
35 Egger's test, P value of greater than 0.05 was determined as no considerable publication
36 bias or small-study effects in studies. As funnel plot asymmetry does not necessarily
37 suggest reporting bias, we will try to distinguish possible reasons for the asymmetry,
38 including poor methodological quality and true heterogeneity of studies.

45 **2.3.9 Subgroup analysis**

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47 When heterogeneity is detected, a subgroup analysis will be conducted to judge the
48 source of heterogeneity. The criteria for a subgroup analysis are as follows:

- 49 (1) Age.
 - 50 (2) Type of MMF.
 - 51 (3) Research type.
 - 52 (4) Participation population.
 - 53 (5) Type of control interventions.
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4 (6) Intervention dosage, frequency and duration.

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6 (7) AQP4-IgG serological status.

7 8 **2.3.10 Sensitivity analysis**

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10 In the case of sufficient trials data, the ROB tool will be used to assess methodological
11 quality. Sensitivity analysis will be performed to assess the robustness of aggregate
12 estimates and to detect whether any single study accounts for a significant proportion
13 of heterogeneity by removing the included studies one by one from the summary
14 analysis. If low-quality articles are deleted, a second meta-analysis will be performed.
15 The results and effect size of the two meta-analyses will be compared and discussed.⁴¹

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21 **2.4 Patient and public involvement** Patients and/or the public will not participate in
22 the study. However, once our findings are disseminated by scientific publications, they
23 are shared through social networks, so that our conclusions can influence the behavior
24 of neuro-ophthalmologist and health policy makers.

25 26 27 28 **3 Discussion**

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31 NMOSD is an inflammatory and heterogeneous astrocyte disorder of the CNS with the
32 characteristic of higher incidence in women and Asian, concerned because of its high
33 pathogenicity, high risk of recurrence and poor prognosis.¹ Most patients with NMOSD
34 have a course of recurrence and remission, which are prone to cause paralysis and
35 blindness,⁵ bringing heavy burdens on the life, work and study of patients, as well as
36 the society and economy of various countries. At present, the treatment of NMOSD is
37 divided into two stages: acute phase (IVCSs, PLEX, and immunoglobulin) and
38 remission phase (MMF, AZA, tacrolimus, cyclosporine, monoclonal antibodies, etc.).¹⁵
39 AEs associated with AZA were seemingly frequent and may contribute to patient
40 nonadherence to prescribed medication.^{16 17} In recent years, rituximab has been
41 recommended to prevent recurrence of NMOSD, but there have also been reports of
42 infusion reactions, infection, and even death,¹⁸⁻²⁰ and its clinical application has been
43 limited by factors such as high price.^{18 21} Therefore, we urgently need to find new
44 immunoregulatory drugs for the treatment of NMOSD.

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A number of studies have confirmed the efficacy and promising prospect of MMF in
the treatment of NMOSD,²¹⁻²⁴ and only a few adverse events (AEs) have been reported.

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4^{21 22} Further studies also suggested that MMF was more effective and caused fewer AEs
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than AZA.^{25 26} However, there are controversial about its therapeutic effect and safety. The primary objective of this systematic review is to evaluate the clinical efficacy and safety of MMF in the treatment of NMO. We will conduct qualitative and quantitative analysis of the overall data included in each study. The presented evidences were collected from RCTs and observational studies with different evidence strengths to provide more comprehensive analysis. Therefore, the heterogeneity of the methodology will be a major limitation in this systematic review, which may lead to some results not being analyzed. We expect that this systematic review will benefit patients with NMOSD, clinicians, healthcare managers and policy-makers.

Author contributions

MYH conceived and designed the protocol, and MYH drafted the protocol manuscript. MYH developed the search strategy, with input from ZQL and LQN. MYH and ZQL planned the data extraction. MYH, Yang Chen and ZJW planned the quality appraisal of all included studies. MYH, ZQL, LQN, Yang Chen, HM, YC, ZJW, YLQ and MJ critically revised the manuscript for methodological and intellectual content. All authors approved the final version.

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Reference

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SUPPLEMENTARY MATERIAL

Table 1 Search strategy used in PubMed database.

Number	Search terms
#1	("Neuromyelitis Optica"[Mesh]) OR (((((neuromyelitis optica spectrum disorders [Title/Abstract]) OR Devic Neuromyelitis Optica [Title/Abstract]) OR Devic's Neuromyelitis Optica [Title/Abstract]) OR Devic's Syndrome [Title/Abstract]) OR NMO spectrum disorders [Title/Abstract])
#2	("Mycophenolic Acid"[Mesh]) OR (((((Mycophenolate Mofetil [Title/Abstract]) OR "Mofetil,Mycophenolate" [Title/Abstract]) OR

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4	Cellcept [Title/Abstract]) OR Myfortic [Title/Abstract]) OR RS61443
5	[Title/Abstract])
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7	#3
8	((("Randomized Controlled Trial" [Publication Type]) OR
9	RCT[Title/Abstract])) OR (("Cohort Studies"[Mesh]) OR ((cohort
10	study[Title/Abstract]) OR "studies, cohort"[Title/Abstract]))) OR
11	(((Case-Referrent Studies[Title/Abstract]) OR Case-Base
12	Studies[Title/Abstract])) OR (("Case-Control Studies"[Mesh]) OR
13	Case-Comparison Studies[Title/Abstract]))
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19	#4
20	#1 and #2 and #3

Figure1. The PRISMA flow chart of the selection process.

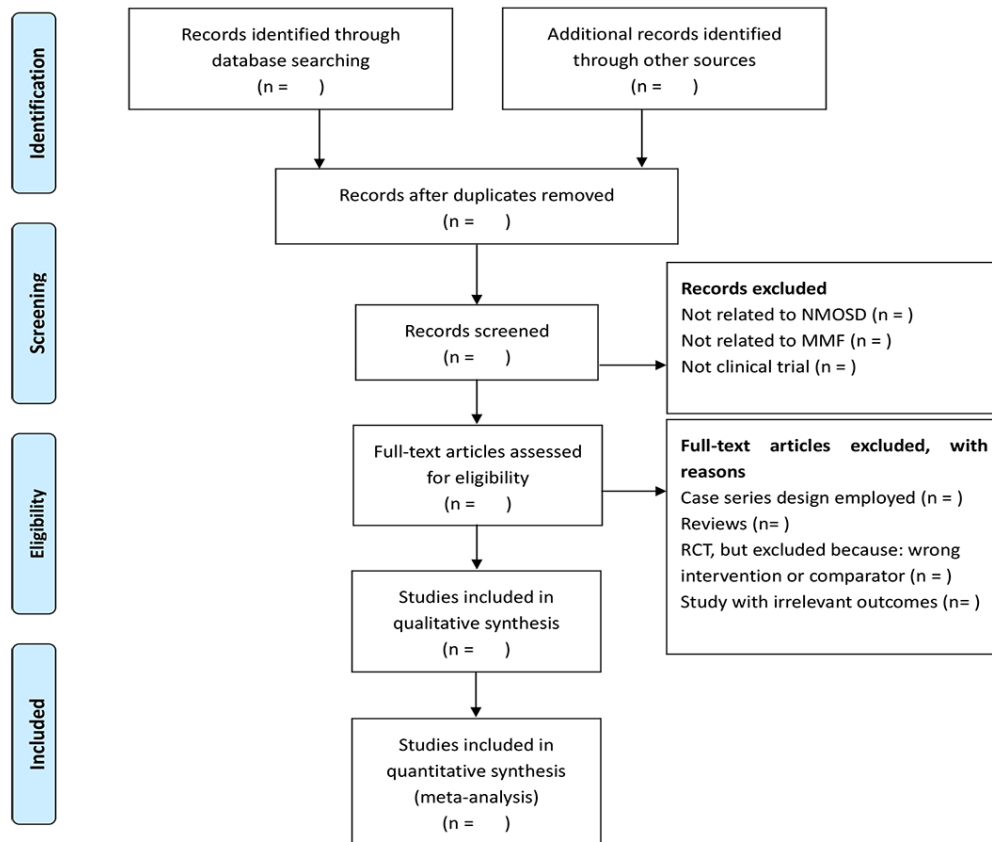


Figure1. The PRISMA flow chart of the selection process.

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Reporting guidelines, and cite them as:

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			Page
		Reporting Item	Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	Page 1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	

1 Registration

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4 [#2](#) If registered, provide the name of the registry (such as Page 2
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6 PROSPERO) and registration number
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9 Authors

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13 Contact [#3a](#) Provide name, institutional affiliation, e-mail address of all Page 1
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15 protocol authors; provide physical mailing address of
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17 corresponding author
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20 Contribution [#3b](#) Describe contributions of protocol authors and identify the Page1,11,12
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22 guarantor of the review
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25 Amendments

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29 [#4](#) If the protocol represents an amendment of a previously
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31 completed or published protocol, identify as such and list
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33 changes; otherwise, state plan for documenting important
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35 protocol amendments
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38 Support

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42 Sources [#5a](#) Indicate sources of financial or other support for the review Page 1
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45 Sponsor [#5b](#) Provide name for the review funder and / or sponsor Page 1
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48 Role of sponsor or [#5c](#) Describe roles of funder(s), sponsor(s), and / or Page 1
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50 funder institution(s), if any, in developing the protocol
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53 Introduction

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56 Rationale [#6](#) Describe the rationale for the review in the context of what Page 2,3,4
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1 is already known
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4	Objectives	#7	Provide an explicit statement of the question(s) the review Page 5,6
5			
6			will address with reference to participants, interventions,
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8			comparators, and outcomes (PICO)
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11	Methods		
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14	Eligibility criteria	#8	Specify the study characteristics (such as PICO, study Page 7,8
15			
16			design, setting, time frame) and report characteristics
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18			(such as years considered, language, publication status) to
19			
20			be used as criteria for eligibility for the review
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24	Information	#9	Describe all intended information sources (such as Page 7,8
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26	sources		electronic databases, contact with study authors, trial
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28			registers or other grey literature sources) with planned
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30			dates of coverage
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34	Search strategy	#10	Present draft of search strategy to be used for at least one Page 7
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36			electronic database, including planned limits, such that it
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38			could be repeated
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41	Study records -	#11a	Describe the mechanism(s) that will be used to manage Page7,8
42			
43	data management		records and data throughout the review
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47	Study records -	#11b	State the process that will be used for selecting studies Page 7,8
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49	selection process		(such as two independent reviewers) through each phase
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51			of the review (that is, screening, eligibility and inclusion in
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53			meta-analysis)
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57	Study records -	#11c	Describe planned method of extracting data from reports Page 7,8,9
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1	data collection		(such as piloting forms, done independently, in duplicate),	
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3	process		any processes for obtaining and confirming data from	
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5			investigators	
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8	Data items	#12	List and define all variables for which data will be sought	Page 8
9				
10			(such as PICO items, funding sources), any pre-planned	
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12			data assumptions and simplifications	
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15	Outcomes and	#13	List and define all outcomes for which data will be sought,	Page5,6
16				
17	prioritization		including prioritization of main and additional outcomes,	
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19			with rationale	
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23	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	Page 8
24				
25	individual studies		individual studies, including whether this will be done at	
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27			the outcome or study level, or both; state how this	
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29			information will be used in data synthesis	
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33	Data synthesis	#15a	Describe criteria under which study data will be	Page 9
34				
35			quantitatively synthesised	
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38	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe	Page 9
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40			planned summary measures, methods of handling data	
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42			and methods of combining data from studies, including any	
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44			planned exploration of consistency (such as I ² , Kendall's	
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50	Data synthesis	#15c	Describe any proposed additional analyses (such as	Page 9,10
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52			sensitivity or subgroup analyses, meta-regression)	
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56	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the	Page 9
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1 type of summary planned

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4 Meta-bias(es) [#16](#) Specify any planned assessment of meta-bias(es) (such Page 8,9
5 as publication bias across studies, selective reporting
6 within studies)
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11 Confidence in [#17](#) Describe how the strength of the body of evidence will be Page 9
12 cumulative assessed (such as GRADE)
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15 evidence

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18 None The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution
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20 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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BMJ Open

Safety and Efficacy of Mycophenolate Mofetil in Treating NMOSD : a protocol for systematic review and meta-analysis.

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Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Neurology, Evidence based practice
Keywords:	OPHTHALMOLOGY, NEUROLOGY, IMMUNOLOGY, Neuro-ophthalmology < NEUROLOGY

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4 Safety and Efficacy of Mycophenolate Mofetil in Treating NMOSD : a protocol
5 for systematic review and meta-analysis.

6 Mengyu Han, PhD^{a,b}, Luqi Nong, MD^{a,b}, Ziqiang Liu, MD^{a,b}, You Chen^b, Yang
7 Chen, MD^{a,b}, Huan Meng, MD^{a,b}, Yali Qin, MD^c, Zhi-Jun Wang, MD^b, Ming
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20 Hospital, No. 2, Yinghua Donglu, Chaoyang District, Beijing 100029, China (e-mail:
21 jinmingyk@163.com).

22 23 24 25 **Abstract**

26
27 **Introduction** Neuromyelitis optica spectrum disorders (NMOSD) is an inflammatory
28 and heterogeneous astrocyte disorder of the central nervous system (CNS) with the
29 characteristic of higher incidence in women and Asian. Most patients with NMOSD
30 have a course of recurrence and remission that is prone to cause paralysis and blindness.
31 Several studies have confirmed the efficacy and promising prospect of mycophenolate
32 mofetil (MMF) in the treatment of NMOSD. Yet its therapeutic effect and safety are
33 controversial. This research aims to perform a systematic review and meta-analysis to
34 evaluate MMF's effectiveness and safety in treating NMOSD.

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42 **Methods and analysis** This systematic review will cover all comparative researches,
43 from randomized controlled trials (RCTs) to cohort studies, and case-control study. A
44 relevant literature search will be conducted in PubMed, Web of Science, EMBASE, the
45 Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang
46 Database, China Science and Technology Journal database (VIP) and Chinese
47 Biomedical Literature database (CBM). We will also search registers of clinical trials,
48 potential gray literature, and abstracts from conferences. There are no limits on
49 language and publication status. The reporting quality and risk of bias will be assessed
50 by two researchers independently. Expanded disability status scales (EDSS),
51 annualized relapse rate (ARR) will be evaluated as the primary outcome. The secondary
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4 outcomes will consist of the frequency and severity of adverse events (AEs), best-
5 corrected visual acuity (BCVA), relapse-free rate and time to the next attack. A meta-
6 analysis will be performed using RevMan5.3 software provided by the Cochrane
7 Collaboration and Stata 12.0.
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11 **Ethics and dissemination** Because the data used for this systematic review will be
12 exclusively extracted from published studies, ethical approval and informed consent of
13 patients will not be required. The systematic review will be published in a peer-
14 reviewed journal, presented at conferences and will be shared on social media platforms.
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17 **PROSPERO registration number:** PROSPERO CRD42020164179.
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21 **Strengths and limitations of this study:**
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23 ▶ This study will carry out an exhaustive literature search to identify studies aimed at
24 evaluating the efficacy and safety of MMF in treating NMOSD.
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26 ▶ One limitation of this study is that differences in patients, interventions and primary
27 outcomes may mean that meta-analysis cannot be performed and there are plans for
28 narrative and meta-analytical syntheses.
29

30 ▶ Although we will include studies published in any language, translation difficulties
31 may arise, which will result in the exclusion of these studies.
32

33 ▶ The analysis of various sources of heterogeneity and the assessment of risk of bias
34 of the included studies is a critical point for extracting and synthesizing evidence-based
35 conclusions.
36

37
38 **Keywords:** mycophenolate mofetil, neuromyelitis optica spectrum disorders, protocol,
39 systematic review, meta-analysis.
40

41
42 **1. Introduction**
43

44 Neuromyelitis Optica (NMO), also known as Devic disease, is generally considered to
45 be a rare autoimmune astrocyte disorder of the central nervous system (CNS), induced
46 by autoantibodies, dominated by humoral immunity and involving numerous immune
47 cells and factors, with optic neuritis(ON) and acute transverse myelitis as typical
48 clinical manifestations.¹ NMO has been known as a subtype of multiple sclerosis (MS)
49 for over 100 years since it was first described and reported.² Until 2004, the discovery
50 and confirmation of anti-aquaporin-4 immunoglobulin G (AQP4-IgG) had made
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4 substantial progress in pathogenesis, diagnosis, and treatment of NMO.^{3 4} The notion
5 of neuromyelitis optica spectrum disorders (NMOSD) was first proposed based on the
6 wide clinical use of specific AQP4-IgG,⁴ which mainly referred to the minimal AQP4-
7 IgG positive NMO. However, the deficiencies of the diagnostic criteria of NMO in
8 2006 and NMOSD in 2007 became prominent with the incremental improvement of the
9 specificity of clinical AQP4-IgG tests. In 2015, a groundbreaking international
10 diagnostic protocol for NMOSD was put forward by the global NMO diagnostic team.⁵
11 NMOSD consists of NMO, ON, longitudinally extensive transverse myelitis and other
12 common cerebral demyelinating syndromes.⁵ There are so far no reliable statistics on
13 the worldwide incidence and prevalence of NMOSD. According to the current
14 epidemiological evidence of small samples, the high incidence of this disease is among
15 middle-aged and young women, with the onset age varying from 32 to 41 years old,
16 and the incidence in females is about 10 times that of males.⁵ The incidence and
17 prevalence of approximately 0.05-0.40 and 0.52-4.40/100,000 vary from region to
18 region.⁶ A populous region of Asia is the region with a high incidence of NMOSD.⁷⁻⁹
19 Most NMOSD patients have a recurrence and remission including ON, myelitis, and
20 lesions in special parts of the brain that are vulnerable to cause paralysis and blindness.⁵
21 NMOSD has become one of the most common causes of non-traumatic disability and
22 blindness in young and middle-aged individuals, putting heavy burdens on the life,
23 work and study, as well as the society and economy of various countries.¹⁰ Clinical
24 studies indicate that approximately 1/4 of patients will not be able to walk
25 independently after an average of 5 years of NMO, approximately 10% will be
26 wheelchair-dependent, and more than half of patients will have serious vision loss in at
27 least one eye.¹¹ In particular, ON associated with NMO (NMO-ON) possesses poor
28 recovery even after traditional therapy, which often progresses into significant bilateral
29 visual loss in the long term, leaving behind varying degrees of optic atrophy, which is
30 different from MS.^{12 13}

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56 Currently, there are no standardized guidelines for the clinical management of NMOSD.
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58 The class of NMOSD drugs is commonly referred to as disease-modifying drugs,¹⁴ and
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60 the treatment is split into two stages: the acute phase and the period of remission. The

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4 former is based on corticosteroids to reduce the severity and frequency of acute attacks
5 that include intravenous corticosteroids (IVCSs), plasma exchange (PLEX), and
6 immunoglobulin. Immunosuppressive agents, including mycophenolate mofetil
7 (MMF), azathioprine (AZA), cyclophosphamide, methotrexate, mitoxantrone,
8 tacrolimus, cyclosporine, and monoclonal antibodies, are frequently used during the
9 process of recovery to avoid recurrence and to mitigate the progression of neurological
10 impairment.^{15 16} Although AZA and rituximab are recommended as first-line therapies
11 obtained from clinical trials and expert opinion from the published guidelines for
12 NMOSD,¹⁶ there are still adverse events (AEs) such as disease recurrence and
13 myelosuppression that result in drug withdrawal or replacement of patients with
14 NMOSD.¹⁷ Rituximab has also been reported in recent years as infusion reactions,
15 infection, and even death,¹⁸⁻²⁰ and its clinical application has been constrained by such
16 factors as high price.^{18 21} Therefore, a better immunosuppressant for the treatment of
17 NMOSD is urgently needed. The application of MMF in NMOSD is still under
18 investigation and is recommended as second-line treatments,¹⁶ but some studies have
19 verified MMF's efficacy and promising potential,²¹⁻²⁴ and only a few AEs were
20 published.^{21 22} Especially, additional studies have also indicated that MMF was more
21 effective and triggered less AEs than AZA.^{25 26} In patients experiencing AEs or poor
22 response to AZA, MMF is recommended as an alternative therapy.¹⁶

23
24 Although MMF is increasingly employed in NMOSD, there is still controversy about
25 its related harms and benefits. At present, only low evidence exists concerning
26 comparative treatment efficacy of MMF with other drugs. Based on current clinical
27 trials, it is therefore timely to perform a systematic review and meta-analysis to
28 elucidate the efficacy and safety of MMF in treating NMOSD.

2. Methods

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30 This protocol has been registered on PROSPERO (registration number: CRD
31 42020164179). Our protocol will follow the Meta-analysis of Observational Studies in
32 Epidemiology (MOOSE),²⁷ the Cochrane Handbook for Systematic Reviews of
33 Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-
34 Analysis Protocol (PRISMA-P) statement guidelines.^{28 29}

2.1 Inclusion criteria for study selection

2.1.1 Types of studies

All comparative researches, from randomized controlled trials (RCTs) to cohort studies, and case-control study, covering at least two interventions, will be included. The current clinical trial results will be objectively integrated, which is conducive to the evaluation of the efficacy and safety of MMF for NMOSD. We will exclude reviews, qualitative studies, animal trials, laboratory studies and studies only involving one intervention.

2.1.2 Types of patients

Patients diagnosed as having NMOSD will be included in this study.^{5 30} There will be no restrictions based on other conditions, such as age at onset, sex, ethnicity, educational or economic status, number of pre-treatment relapses, previous treatment, duration of illness, disease severity, and baseline expanded disability status scales (EDSS), AQP4-IgG serological status.

2.1.3 Types of interventions

Trials comparing MMF to placebo or any other active substances, including AZA, cyclophosphamide, methotrexate, mitoxantrone, tacrolimus, cyclosporine, and monoclonal antibodies, will be considered. Besides, the types, dosage, and frequency of MMF were not limited. Studies that MMF with combination therapy fail to objectively evaluate the efficacy and safety of MMF will be eliminated.

2.1.4 Types of outcome measures

2.1.4.1 Primary outcomes

- (1) EDSS: Disability progression was characterized as an increase in the Kurtzke EDSS by at least 1 point above the pre-treatment score if baseline score < 5.5, and by at least half-point if baseline score > 5.5. Outcome measured was the mean changes of EDSS before and after MMF treatment.^{31 32}
- (2) Annualized relapse rate (ARR): Relapse is equivalent to a neurologic symptom lasting for > 24 h, which occurs at least 30 days after the onset of a preceding event. ARR is computed as the number of relapses divided by the time in years (days). Post-treatment ARR was contrasted with pre-treatment ARR.³³

2.1.4.2 Secondary outcomes

- (1) The frequency and extent of AEs: During treatment and follow-up periods, any symptomatic events which had a possible, probable or definite causal relationship to MMF treatment were defined as AEs.
- (2) Relapse-free rate: The absence of relapse during the observation period of the study reported as percentage per study.³²
- (3) Best-corrected visual acuity (BCVA): BCVA was measured using a standardized test, such as the ETDRS chart, Snellen chart or similar method, and other visual acuity measures would be allowed if findings could be justified as well as validated concerning accepted relevant standard measures. Outcome measured was the mean change of BCVA from before and after MMF treatment.³⁴
- (4) Time to the next attack.

2.1.4.3 Security index

The safety was assessed by the occurrence of AEs. Any unexpected events that occurred during the studies will be recorded on an AEs report form, including:³⁵

- (1) General physical examination (temperature, pulse, respiration, blood pressure).
- (2) Routine examination of blood, urine and stool.
- (3) Liver and kidney function examination.
- (4) Gastrointestinal discomfort.
- (5) Hair loss or Alopecia.
- (6) Allergic or Anaphylactoid reactions.
- (7) Drug discontinued due to drug-related AEs.
- (8) Possible AEs and related detection indicators.

2.2 Search methods for the identification of studies

2.2.1 Electronic searches

A relevant literature search by sensitive search strategies was conducted using the following electronic databases from their inception to June 31, 2020: PubMed, Web of Science, EMBASE, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal database (VIP) and Chinese Biomedical Literature database (CBM). Search methods of MeSH terms with free words were applied in English databases. The related terms are as follows:

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4 Participants (neuromyelitis optica, neuromyelitis optica spectrum disorders, Devic
5 Neuromyelitis Optica, Devic's Neuromyelitis Optica, Devic's Syndrome, NMO
6 spectrum disorders), Intervention (mycophenolic acid, mycophenolate mofetil, “mofetil,
7 mycophenolate”, cellcept, myfortic, RS61443). The search strategy for PubMed is
8 described in Table 1, which will include all search terms, and other searches will be
9 carried out based on those results. This will be suitably adapted to search in the other
10 databases. There are no limits on language and publication status.

17 **2.2.2 Searching other resources**

18 we will also search PROSPERO, the International Clinical Trials Registry Platform
19 (ICTRP), ClinicalTrials.gov, dissertations, and gray literature to identify systematic
20 reviews or clinical trials related to mycophenolate mofetil and neuromyelitis optica
21 spectrum disorders. Manual searches will be conducted for related journals and
22 conference processes. We will also review papers and bibliographies included in the
23 trials.

31 **2.3 Data collection and analysis**

33 **2.3.1 Selection of studies**

34 Two reviewers (MYH and ZQL) will independently browse the titles and abstracts of
35 all of the retrieved records to distinguish and exclude any irrelevant articles. Studies
36 only related to human subjects are to be included. Any discord will be resolved by
37 discussion between the two authors and an arbiter (MJ). The selection procedure for the
38 study is shown in a PRISMA flow chart (Fig. 1).

45 **2.3.2 Data extraction and management**

46 Based on the inclusion criteria, a standard form of data collection will be produced prior
47 to data extraction. Search results will be entered into an EndNote X9 database and
48 duplicate entries removed. Two authors (MYH and ZQL) will extract the data of
49 interest from the eligible study and enter the data extraction sheet as follows: The basic
50 characteristics of each study (study design or methods, author, title, source/journal, time
51 of publication, country, hospital setting); participants characteristics (average age,
52 gender, sample size, inclusion and exclusion criteria, baseline situation); Interventions
53 (type, duration, frequency and dosage of MMF, randomization, allocation concealment,
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4 blinding methods); Comparators (AZA, tacrolimus, cyclosporine, monoclonal
5 antibodies, and placebo, etc); Outcomes (measures, main outcomes, security indexes,
6 and follow up); If funded, it will also be recorded. When the consensus on data
7 extraction is not available through discussion, the third reviewer (MJ) will make a
8 decision.
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13 **2.3.3 Assessment of risk of bias**

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15 Two authors (Yang Chen and LQN) will independently estimate the risk and bias using
16 the Cochrane risk of bias (ROB) assessment tool for RCTs.³⁶ Methodological quality
17 evaluation of the included observational studies will be carried out using the
18 Newcastle–Ottawa Scale (NOS).³⁷ The RevMan software program (V.5.3) will
19 document the selected details of each study.³⁸
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25 **2.3.4 Measures of treatment effect**

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27 The risk ratio (RR) and 95% confidence interval (CI) will be used to analyze
28 dichotomous data and calculate the treatment effect. A weighted mean difference
29 (WMD) or a standard mean difference (SMD) with 95% CIs will be used to analyze
30 continuous outcomes.
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35 **2.3.5 Unit of analysis issue**

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37 We will only extract the 1st experimental period data of crossover trials to avoid
38 carryover effects. In the meantime, given that there are multiple intervention groups in
39 trials, we will combine all analogous groups into a single pairwise comparison to avoid
40 the issue of a unit of analysis.
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45 **2.3.6 Management of missing data**

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47 Reviewer (YLQ and You Chen) will contact the appropriate author of the included trials
48 for clarification or more details via email and telephone if necessary. The missing data
49 will be deleted, if there is no response from the author. That will be addressed in the
50 discussion in this case. If quantitative data were not available, then the qualitative
51 analysis should be used.
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56 **2.3.7 Assessment of heterogeneity and data synthesis**

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58 We will use all of the case data for the analysis data. Heterogeneity will be tested with
59 a standard Chisquare test.³⁹ To quantify the impact of the statistical heterogeneity on
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4 the systematic review, the I^2 value will be applied to calculate and present the
5 heterogeneity degree. If $P > 0.1$, $I^2 < 50\%$, it is considered that there is no heterogeneity
6 between the trials, and the model of fixed effect will be used, otherwise, the model of
7 random effect will be adopted. All statistical analyzes will be performed using the
8 RevMan5.3 software provided by the Cochrane Collaboration. Using the software to
9 obtain forest plots and test the heterogeneity between the included studies. The Grades
10 of Recommendation, Assessment, Development and Evaluation (GRADE) will be used
11 to assess the meta-analysis findings and determine the quality of evidence. Where meta-
12 analysis is not feasible due to lack of clinical trials or heterogeneity, systematic
13 narrative synthesis is adopted.

23 **2.3.8 Assessment of reporting biases**

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25 When 10 or more studies are included in a meta-analysis, we will evaluate funnel plot
26 asymmetry for reporting biases and small-study effects using Egger's method.⁴⁰ For
27 Egger's test, P value of greater than 0.05 was determined as no significant publishing
28 bias or small-study effects in studies. As funnel plot asymmetry does not necessarily
29 suggest reporting bias, we will attempt to recognize potential causes for the asymmetry,
30 including poor methodological quality and true heterogeneity of studies.

36 **2.3.9 Subgroup analysis**

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38 Upon detection of heterogeneity, a subgroup analysis will be carried out to judge the
39 source of heterogeneity. The criteria for a subgroup analysis are as follows:

- 42 (1) Age.
- 44 (2) Type of MMF.
- 46 (3) Research type.
- 48 (4) Participation population.
- 50 (5) Type of control interventions.
- 52 (6) Intervention dosage, frequency and duration.
- 54 (7) AQP4-IgG serological status.

56 **2.3.10 Sensitivity analysis**

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58 The ROB tool will be used to estimate methodological quality in the case of sufficient
59 data from trials. Sensitivity analysis will be performed to determine the robustness of
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4 aggregate estimates and to detect whether any single study accounts for a substantial
5 proportion of heterogeneity by eliminating the included studies from the summary
6 review one by one. If low-quality articles are deleted, then a second meta-analysis will
7 be carried out. Comparison and discussion of the results and effect size of the two meta-
8 analyses will be held. ⁴¹

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13 **2.4 Patient and public involvement** Patients and/or the public will not participate in
14 the study. However, once scientific publications disseminate our findings, they are
15 circulated across social networks so that our conclusions will affect the actions of
16 neuro-ophthalmologists and health policymakers.

21 **3 Discussion**

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23 Pathogenesis, diagnosis and treatment of NMO are rapidly growing areas of research
24 as AQP4-IgG were first identified. Patients with NMOSD should receive standardized
25 and personalized immunotherapy as soon as possible, as any further acute episodes may
26 result in severe and often irreversible disability. The challenges in discovering new and
27 better drugs for NMO are the rareness of the disease and the unfavorable prognosis in
28 many cases, which make clinical studies with placebo groups difficult.¹⁶ Many studies
29 have confirmed the efficacy and promising prospect of MMF in the treatment of
30 NMOSD,²¹⁻²⁴ and only a few AEs were reported.^{21 22} Additional studies have also
31 indicated that MMF was more effective and triggered less AEs than AZA.^{25 26} However,
32 its therapeutic effect and safety remain controversial. The primary aim of this
33 systematic review is to determine MMF's clinical effectiveness and safety in treating
34 NMOSD. The overall data used in each analysis will be evaluated qualitatively and
35 quantitatively. To provide a more detailed review, the evidence provided was obtained
36 from RCTs and observational studies with different evidence strengths. Hence, the
37 methodology's variability would be a significant weakness of this systematic analysis,
38 which may result in certain results not being evaluated. We expect that this systematic
39 review will benefit patients with NMOSD, physicians, health care administrators and
40 policy-makers.

56 **Author contributions**

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3 MYH conceived and designed the protocol, and MYH drafted the protocol manuscript.
4 MYH developed the search strategy, with input from ZQL and LQN. MYH and ZQL
5 planned data extraction. MYH, Yang Chen and ZJW planned the quality appraisal of
6 all included studies. MYH, ZQL, LQN, Yang Chen, HM, You Chen, ZJW, YLQ and
7 MJ critically revised the manuscript for methodological and intellectual content. All
8 authors approved the final version.
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13 **Conceptualization:** Meng-Yu Han, Zi-Qiang Liu, Zhi-Jun Wang, Ming Jin.

14 **Data curation:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Huan Meng.

15 **Formal analysis:** Meng-Yu Han, Zi-Qiang Liu.

16 **Funding acquisition:** Meng-Yu Han.

17 **Investigation:** Ming Jin.

18 **Methodology:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, You Chen.

19 **Project administration:** Ming Jin.

20 **Resources:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

21 **Software:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong.

22 **Supervision:** Meng-Yu Han, Zhi-Jun Wang, Ming Jin.

23 **Validation:** Huan Meng, Yang Chen, Ya-li Qin, Ming Jin.

24 **Visualization:** Huan Meng, Yang Chen, Ya-li Qin, Ming Jin.

25 **Writing – original draft:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

26 **Writing – review & editing:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

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35 study.
36

37 **Competing interests:** None declared.
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Table 1 Search strategy used in PubMed database.

Number	Search terms
#1	("Neuromyelitis Optica"[Mesh]) OR (((((neuromyelitis optica spectrum disorders [Title/Abstract]) OR Devic Neuromyelitis Optica [Title/Abstract]) OR Devic's Neuromyelitis Optica [Title/Abstract]) OR Devic's Syndrome [Title/Abstract]) OR NMO spectrum disorders [Title/Abstract])
#2	("Mycophenolic Acid"[Mesh]) OR (((((Mycophenolate Mofetil [Title/Abstract]) OR "Mofetil,Mycophenolate" [Title/Abstract]) OR Cellcept [Title/Abstract]) OR Myfortic [Title/Abstract]) OR RS61443 [Title/Abstract])
#3	#1 and #2

Figure1. The PRISMA flow chart of the selection process.

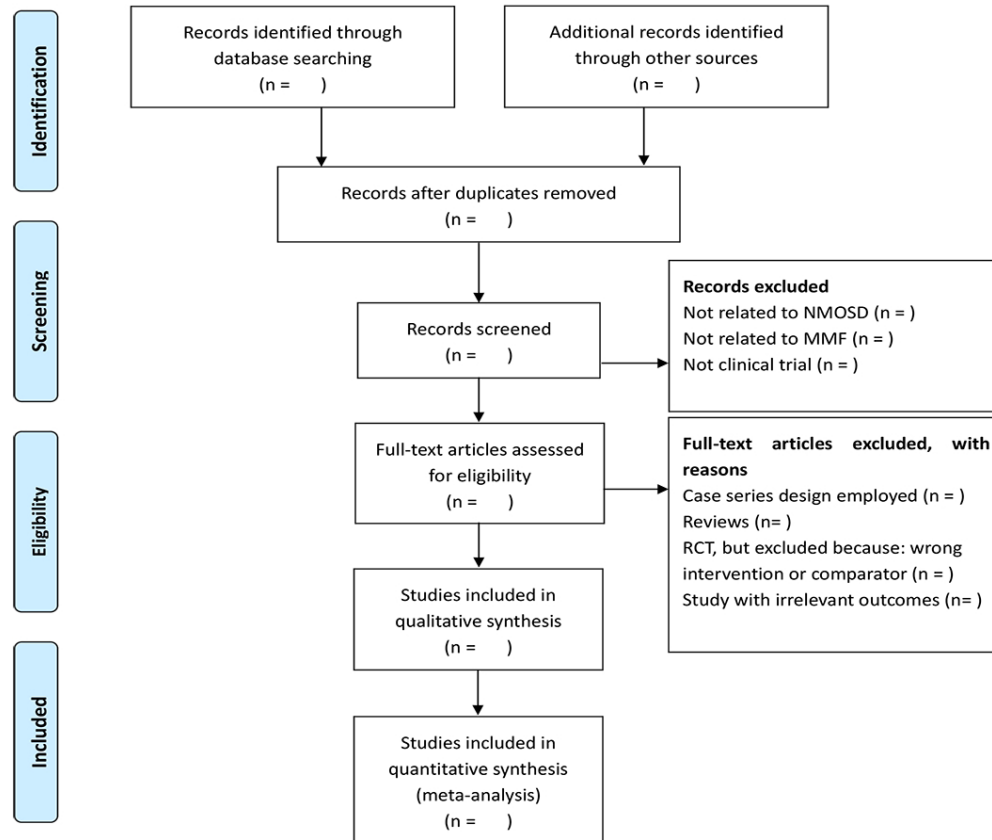


Figure1. The PRISMA flow chart of the selection process.

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

			Page
	Reporting Item		Number
Title			
Identification	#1a Identify the report as a protocol of a systematic review		Page 1
Update	#1b If the protocol is for an update of a previous systematic review, identify as such		

1 **Registration**

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4 [#2](#) If registered, provide the name of the registry (such as Page 2

5

6 PROSPERO) and registration number

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10 **Authors**

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13 **Contact** [#3a](#) Provide name, institutional affiliation, e-mail address of all Page 1

14

15 protocol authors; provide physical mailing address of

16

17 corresponding author

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19

20 **Contribution** [#3b](#) Describe contributions of protocol authors and identify the Page1,11

21

22 guarantor of the review

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26 **Amendments**

27

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29 [#4](#) If the protocol represents an amendment of a previously

30

31 completed or published protocol, identify as such and list

32

33 changes; otherwise, state plan for documenting important

34

35 protocol amendments

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39 **Support**

40

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42 **Sources** [#5a](#) Indicate sources of financial or other support for the review Page 1

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45 **Sponsor** [#5b](#) Provide name for the review funder and / or sponsor Page 1

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48 **Role of sponsor or** [#5c](#) Describe roles of funder(s), sponsor(s), and / or institution(s), Page 1

49

50 funder

51 if any, in developing the protocol

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54 **Introduction**

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57 **Rationale** [#6](#) Describe the rationale for the review in the context of what is Page

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1		already known	2,3,4
2			
3			
4	Objectives	#7 Provide an explicit statement of the question(s) the review	Page 5,6
5		will address with reference to participants, interventions,	
6		comparators, and outcomes (PICO)	
7			
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10			
11	Methods		
12			
13			
14	Eligibility criteria	#8 Specify the study characteristics (such as PICO, study	Page 7,8
15		design, setting, time frame) and report characteristics (such	
16		as years considered, language, publication status) to be	
17		used as criteria for eligibility for the review	
18			
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24	Information	#9 Describe all intended information sources (such as electronic	Page 7,8
25		databases, contact with study authors, trial registers or other	
26	sources	grey literature sources) with planned dates of coverage	
27			
28			
29			
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32	Search strategy	#10 Present draft of search strategy to be used for at least one	Page 7
33		electronic database, including planned limits, such that it	
34		could be repeated	
35			
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39	Study records -	#11a Describe the mechanism(s) that will be used to manage	Page7,8
40		records and data throughout the review	
41	data management		
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44			
45	Study records -	#11b State the process that will be used for selecting studies (such	Page 7,8
46		as two independent reviewers) through each phase of the	
47	selection process	review (that is, screening, eligibility and inclusion in meta-	
48		analysis)	
49			
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54	Study records -	#11c Describe planned method of extracting data from reports	Page
55		(such as piloting forms, done independently, in duplicate),	7,8,9
56	data collection		
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1	process		any processes for obtaining and confirming data from	
2			investigators	
3				
4				
5				
6	Data items	#12	List and define all variables for which data will be sought	Page 8
7			(such as PICO items, funding sources), any pre-planned	
8			data assumptions and simplifications	
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12				
13	Outcomes and	#13	List and define all outcomes for which data will be sought,	Page5,6
14	prioritization		including prioritization of main and additional outcomes, with	
15			rationale	
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21	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	Page 7,8
22	individual studies		individual studies, including whether this will be done at the	
23			outcome or study level, or both; state how this information	
24			will be used in data synthesis	
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31	Data synthesis	#15a	Describe criteria under which study data will be quantitatively	Page 9
32			synthesised	
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36	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe	Page 9
37			planned summary measures, methods of handling data and	
38			methods of combining data from studies, including any	
39			planned exploration of consistency (such as I ² , Kendall's τ)	
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46	Data synthesis	#15c	Describe any proposed additional analyses (such as	Page 9,10
47			sensitivity or subgroup analyses, meta-regression)	
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51	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type	Page 9
52			of summary planned	
53				
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56				
57	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	Page 8,9
58				
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60				

1 publication bias across studies, selective reporting within
2
3 studies)
4

5
6 Confidence in [#17](#) Describe how the strength of the body of evidence will be Page 9
7
8 cumulative assessed (such as GRADE)
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10 evidence
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13 None The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution
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16 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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BMJ Open

Safety and Efficacy of Mycophenolate Mofetil in Treating NMOSD : a protocol for systematic review and meta-analysis.

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4 Safety and Efficacy of Mycophenolate Mofetil in Treating NMOSD : a protocol
5 for systematic review and meta-analysis.

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22 23 24 25 **Abstract**

26
27 **Introduction** Neuromyelitis optica spectrum disorders (NMOSD) is an inflammatory
28 and heterogeneous astrocyte disorder of the central nervous system (CNS) with the
29 characteristic of higher incidence in women and Asian people. Most patients with
30 NMOSD have a course of recurrence and remission that is prone to cause paralysis and
31 blindness. Several studies have confirmed the efficacy and promising prospect of
32 mycophenolate mofetil (MMF) in the treatment of NMOSD. Yet its therapeutic effect
33 and safety are controversial. Although there has been two published literature that is
34 relevant to the topic of this study, both of them have certain defects, and they can only
35 provide answers about the efficacy or safety of MMF in the treatment of NMOSD from
36 partial perspectives or conclusions. This research aims to perform a direct and
37 comprehensive systematic review and meta-analysis to evaluate MMF's effectiveness
38 and safety in treating NMOSD.

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51 **Methods and analysis** This systematic review will cover all comparative researches,
52 from randomized controlled trials (RCTs) to cohort studies, and case-control study. A
53 relevant literature search will be conducted in PubMed, Web of Science, EMBASE, the
54 Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang
55 Database, China Science and Technology Journal database (VIP) and Chinese
56 Biomedical Literature database (CBM). We will also search registers of clinical trials,
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4 potential gray literature, and abstracts from conferences. There are no limits on
5 language and publication status. The reporting quality and risk of bias will be assessed
6 by two researchers independently. Expanded disability status scales (EDSS),
7 annualized relapse rate (ARR) will be evaluated as the primary outcome. The secondary
8 outcomes will consist of the frequency and severity of adverse events (AEs), best-
9 corrected visual acuity (BCVA), relapse-free rate and time to the next attack. A meta-
10 analysis will be performed using RevMan5.3 software provided by the Cochrane
11 Collaboration and Stata 12.0.

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19 **Ethics and dissemination** Because the data used for this systematic review will be
20 exclusively extracted from published studies, ethical approval and informed consent of
21 patients will not be required. The systematic review will be published in a peer-
22 reviewed journal, presented at conferences and will be shared on social media platforms.

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27 **PROSPERO registration number:** PROSPERO CRD42020164179.

28 29 **Strengths and limitations of this study:**

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31 ▶ This study will carry out an exhaustive literature search to identify studies aimed at
32 evaluating the efficacy and safety of MMF in treating NMOSD.

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34 ▶ One limitation of this study is that differences in patients, interventions and primary
35 outcomes may mean that meta-analysis cannot be performed and there are plans for
36 narrative and meta-analytical syntheses.

37
38 ▶ Although we will include studies published in any language, translation difficulties
39 may arise, which will result in the exclusion of these studies.

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41 ▶ The analysis of various sources of heterogeneity and the assessment of risk of bias
42 of the included studies is a critical point for extracting and synthesizing evidence-based
43 conclusions.

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50 **Keywords:** mycophenolate mofetil, neuromyelitis optica spectrum disorders, protocol,
51 systematic review, meta-analysis.

52 53 **1. Introduction**

54
55 Neuromyelitis Optica (NMO), also known as Devic disease, is generally considered to
56 be a rare autoimmune astrocyte disorder of the central nervous system (CNS), induced
57 by autoantibodies, dominated by humoral immunity and involving numerous immune
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4 cells and factors, with optic neuritis(ON) and acute transverse myelitis as typical
5 clinical manifestations.¹ NMO has been known as a subtype of multiple sclerosis (MS)
6 for over 100 years since it was first described and reported.² Until 2004, the discovery
7 and confirmation of anti-aquaporin-4 immunoglobulin G (AQP4-IgG) had made
8 substantial progress in pathogenesis, diagnosis, and treatment of NMO.^{3 4} The notion
9 of neuromyelitis optica spectrum disorders (NMOSD) was first proposed based on the
10 wide clinical use of specific AQP4-IgG,⁴ which mainly referred to the minimal AQP4-
11 IgG positive NMO. However, the deficiencies of the diagnostic criteria of NMO in
12 2006 and NMOSD in 2007 became prominent with the incremental improvement of the
13 specificity of clinical AQP4-IgG tests. In 2015, a groundbreaking international
14 diagnostic protocol for NMOSD was put forward by the global NMO diagnostic team.⁵
15 NMOSD consists of NMO, ON, longitudinally extensive transverse myelitis and other
16 common cerebral demyelinating syndromes.⁵ There are so far no reliable statistics on
17 the worldwide incidence and prevalence of NMOSD. According to the current
18 epidemiological evidence of small samples, the high incidence of this disease is among
19 middle-aged and young women, with the onset age varying from 32 to 41 years old,
20 and the incidence in females is about 10 times that of males.⁵ The incidence and
21 prevalence of approximately 0.05-0.40 and 0.52-4.40/100,000 vary from region to
22 region.⁶ A populous region of Asia is the region with a high incidence of NMOSD.⁷⁻⁹
23 Most NMOSD patients have a recurrence and remission including ON, myelitis, and
24 lesions in special parts of the brain that are vulnerable to cause paralysis and blindness.⁵
25 NMOSD has become one of the most common causes of non-traumatic disability and
26 blindness in young and middle-aged individuals, putting heavy burdens on the life,
27 work and study, as well as the society and economy of various countries.¹⁰ Clinical
28 studies indicate that approximately 1/4 of patients will not be able to walk
29 independently after an average of 5 years of NMO, approximately 10% will be
30 wheelchair-dependent, and more than half of patients will have serious vision loss in at
31 least one eye.¹¹ In particular, ON associated with NMO (NMO-ON) possesses poor
32 recovery even after traditional therapy, which often progresses into significant bilateral
33 visual loss in the long term, leaving behind varying degrees of optic atrophy, which is
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4 different from MS.^{12 13}

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6 Currently, there are no standardized guidelines for the clinical management of NMOSD.
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8 The class of NMOSD drugs is commonly referred to as disease-modifying drugs,¹⁴ and
9
10 the treatment is split into two stages: the acute phase and the period of remission. The
11
12 former is based on corticosteroids to reduce the severity and frequency of acute attacks
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14 that include intravenous corticosteroids (IVCSs), plasma exchange (PLEX), and
15
16 immunoglobulin. Immunosuppressive agents, including mycophenolate mofetil
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18 (MMF), azathioprine (AZA), cyclophosphamide, methotrexate, mitoxantrone,
19
20 tacrolimus, cyclosporine, and monoclonal antibodies, are frequently used during the
21
22 process of recovery to avoid recurrence and to mitigate the progression of neurological
23
24 impairment.^{15 16} Although AZA and rituximab are recommended as first-line therapies
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26 obtained from clinical trials and expert opinion from the published guidelines for
27
28 NMOSD,¹⁶ there are still adverse events (AEs) such as disease recurrence and
29
30 myelosuppression that results in drug withdrawal or replacement of these drugs in
31
32 patients with NMOSD.¹⁷ Other AEs for Rituximab have also been reported in recent
33
34 years such as infusion reactions, infection, and even death,¹⁸⁻²⁰ and its clinical
35
36 application has been constrained by such factors as high price.^{18 21} Therefore, a better
37
38 immunosuppressant for the treatment of NMOSD is urgently needed. The application
39
40 of MMF in NMOSD is still under investigation and is recommended as second-line
41
42 treatments,¹⁶ but some studies have verified MMF's efficacy and promising potential,²¹⁻
43
44 ²⁴ and only a few AEs were published.^{21 22} Especially, additional studies have also
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46 indicated that MMF was more effective and triggered less AEs than AZA.^{25 26} In
47
48 patients experiencing AEs or poor response to AZA, MMF is recommended as an
49
50 alternative therapy.¹⁶

51
52 Although MMF is increasingly employed in NMOSD, there is still controversy about
53
54 its related harms and benefits. At present, there are mainly two published articles that
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56 are relevant to the topic and purpose of our research.^{27 28} Nevertheless, these two studies
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58 have some imperfections in the direct evaluation of the efficacy and safety of MMF in
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60 the treatment of NMOSD patients. For example, the Espiritu and Pasco paper did not
quantitatively evaluate the efficacy of MMF in the treatment of NMOSD and did not

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4 compare the AEs of MMF with other drugs in the treatment of NMOSD. Additionally,
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6 Huang et al. 's research was a network meta-analysis and the literature related to MMF
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8 in this paper was three observational studies that made the number of included studies
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10 and closed loops per comparison were few, which might lower the reliability of the
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12 findings. In our study, the database we searched includes not only the English database
13
14 but also the Chinese database. The retrieval time is limited to June 2020, and we will
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16 add 3 retrospective studies involving 471 patients with NMOSD,²⁹⁻³¹ which makes the
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18 retrieval literature more comprehensive. At the same time, the conclusions of the
19
20 previously published literature about the clinical effect of MMF were inconsistent.
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22 Poupart argued that RTX was clinically better tolerated than MMF.³⁰ But Huang et al
23
24 argued that MMF had the best drug tolerance and was superior to RTX.³¹ We expect
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26 our research to help solve this problem as well.

27 **2. Methods**

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29 This protocol has been registered on PROSPERO (registration number: CRD
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31 42020164179). Our protocol will follow the Meta-analysis of Observational Studies in
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33 Epidemiology (MOOSE),³² the Cochrane Handbook for Systematic Reviews of
34
35 Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-
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37 Analysis Protocol (PRISMA-P) statement guidelines.^{33 34}

38 **2.1 Inclusion criteria for study selection**

39 **2.1.1 Types of studies**

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41 All comparative researches, from randomized controlled trials (RCTs) to cohort studies,
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43 and case-control study, covering at least two interventions, will be included. The current
44
45 clinical trial results will be objectively integrated, which is conducive to the evaluation
46
47 of the efficacy and safety of MMF for NMOSD. We will exclude reviews, qualitative
48
49 studies, animal trials, laboratory studies and studies only involving one intervention.
50
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52 **2.1.2 Types of patients**

53
54 Patients diagnosed as having NMOSD will be included in this study.^{5 35} There will be
55
56 no restrictions based on other conditions, such as age at onset, sex, ethnicity,
57
58 educational or economic status, number of pre-treatment relapses, previous treatment,
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60 duration of illness, disease severity, and baseline expanded disability status scales

(EDSS), AQP4-IgG serological status.

2.1.3 Types of interventions

Trials comparing MMF to placebo or any other active substances, including AZA, cyclophosphamide, methotrexate, mitoxantrone, tacrolimus, cyclosporine, and monoclonal antibodies, will be considered. Besides, the types, dosage, and frequency of MMF were not limited. Studies that MMF with combination therapy fail to objectively evaluate the efficacy and safety of MMF will be eliminated.

2.1.4 Types of outcome measures

2.1.4.1 Primary outcomes

- (1) EDSS: Disability progression was characterized as an increase in the Kurtzke EDSS by at least 1 point above the pre-treatment score if baseline score < 5.5, and by at least half-point if baseline score > 5.5. Outcome measured was the mean changes of EDSS before and after MMF treatment.^{36 37}
- (2) Annualized relapse rate (ARR): Relapse is equivalent to a neurologic symptom lasting for > 24 h, which occurs at least 30 days after the onset of a preceding event. ARR is computed as the number of relapses divided by the time in years (days). Post-treatment ARR was contrasted with pre-treatment ARR.³⁸

2.1.4.2 Secondary outcomes

- (1) The frequency and extent of AEs: During treatment and follow-up periods, any symptomatic events which had a possible, probable or definite causal relationship to MMF treatment were defined as AEs.
- (2) Relapse-free rate: The absence of relapse during the observation period of the study reported as percentage per study.³⁵
- (3) Best-corrected visual acuity (BCVA): BCVA was measured using a standardized test, such as the ETDRS chart, Snellen chart or similar method, and other visual acuity measures would be allowed if findings could be justified as well as validated concerning accepted relevant standard measures. Outcome measured was the mean change of BCVA from before and after MMF treatment.³⁹
- (4) Time to the next attack.

2.1.4.3 Security index

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4 The safety was assessed by the occurrence of AEs. Any unexpected events that occurred
5 during the studies will be recorded on an AEs report form, including:²⁸
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- 7
8 (1) General physical examination (temperature, pulse, respiration, blood pressure).
9
10 (2) Routine examination of blood, urine and stool.
11
12 (3) Liver and kidney function examination.
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14 (4) Gastrointestinal discomfort.
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16 (5) Hair loss or Alopecia.
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18 (6) Allergic or Anaphylactoid reactions.
19
20 (7) Drug discontinued due to drug-related AEs.
21
22 (8) Possible AEs and related detection indicators.

23 **2.2 Search methods for the identification of studies**

24 **2.2.1 Electronic searches**

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26
27 A relevant literature search by sensitive search strategies was conducted using the
28 following electronic databases from their inception to June 31, 2020: PubMed, Web of
29 Science, EMBASE, the Cochrane Library, China National Knowledge Infrastructure
30 (CNKI), Wanfang Database, China Science and Technology Journal database (VIP)
31 and Chinese Biomedical Literature database (CBM). Search methods of MeSH terms
32 with free words were applied in English databases. The related terms are as follows:
33 Participants (neuromyelitis optica, neuromyelitis optica spectrum disorders, Devic
34 Neuromyelitis Optica, Devic's Neuromyelitis Optica, Devic's Syndrome, NMO
35 spectrum disorders), Intervention (mycophenolic acid, mycophenolate mofetil, “mofetil,
36 mycophenolate”, cellcept, myfortic, RS61443). The search strategy for PubMed is
37 described in Table 1, which will include all search terms, and other searches will be
38 carried out based on those results. This will be suitably adapted to search in the other
39 databases. There are no limits on language and publication status.

40 **2.2.2 Searching other resources**

41
42 we will also search PROSPERO, the International Clinical Trials Registry Platform
43 (ICTRP), ClinicalTrials.gov, dissertations, and gray literature to identify systematic
44 reviews or clinical trials related to mycophenolate mofetil and neuromyelitis optica
45 spectrum disorders. Manual searches will be conducted for related journals and
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4 conference processes. We will also review papers and bibliographies included in the
5 trials.

6 7 **2.3 Data collection and analysis**

8 9 **2.3.1 Selection of studies**

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11 Two reviewers (MYH and ZQL) will independently browse the titles and abstracts of
12 all of the retrieved records to distinguish and exclude any irrelevant articles. Studies
13 only related to human subjects are to be included. Any discord will be resolved by
14 discussion between the two authors and an arbiter (MJ). The selection procedure for the
15 study is shown in a PRISMA flow chart (Fig. 1).

16 17 **2.3.2 Data extraction and management**

18
19 Based on the inclusion criteria, a standard form of data collection will be produced prior
20 to data extraction. Search results will be entered into an EndNote X9 database and
21 duplicate entries removed. Two authors (MYH and ZQL) will extract the data of
22 interest from the eligible study and enter the data extraction sheet as follows: The basic
23 characteristics of each study (study design or methods, author, title, source/journal, time
24 of publication, country, hospital setting); participants characteristics (average age,
25 gender, sample size, inclusion and exclusion criteria, baseline situation); Interventions
26 (type, duration, frequency and dosage of MMF, randomization, allocation concealment,
27 blinding methods); Comparators (AZA, tacrolimus, cyclosporine, monoclonal
28 antibodies, and placebo, etc); Outcomes (measures, main outcomes, security indexes,
29 and follow up); If funded, it will also be recorded. When the consensus on data
30 extraction is not available through discussion, the third reviewer (MJ) will make a
31 decision.

32 33 **2.3.3 Assessment of risk of bias**

34
35 Two authors (Yang Chen and LQN) will independently estimate the risk and bias using
36 the Cochrane risk of bias (ROB) assessment tool for RCTs.⁴⁰ Methodological quality
37 evaluation of the included observational studies will be carried out using the
38 Newcastle–Ottawa Scale (NOS).⁴¹ The RevMan software program (V.5.3) will
39 document the selected details of each study.⁴²

40 41 **2.3.4 Measures of treatment effect**

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4 The risk ratio (RR) and 95% confidence interval (CI) will be used to analyze
5 dichotomous data and calculate the treatment effect. A weighted mean difference
6 (WMD) or a standard mean difference (SMD) with 95% CIs will be used to analyze
7 continuous outcomes.
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11 **2.3.5 Unit of analysis issue**

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13 We will only extract the 1st experimental period data of crossover trials to avoid
14 carryover effects. In the meantime, given that there are multiple intervention groups in
15 trials, we will combine all analogous groups into a single pairwise comparison to avoid
16 a unit of analysis issue.
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21 **2.3.6 Management of missing data**

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23 Reviewer (YLQ and You Chen) will contact the appropriate author of the included trials
24 for clarification or more details via email and telephone if necessary. The missing data
25 will be deleted, if there is no response from the author. That will be addressed in the
26 discussion in this case. If quantitative data were not available, then the qualitative
27 analysis should be used.
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33 **2.3.7 Assessment of heterogeneity and data synthesis**

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35 We will use all of the case data for the analysis data. Heterogeneity will be tested with
36 a standard Chisquare test.⁴³ To quantify the impact of the statistical heterogeneity on
37 the systematic review, the I^2 value will be applied to calculate and present the
38 heterogeneity degree. If $P > 0.1$, $I^2 < 50\%$, it is considered that there is no heterogeneity
39 between the trials, and the model of fixed effect will be used, otherwise, the model of
40 random effect will be adopted. All statistical analyzes will be performed using the
41 RevMan5.3 software provided by the Cochrane Collaboration. Using the software to
42 obtain forest plots and test the heterogeneity between the included studies. The Grades
43 of Recommendation, Assessment, Development and Evaluation (GRADE) will be used
44 to assess the meta-analysis findings and determine the quality of evidence. Where meta-
45 analysis may not be not feasible due to lack of clinical trials or heterogeneity, systematic
46 narrative synthesis will be adopted.
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58 **2.3.8 Assessment of reporting biases**

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60 When 10 or more studies are included in a meta-analysis, we will evaluate funnel plot

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4 asymmetry for reporting biases and small-study effects using Egger's method.⁴⁴ For
5 Egger's test, P value of greater than 0.05 was determined as no significant publishing
6 bias or small-study effects in studies. As funnel plot asymmetry does not necessarily
7 suggest reporting bias, we will attempt to recognize potential causes for the asymmetry,
8 including poor methodological quality and true heterogeneity of studies.
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13 **2.3.9 Subgroup analysis**

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15 Upon detection of heterogeneity, a subgroup analysis will be carried out to judge the
16 source of heterogeneity. The criteria for a subgroup analysis are as follows:
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- 18 (1) Age.
- 19 (2) Type of MMF.
- 20 (3) Research type.
- 21 (4) Participation population.
- 22 (5) Type of control interventions.
- 23 (6) Intervention dosage, frequency and duration.
- 24 (7) AQP4-IgG serological status.

25 **2.3.10 Sensitivity analysis**

26
27 The ROB tool will be used to estimate methodological quality in the case of sufficient
28 data from trials. Sensitivity analysis will be performed to determine the robustness of
29 aggregate estimates and to detect whether any single study accounts for a substantial
30 proportion of heterogeneity by eliminating the included studies from the summary
31 review one by one. If low-quality articles are deleted, then a second meta-analysis will
32 be carried out. Comparison and discussion of the results and effect size of the two meta-
33 analyses will be held.⁴⁵
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36 **2.4 Patient and public involvement** Patients and/or the public will not participate in
37 the study. However, once scientific publications disseminate our findings, they are
38 circulated across social networks so that our conclusions will affect the actions of
39 neuro-ophthalmologists and health policymakers.
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48 **3 Discussion**

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50 Pathogenesis, diagnosis and treatment of NMO are rapidly growing areas of research
51 as AQP4-IgG were first identified. Patients with NMOSD should receive standardized
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4 and personalized immunotherapy as soon as possible, as any further acute episodes may
5 result in severe and often irreversible disability. The challenges in discovering new and
6 better drugs for NMO are the rareness of the disease and the unfavorable prognosis in
7 many cases, which make clinical studies with placebo groups difficult.¹⁶ Many studies
8 have confirmed the efficacy and promising prospect of MMF in the treatment of
9 NMOSD,²¹⁻²⁴ and only a few AEs were reported.^{21 22} Additional studies have also
10 indicated that MMF was more effective and triggered less AEs than AZA.^{25 26} However,
11 its therapeutic effect and safety remain controversial. Although there has been two
12 published literature that is relevant to the topic of this study,^{27 28} both of them have
13 certain defects, and they can only provide answers about the efficacy or safety of MMF
14 in the treatment of NMOSD from partial perspectives or conclusions. If our paper is
15 completed, it will be a currently searchable protocol for a traditional meta-and
16 systematic review that directly and synthetically evaluates the efficacy and safety of
17 MMF in the treatment of NMOSD. One of the strengths of this protocol will use a
18 comprehensive search strategy of published literature. The overall data used in each
19 analysis will be evaluated qualitatively and quantitatively. The sources of heterogeneity
20 and different subgroups of the articles will be analyzed to comprehensively evaluate
21 the efficacy and safety of MMF in the treatment of NMOSD, and to increase the
22 credibility of the article content and conclusions. We expect that this systematic review
23 will benefit patients with NMOSD, physicians, health care administrators and policy-
24 makers.

25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 **Author contributions**

48 MYH conceived and designed the protocol, and MYH drafted the protocol manuscript.
49 MYH developed the search strategy, with input from ZQL and LQN. MYH and ZQL
50 planned data extraction. MYH, Yang Chen and ZJW planned the quality appraisal of
51 all included studies. MYH, ZQL, LQN, Yang Chen, HM, You Chen, ZJW, YLQ and
52 MJ critically revised the manuscript for methodological and intellectual content. All
53 authors approved the final version.
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4 **Conceptualization:** Meng-Yu Han, Zi-Qiang Liu, Zhi-Jun Wang, Ming Jin.

5 **Data curation:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Huan Meng.

6
7 **Formal analysis:** Meng-Yu Han, Zi-Qiang Liu.

8
9 **Funding acquisition:** Meng-Yu Han.

10
11 **Investigation:** Ming Jin.

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13 **Methodology:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, You Chen.

14
15 **Project administration:** Ming Jin.

16
17 **Resources:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

18
19 **Software:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong.

20
21 **Supervision:** Meng-Yu Han, Zhi-Jun Wang, Ming Jin.

22
23 **Validation:** Huan Meng, Yang Chen, Ya-li Qin, Ming Jin.

24
25 **Visualization:** Huan Meng, Yang Chen, Ya-li Qin, Ming Jin.

26
27 **Writing – original draft:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

28
29 **Writing – review & editing:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

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31
32
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35 study.
36
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39 **Competing interests:** None declared.

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Table 1 Search strategy used in PubMed database.

Number	Search terms
#1	("Neuromyelitis Optica"[Mesh]) OR (((((neuromyelitis optica spectrum disorders [Title/Abstract]) OR Devic Neuromyelitis Optica [Title/Abstract]) OR Devic's Neuromyelitis Optica [Title/Abstract]) OR Devic's Syndrome [Title/Abstract]) OR NMO spectrum disorders [Title/Abstract])
#2	("Mycophenolic Acid"[Mesh]) OR (((((Mycophenolate Mofetil [Title/Abstract]) OR "Mofetil,Mycophenolate" [Title/Abstract]) OR Cellcept [Title/Abstract]) OR Myfortic [Title/Abstract]) OR RS61443 [Title/Abstract])

#3	#1 and #2
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Figure 1. The PRISMA flow chart of the selection process.

For peer review only

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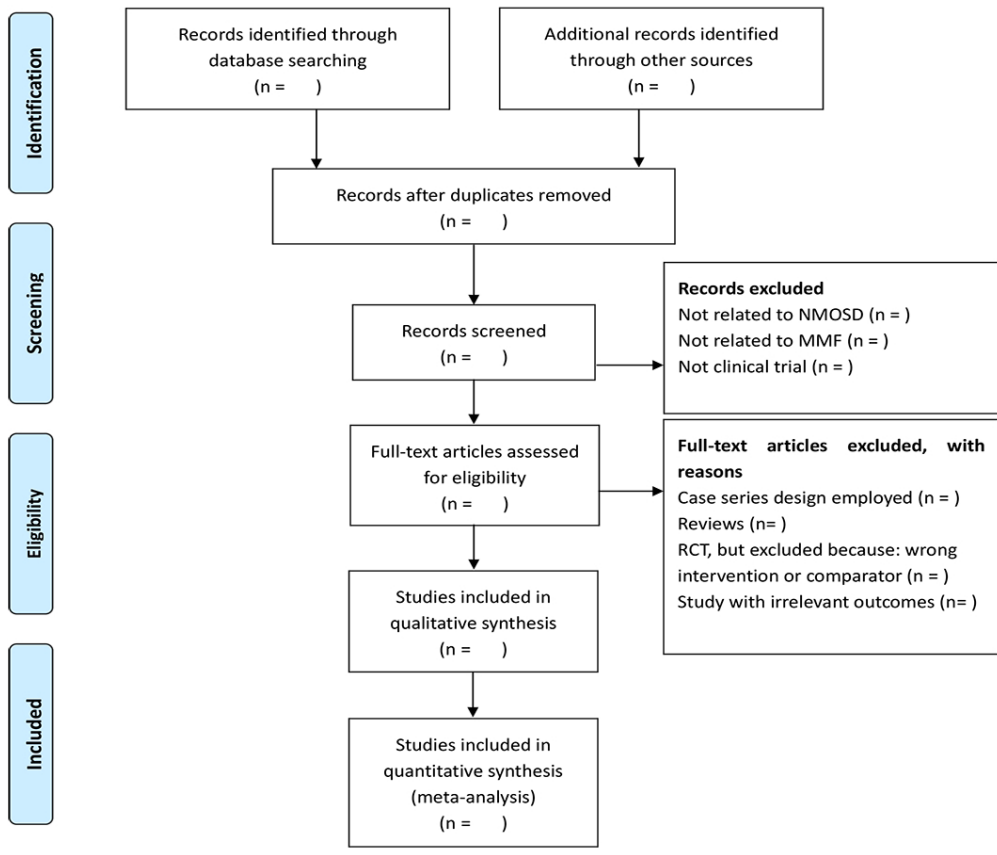


Figure1. The PRISMA flow chart of the selection process.

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Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

			Page
	Reporting Item		Number
Title			
Identification	#1a Identify the report as a protocol of a systematic review		Page 1
Update	#1b If the protocol is for an update of a previous systematic review, identify as such		

1 **Registration**

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4 [#2](#) If registered, provide the name of the registry (such as Page 2

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10 **Authors**

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13 **Contact** [#3a](#) Provide name, institutional affiliation, e-mail address of all Page 1

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15 protocol authors; provide physical mailing address of

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17 corresponding author

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20 **Contribution** [#3b](#) Describe contributions of protocol authors and identify the Page1,11,12

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22 guarantor of the review

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26 **Amendments**

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29 [#4](#) If the protocol represents an amendment of a previously

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31 completed or published protocol, identify as such and list

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33 changes; otherwise, state plan for documenting important

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35 protocol amendments

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39 **Support**

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42 **Sources** [#5a](#) Indicate sources of financial or other support for the review Page 12

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45 **Sponsor** [#5b](#) Provide name for the review funder and / or sponsor Page 12

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48 **Role of sponsor or** [#5c](#) Describe roles of funder(s), sponsor(s), and / or Page 12

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50 funder

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52 institution(s), if any, in developing the protocol

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54 **Introduction**

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57 **Rationale** [#6](#) Describe the rationale for the review in the context of what Page 2,3,4,5

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1 is already known

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4 Objectives [#7](#) Provide an explicit statement of the question(s) the review Page 5,6,7
5 will address with reference to participants, interventions,
6 comparators, and outcomes (PICO)
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10 Methods

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14 Eligibility criteria [#8](#) Specify the study characteristics (such as PICO, study Page 7,8
15 design, setting, time frame) and report characteristics
16 (such as years considered, language, publication status) to
17 be used as criteria for eligibility for the review
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24 Information [#9](#) Describe all intended information sources (such as Page 7,8
25 sources electronic databases, contact with study authors, trial
26 registers or other grey literature sources) with planned
27 dates of coverage
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34 Search strategy [#10](#) Present draft of search strategy to be used for at least one Page 7
35 electronic database, including planned limits, such that it
36 could be repeated
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41 Study records - [#11a](#) Describe the mechanism(s) that will be used to manage Page 8
42 data management records and data throughout the review
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47 Study records - [#11b](#) State the process that will be used for selecting studies Page 8
48 selection process (such as two independent reviewers) through each phase
49 of the review (that is, screening, eligibility and inclusion in
50 meta-analysis)
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57 Study records - [#11c](#) Describe planned method of extracting data from reports Page 8,9
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1	data collection		(such as piloting forms, done independently, in duplicate),	
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8	Data items	#12	List and define all variables for which data will be sought	Page 8
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12			data assumptions and simplifications	
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15	Outcomes and	#13	List and define all outcomes for which data will be sought,	Page 6,7
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17	prioritization		including prioritization of main and additional outcomes,	
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23	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	Page 8
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25	individual studies		individual studies, including whether this will be done at	
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29			information will be used in data synthesis	
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33	Data synthesis	#15a	Describe criteria under which study data will be	Page 9
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35			quantitatively synthesised	
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38	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe	Page 9
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40			planned summary measures, methods of handling data	
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50	Data synthesis	#15c	Describe any proposed additional analyses (such as	Page 9,10
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56	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the	Page 9
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1 type of summary planned

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4 Meta-bias(es) [#16](#) Specify any planned assessment of meta-bias(es) (such Page 8,9,10
5 as publication bias across studies, selective reporting
6 within studies)
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11 Confidence in [#17](#) Describe how the strength of the body of evidence will be Page 9
12 cumulative assessed (such as GRADE)
13 evidence
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18 None The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution
19 License CC-BY 4.0. This checklist can be completed online using <https://www.goodreports.org/>, a tool
20 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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BMJ Open

Safety and Efficacy of Mycophenolate Mofetil in Treating Neuromyelitis Optica Spectrum Disorders : a protocol for systematic review and meta-analysis.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-040371.R3
Article Type:	Protocol
Date Submitted by the Author:	12-Oct-2020
Complete List of Authors:	han, mengyu; Beijing University of Chinese Medicine; China-Japan Friendship Hospital, Ophthalmology Nong, Luqi; Beijing University of Chinese Medicine, Graduate School ; China-Japan Friendship Hospital, Ophthalmology Liu, Ziqiang; Beijing University of Chinese Medicine, Graduate School ; China-Japan Friendship Hospital, Ophthalmology Chen, You; China-Japan Friendship Hospital Chen, Yang; Beijing University of Chinese Medicine Meng, Huan; Beijing University of Chinese Medicine, Graduate School; China-Japan Friendship Hospital, Ophthalmology Qin, Yali; Sun Yat-Sen University Zhongshan Ophthalmic Center Wang, Zhijun; China-Japan Friendship Hospital, ophthalmology department Jin, Ming; China-Japan Friendship Hospital, Ophthalmology
Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Neurology, Evidence based practice
Keywords:	OPHTHALMOLOGY, NEUROLOGY, IMMUNOLOGY, Neuro-ophthalmology < NEUROLOGY

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3 Safety and Efficacy of Mycophenolate Mofetil in Treating Neuromyelitis Optica
4 Spectrum Disorders : a protocol for systematic review and meta-analysis.
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8 Chen, MD^{a,b}, Huan Meng, MD^{a,b}, Yali Qin, MD^c, Zhi-Jun Wang, MD^b, Ming
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21 jinmingyk@163.com).
22
23

24 Abstract

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27 **Introduction** Neuromyelitis optica spectrum disorders (NMOSD) is an inflammatory
28 and heterogeneous astrocyte disorder of the central nervous system (CNS) with the
29 characteristic of higher incidence in women and Asian people. Most patients with
30 NMOSD have a course of recurrence and remission that is prone to cause paralysis and
31 blindness. Several studies have confirmed the efficacy and promising prospect of
32 mycophenolate mofetil (MMF) in the treatment of NMOSD. Yet its therapeutic effect
33 and safety are controversial. Although there has been two published literature that is
34 relevant to the topic of this study, both of them have certain defects, and they can only
35 provide answers about the efficacy or safety of MMF in the treatment of NMOSD from
36 partial perspectives or conclusions. This research aims to perform a direct and
37 comprehensive systematic review and meta-analysis to evaluate MMF's effectiveness
38 and safety in treating NMOSD.
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51 **Methods and analysis** This systematic review will cover all comparative researches,
52 from randomized controlled trials (RCTs) to cohort studies, and case-control study. A
53 relevant literature search will be conducted in PubMed, Web of Science, EMBASE, the
54 Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang
55 Database, China Science and Technology Journal database (VIP) and Chinese
56 Biomedical Literature database (CBM) from their inception to June 31, 2020. We will
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4 also search registers of clinical trials, potential gray literature, and abstracts from
5 conferences. There are no limits on language and publication status. The reporting
6 quality and risk of bias will be assessed by two researchers independently. Expanded
7 disability status scales (EDSS), annualized relapse rate (ARR) will be evaluated as the
8 primary outcome. The secondary outcomes will consist of the frequency and severity
9 of adverse events (AEs), best-corrected visual acuity (BCVA), relapse-free rate and
10 time to the next attack. A meta-analysis will be performed using RevMan5.3 software
11 provided by the Cochrane Collaboration and Stata 12.0.
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19 **Ethics and dissemination** Because the data used for this systematic review will be
20 exclusively extracted from published studies, ethical approval and informed consent of
21 patients will not be required. The systematic review will be published in a peer-
22 reviewed journal, presented at conferences and will be shared on social media platforms.
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27 **PROSPERO registration number:** PROSPERO CRD42020164179.
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29 **Strengths and limitations of this study:**

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31 ▶ This study will carry out an exhaustive literature search to identify studies aimed at
32 evaluating the efficacy and safety of MMF in treating NMOSD.
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34 ▶ One limitation of this study is that differences in patients, interventions and primary
35 outcomes may mean that meta-analysis cannot be performed and there are plans for
36 narrative and meta-analytical syntheses.
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39 ▶ Although we will include studies published in any language, translation difficulties
40 may arise, which will result in the exclusion of these studies.
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43 ▶ The analysis of various sources of heterogeneity and the assessment of risk of bias
44 of the included studies is a critical point for extracting and synthesizing evidence-based
45 conclusions.
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49
50 **Keywords:** mycophenolate mofetil, neuromyelitis optica spectrum disorders, protocol,
51 systematic review, meta-analysis.
52

53 **1. Introduction**

54 Neuromyelitis Optica (NMO), also known as Devic disease, is generally considered to
55 be a rare autoimmune astrocyte disorder of the central nervous system (CNS), induced
56 by autoantibodies, dominated by humoral immunity and involving numerous immune
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4 cells and factors, with optic neuritis(ON) and acute transverse myelitis as typical
5 clinical manifestations.¹ NMO has been known as a subtype of multiple sclerosis (MS)
6 for over 100 years since it was first described and reported.² Until 2004, the discovery
7 and confirmation of anti-aquaporin-4 immunoglobulin G (AQP4-IgG) had made
8 substantial progress in pathogenesis, diagnosis, and treatment of NMO.^{3 4} The notion
9 of neuromyelitis optica spectrum disorders (NMOSD) was first proposed based on the
10 wide clinical use of specific AQP4-IgG,⁴ which mainly referred to the minimal AQP4-
11 IgG positive NMO. However, the deficiencies of the diagnostic criteria of NMO in
12 2006 and NMOSD in 2007 became prominent with the incremental improvement of the
13 specificity of clinical AQP4-IgG tests. In 2015, a groundbreaking international
14 diagnostic protocol for NMOSD was put forward by the global NMO diagnostic team.⁵
15 NMOSD consists of NMO, ON, longitudinally extensive transverse myelitis and other
16 common cerebral demyelinating syndromes.⁵ There are so far no reliable statistics on
17 the worldwide incidence and prevalence of NMOSD. According to the current
18 epidemiological evidence of small samples, the high incidence of this disease is among
19 middle-aged and young women, with the onset age varying from 32 to 41 years old,
20 and the incidence in females is about 10 times that of males.⁵ The incidence and
21 prevalence of approximately 0.05-0.40 and 0.52-4.40/100,000 vary from region to
22 region.⁶ A populous region of Asia is the region with a high incidence of NMOSD.⁷⁻⁹
23 Most NMOSD patients have a recurrence and remission including ON, myelitis, and
24 lesions in special parts of the brain that are vulnerable to cause paralysis and blindness.⁵
25 NMOSD has become one of the most common causes of non-traumatic disability and
26 blindness in young and middle-aged individuals, putting heavy burdens on the life,
27 work and study, as well as the society and economy of various countries.¹⁰ Clinical
28 studies indicate that approximately 1/4 of patients will not be able to walk
29 independently after an average of 5 years of NMO, approximately 10% will be
30 wheelchair-dependent, and more than half of patients will have serious vision loss in at
31 least one eye.¹¹ In particular, ON associated with NMO (NMO-ON) possesses poor
32 recovery even after traditional therapy, which often progresses into significant bilateral
33 visual loss in the long term, leaving behind varying degrees of optic atrophy, which is
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4 different from MS.^{12 13}

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6 Currently, there are no standardized guidelines for the clinical management of NMOSD.
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8 The class of NMOSD drugs is commonly referred to as disease-modifying drugs,¹⁴ and
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10 the treatment is split into two stages: the acute phase and the period of remission. The
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12 former is based on corticosteroids to reduce the severity and frequency of acute attacks
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14 that include intravenous corticosteroids (IVCSs), plasma exchange (PLEX), and
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16 immunoglobulin. Immunosuppressive agents, including mycophenolate mofetil
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18 (MMF), azathioprine (AZA), cyclophosphamide, methotrexate, mitoxantrone,
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20 tacrolimus, cyclosporine, and monoclonal antibodies, are frequently used during the
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22 process of recovery to avoid recurrence and to mitigate the progression of neurological
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24 impairment.^{15 16} Although AZA and rituximab are recommended as first-line therapies
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26 obtained from clinical trials and expert opinion from the published guidelines for
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28 NMOSD,¹⁶ there are still adverse events (AEs) such as disease recurrence and
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30 myelosuppression that results in drug withdrawal or replacement of these drugs in
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32 patients with NMOSD.¹⁷ Other AEs for Rituximab have also been reported in recent
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34 years such as infusion reactions, infection, and even death,¹⁸⁻²⁰ and its clinical
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36 application has been constrained by such factors as high price.^{18 21} Therefore, a better
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38 immunosuppressant for the treatment of NMOSD is urgently needed. The application
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40 of MMF in NMOSD is still under investigation and is recommended as second-line
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42 treatments,¹⁶ but some studies have verified MMF's efficacy and promising potential,²¹⁻
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44 ²⁴ and only a few AEs were published.^{21 22} Especially, additional studies have also
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46 indicated that MMF was more effective and triggered less AEs than AZA.^{25 26} In
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48 patients experiencing AEs or poor response to AZA, MMF is recommended as an
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50 alternative therapy.¹⁶

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52 Although MMF is increasingly employed in NMOSD, there is still controversy about
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54 its related harms and benefits. At present, there are mainly two published articles that
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56 are relevant to the topic and purpose of our research.^{27 28} Nevertheless, these two studies
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58 have some imperfections in the direct evaluation of the efficacy and safety of MMF in
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60 the treatment of NMOSD patients. For example, the Espiritu and Pasco paper did not
quantitatively evaluate the efficacy of MMF in the treatment of NMOSD and did not

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4 compare the AEs of MMF with other drugs in the treatment of NMOSD. Additionally,
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6 Huang et al. 's research was a network meta-analysis and the literature related to MMF
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8 in this paper was three observational studies that made the number of included studies
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10 and closed loops per comparison were few, which might lower the reliability of the
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12 findings. In our study, the database we searched includes not only the English database
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14 but also the Chinese database. The retrieval time is limited to June 2020, and we will
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16 add 3 retrospective studies involving 471 patients with NMOSD,²⁹⁻³¹ which makes the
17
18 retrieval literature more comprehensive. At the same time, the conclusions of the
19
20 previously published literature about the clinical effect of MMF were inconsistent.
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22 Poupart argued that RTX was clinically better tolerated than MMF.³⁰ But Huang et al
23
24 argued that MMF had the best drug tolerance and was superior to RTX.³¹ We expect
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26 our research to help solve this problem as well.

27 **2. Methods**

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29 This protocol has been registered on PROSPERO (registration number: CRD
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31 42020164179). Our protocol will follow the Meta-analysis of Observational Studies in
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33 Epidemiology (MOOSE),³² the Cochrane Handbook for Systematic Reviews of
34
35 Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-
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37 Analysis Protocol (PRISMA-P) statement guidelines.^{33 34}

38 **2.1 Inclusion criteria for study selection**

39 **2.1.1 Types of studies**

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41 All comparative researches, from randomized controlled trials (RCTs) to cohort studies,
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43 and case-control study, covering at least two interventions, will be included. The current
44
45 clinical trial results will be objectively integrated, which is conducive to the evaluation
46
47 of the efficacy and safety of MMF for NMOSD. We will exclude reviews, qualitative
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49 studies, animal trials, laboratory studies and studies only involving one intervention.
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52 **2.1.2 Types of patients**

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54 Patients diagnosed as having NMOSD will be included in this study.^{5 35} There will be
55
56 no restrictions based on other conditions, such as age at onset, sex, ethnicity,
57
58 educational or economic status, number of pre-treatment relapses, previous treatment,
59
60 duration of illness, disease severity, and baseline expanded disability status scales

(EDSS), AQP4-IgG serological status.

2.1.3 Types of interventions

Trials comparing MMF to placebo or any other active substances, including AZA, cyclophosphamide, methotrexate, mitoxantrone, tacrolimus, cyclosporine, and monoclonal antibodies, will be considered. Besides, the types, dosage, and frequency of MMF were not limited. Studies that MMF with combination therapy fail to objectively evaluate the efficacy and safety of MMF will be eliminated.

2.1.4 Types of outcome measures

2.1.4.1 Primary outcomes

- (1) EDSS: Disability progression was characterized as an increase in the Kurtzke EDSS by at least 1 point above the pre-treatment score if baseline score < 5.5, and by at least half-point if baseline score > 5.5. Outcome measured was the mean changes of EDSS before and after MMF treatment.^{36 37}
- (2) Annualized relapse rate (ARR): Relapse is equivalent to a neurologic symptom lasting for > 24 h, which occurs at least 30 days after the onset of a preceding event. ARR is computed as the number of relapses divided by the time in years (days). Post-treatment ARR was contrasted with pre-treatment ARR.³⁸

2.1.4.2 Secondary outcomes

- (1) The frequency and extent of AEs: During treatment and follow-up periods, any symptomatic events which had a possible, probable or definite causal relationship to MMF treatment were defined as AEs.
- (2) Relapse-free rate: The absence of relapse during the observation period of the study reported as percentage per study.³⁵
- (3) Best-corrected visual acuity (BCVA): BCVA was measured using a standardized test, such as the ETDRS chart, Snellen chart or similar method, and other visual acuity measures would be allowed if findings could be justified as well as validated concerning accepted relevant standard measures. Outcome measured was the mean change of BCVA from before and after MMF treatment.³⁹
- (4) Time to the next attack.

2.1.4.3 Security index

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4 The safety was assessed by the occurrence of AEs. Any unexpected events that occurred
5 during the studies will be recorded on an AEs report form, including:²⁸
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8 (1) General physical examination (temperature, pulse, respiration, blood pressure).
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10 (2) Routine examination of blood, urine and stool.
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12 (3) Liver and kidney function examination.
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14 (4) Gastrointestinal discomfort.
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16 (5) Hair loss or Alopecia.
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18 (6) Allergic or Anaphylactoid reactions.
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20 (7) Drug discontinued due to drug-related AEs.
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22 (8) Possible AEs and related detection indicators.

23 **2.2 Search methods for the identification of studies**

24 **2.2.1 Electronic searches**

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26 A relevant literature search by sensitive search strategies was conducted using the
27 following electronic databases from their inception to June 31, 2020: PubMed, Web of
28 Science, EMBASE, the Cochrane Library, China National Knowledge Infrastructure
29 (CNKI), Wanfang Database, China Science and Technology Journal database (VIP)
30 and Chinese Biomedical Literature database (CBM). Search methods of MeSH terms
31 with free words were applied in English databases. The related terms are as follows:
32 Participants (neuromyelitis optica, neuromyelitis optica spectrum disorders, Devic
33 Neuromyelitis Optica, Devic's Neuromyelitis Optica, Devic's Syndrome, NMO
34 spectrum disorders), Intervention (mycophenolic acid, mycophenolate mofetil, “mofetil,
35 mycophenolate”, cellcept, myfortic, RS61443). The search strategy for PubMed is
36 described in Table 1, which will include all search terms, and other searches will be
37 carried out based on those results. This will be suitably adapted to search in the other
38 databases. There are no limits on language and publication status.
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52 **2.2.2 Searching other resources**

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54 we will also search PROSPERO, the International Clinical Trials Registry Platform
55 (ICTRP), ClinicalTrials.gov, dissertations, and gray literature to identify systematic
56 reviews or clinical trials related to mycophenolate mofetil and neuromyelitis optica
57 spectrum disorders. Manual searches will be conducted for related journals and
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conference processes. We will also review papers and bibliographies included in the trials.

2.3 Data collection and analysis

2.3.1 Selection of studies

Two reviewers (MYH and ZQL) will independently browse the titles and abstracts of all of the retrieved records to distinguish and exclude any irrelevant articles. Studies only related to human subjects are to be included. Any discord will be resolved by discussion between the two authors and an arbiter (MJ). The selection procedure for the study is shown in a PRISMA flow chart (Fig. 1).

2.3.2 Data extraction and management

Based on the inclusion criteria, a standard form of data collection will be produced prior to data extraction. Search results will be entered into an EndNote X9 database and duplicate entries removed. Two authors (MYH and ZQL) will extract the data of interest from the eligible study and enter the data extraction sheet as follows: The basic characteristics of each study (study design or methods, author, title, source/journal, time of publication, country, hospital setting); participants characteristics (average age, gender, sample size, inclusion and exclusion criteria, baseline situation); Interventions (type, duration, frequency and dosage of MMF, randomization, allocation concealment, blinding methods); Comparators (AZA, tacrolimus, cyclosporine, monoclonal antibodies, and placebo, etc); Outcomes (measures, main outcomes, security indexes, and follow up); If funded, it will also be recorded. When the consensus on data extraction is not available through discussion, the third reviewer (MJ) will make a decision.

2.3.3 Assessment of risk of bias

Two authors (Yang Chen and LQN) will independently estimate the risk and bias using the Cochrane risk of bias (ROB) assessment tool for RCTs.⁴⁰ Methodological quality evaluation of the included observational studies will be carried out using the Newcastle–Ottawa Scale (NOS).⁴¹ The RevMan software program (V.5.3) will document the selected details of each study.⁴²

2.3.4 Measures of treatment effect

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4 The risk ratio (RR) and 95% confidence interval (CI) will be used to analyze
5 dichotomous data and calculate the treatment effect. A weighted mean difference
6 (WMD) or a standard mean difference (SMD) with 95% CIs will be used to analyze
7 continuous outcomes.
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11 **2.3.5 Unit of analysis issue**

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13 We will only extract the 1st experimental period data of crossover trials to avoid
14 carryover effects. In the meantime, given that there are multiple intervention groups in
15 trials, we will combine all analogous groups into a single pairwise comparison to avoid
16 a unit of analysis issue.
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21 **2.3.6 Management of missing data**

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23 Reviewer (YLQ and You Chen) will contact the appropriate author of the included trials
24 for clarification or more details via email and telephone if necessary. The missing data
25 will be deleted, if there is no response from the author. That will be addressed in the
26 discussion in this case. If quantitative data were not available, then the qualitative
27 analysis should be used.
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33 **2.3.7 Assessment of heterogeneity and data synthesis**

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35 We will use all of the case data for the analysis data. Heterogeneity will be tested with
36 a standard Chisquare test.⁴³ To quantify the impact of the statistical heterogeneity on
37 the systematic review, the I^2 value will be applied to calculate and present the
38 heterogeneity degree. If $P > 0.1$, $I^2 < 50\%$, it is considered that there is no heterogeneity
39 between the trials, and the model of fixed effect will be used, otherwise, the model of
40 random effect will be adopted. All statistical analyzes will be performed using the
41 RevMan5.3 software provided by the Cochrane Collaboration. Using the software to
42 obtain forest plots and test the heterogeneity between the included studies. The Grades
43 of Recommendation, Assessment, Development and Evaluation (GRADE) will be used
44 to assess the meta-analysis findings and determine the quality of evidence. Where meta-
45 analysis may not be not feasible due to lack of clinical trials or heterogeneity, systematic
46 narrative synthesis will be adopted.
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58 **2.3.8 Assessment of reporting biases**

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60 When 10 or more studies are included in a meta-analysis, we will evaluate funnel plot

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4 asymmetry for reporting biases and small-study effects using Egger's method.⁴⁴ For
5 Egger's test, P value of greater than 0.05 was determined as no significant publishing
6 bias or small-study effects in studies. As funnel plot asymmetry does not necessarily
7 suggest reporting bias, we will attempt to recognize potential causes for the asymmetry,
8 including poor methodological quality and true heterogeneity of studies.
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13 **2.3.9 Subgroup analysis**

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15 Upon detection of heterogeneity, a subgroup analysis will be carried out to judge the
16 source of heterogeneity. The criteria for a subgroup analysis are as follows:
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- 18 (1) Age.
- 19 (2) Type of MMF.
- 20 (3) Research type.
- 21 (4) Participation population.
- 22 (5) Type of control interventions.
- 23 (6) Intervention dosage, frequency and duration.
- 24 (7) AQP4-IgG serological status.

25 **2.3.10 Sensitivity analysis**

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27 The ROB tool will be used to estimate methodological quality in the case of sufficient
28 data from trials. Sensitivity analysis will be performed to determine the robustness of
29 aggregate estimates and to detect whether any single study accounts for a substantial
30 proportion of heterogeneity by eliminating the included studies from the summary
31 review one by one. If low-quality articles are deleted, then a second meta-analysis will
32 be carried out. Comparison and discussion of the results and effect size of the two meta-
33 analyses will be held.⁴⁵
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36 **2.4 Patient and public involvement** Patients and/or the public will not participate in
37 the study. However, once scientific publications disseminate our findings, they are
38 circulated across social networks so that our conclusions will affect the actions of
39 neuro-ophthalmologists and health policymakers.
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49 **2.5 Ethics and dissemination** Because the data used for this systematic review will be
50 exclusively extracted from published studies, ethical approval and informed consent of
51 patients will not be required. The systematic review will be published in a peer-
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3 reviewed journal, presented at conferences and will be shared on social media platforms.
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7 **3 Discussion**

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9 Pathogenesis, diagnosis and treatment of NMO are rapidly growing areas of research
10 as AQP4-IgG were first identified. Patients with NMOSD should receive standardized
11 and personalized immunotherapy as soon as possible, as any further acute episodes may
12 result in severe and often irreversible disability. The challenges in discovering new and
13 better drugs for NMO are the rareness of the disease and the unfavorable prognosis in
14 many cases, which make clinical studies with placebo groups difficult.¹⁶ Many studies
15 have confirmed the efficacy and promising prospect of MMF in the treatment of
16 NMOSD,²¹⁻²⁴ and only a few AEs were reported.^{21 22} Additional studies have also
17 indicated that MMF was more effective and triggered less AEs than AZA.^{25 26} However,
18 its therapeutic effect and safety remain controversial. Although there has been two
19 published literature that is relevant to the topic of this study,^{27 28} both of them have
20 certain defects, and they can only provide answers about the efficacy or safety of MMF
21 in the treatment of NMOSD from partial perspectives or conclusions. If our paper is
22 completed, it will be a currently searchable protocol for a traditional meta-and
23 systematic review that directly and synthetically evaluates the efficacy and safety of
24 MMF in the treatment of NMOSD. One of the strengths of this protocol will use a
25 comprehensive search strategy of published literature. The overall data used in each
26 analysis will be evaluated qualitatively and quantitatively. The sources of heterogeneity
27 and different subgroups of the articles will be analyzed to comprehensively evaluate
28 the efficacy and safety of MMF in the treatment of NMOSD, and to increase the
29 credibility of the article content and conclusions. We expect that this systematic review
30 will benefit patients with NMOSD, physicians, health care administrators and policy-
31 makers.
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54 **Author contributions**

55
56 MYH conceived and designed the protocol, and MYH drafted the protocol manuscript.
57
58 MYH developed the search strategy, with input from ZQL and LQN. MYH and ZQL
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4 planned data extraction. MYH, Yang Chen and ZJW planned the quality appraisal of
5 all included studies. MYH, ZQL, LQN, Yang Chen, HM, You Chen, ZJW, YLQ and
6 MJ critically revised the manuscript for methodological and intellectual content. All
7 authors approved the final version.
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13 **Conceptualization:** Meng-Yu Han, Zi-Qiang Liu, Zhi-Jun Wang, Ming Jin.

14 **Data curation:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Huan Meng.

15 **Formal analysis:** Meng-Yu Han, Zi-Qiang Liu.

16 **Funding acquisition:** Meng-Yu Han.

17 **Investigation:** Ming Jin.

18 **Methodology:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, You Chen.

19 **Project administration:** Ming Jin.

20 **Resources:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

21 **Software:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong.

22 **Supervision:** Meng-Yu Han, Zhi-Jun Wang, Ming Jin.

23 **Validation:** Huan Meng, Yang Chen, Ya-li Qin, Ming Jin.

24 **Visualization:** Huan Meng, Yang Chen, Ya-li Qin, Ming Jin.

25 **Writing – original draft:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

26 **Writing – review & editing:** Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

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38 **Competing interests:** None declared.
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Table 1 Search strategy used in PubMed database.

Number	Search terms
#1	("Neuromyelitis Optica"[Mesh]) OR (((((neuromyelitis optica spectrum disorders [Title/Abstract]) OR Devic Neuromyelitis Optica [Title/Abstract]) OR Devic's Neuromyelitis Optica [Title/Abstract]) OR Devic's Syndrome [Title/Abstract]) OR NMO spectrum disorders

	[Title/Abstract])
#2	("Mycophenolic Acid"[Mesh]) OR (((((Mycophenolate Mofetil [Title/Abstract]) OR "Mofetil,Mycophenolate" [Title/Abstract]) OR Cellcept [Title/Abstract]) OR Myfortic [Title/Abstract]) OR RS61443 [Title/Abstract])
#3	#1 and #2

Figure 1. The PRISMA flow chart of the selection process.

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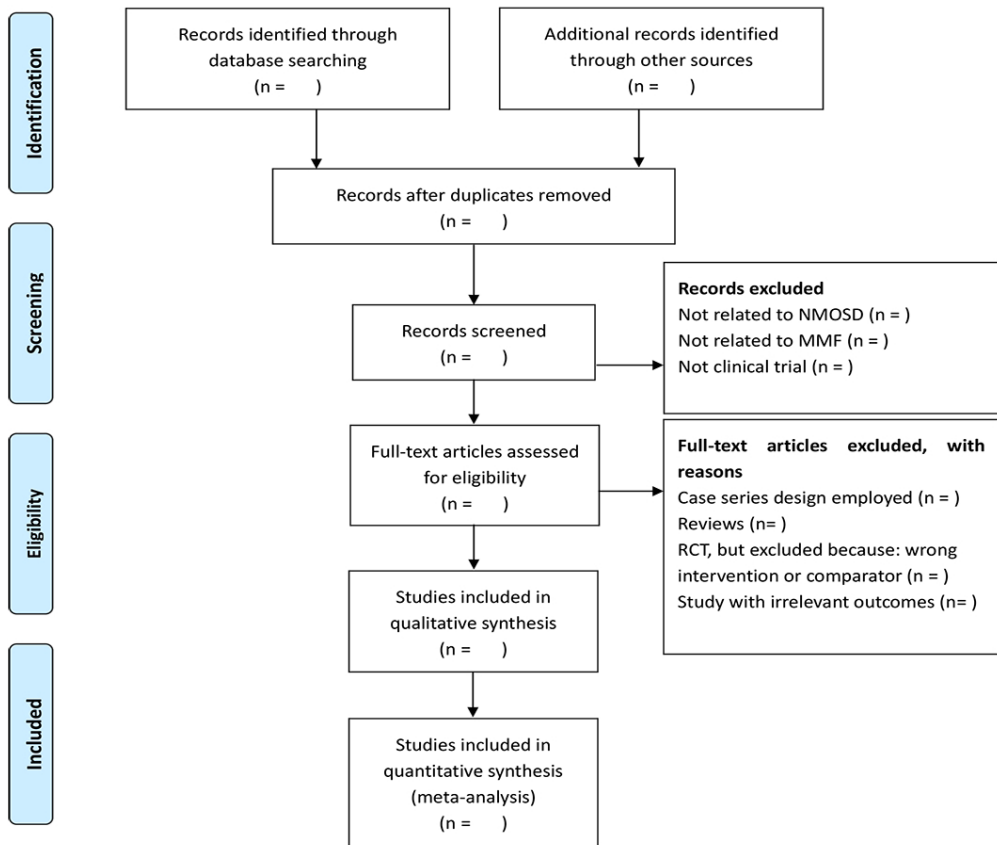


Figure1. The PRISMA flow chart of the selection process.

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

			Page
	Reporting Item		Number
Title			
Identification	#1a Identify the report as a protocol of a systematic review		Page 1
Update	#1b If the protocol is for an update of a previous systematic review, identify as such		

1 **Registration**

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4 [#2](#) If registered, provide the name of the registry (such as Page 2

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6 PROSPERO) and registration number

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10 **Authors**

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13 **Contact** [#3a](#) Provide name, institutional affiliation, e-mail address of all Page 1

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15 protocol authors; provide physical mailing address of

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17 corresponding author

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20 **Contribution** [#3b](#) Describe contributions of protocol authors and identify the Page1,11,12

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22 guarantor of the review

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26 **Amendments**

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29 [#4](#) If the protocol represents an amendment of a previously

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31 completed or published protocol, identify as such and list

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33 changes; otherwise, state plan for documenting important

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35 protocol amendments

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39 **Support**

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42 **Sources** [#5a](#) Indicate sources of financial or other support for the review Page 12

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45 **Sponsor** [#5b](#) Provide name for the review funder and / or sponsor Page 12

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48 **Role of sponsor or** [#5c](#) Describe roles of funder(s), sponsor(s), and / or Page 12

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50 funder

51 institution(s), if any, in developing the protocol

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54 **Introduction**

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57 **Rationale** [#6](#) Describe the rationale for the review in the context of what Page 2,3,4,5

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1 is already known
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4 Objectives [#7](#) Provide an explicit statement of the question(s) the review Page 5,6,7
5 will address with reference to participants, interventions,
6 comparators, and outcomes (PICO)
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10 Methods

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14 Eligibility criteria [#8](#) Specify the study characteristics (such as PICO, study Page 7,8
15 design, setting, time frame) and report characteristics
16 (such as years considered, language, publication status) to
17 be used as criteria for eligibility for the review
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24 Information [#9](#) Describe all intended information sources (such as Page 7,8
25 sources electronic databases, contact with study authors, trial
26 registers or other grey literature sources) with planned
27 dates of coverage
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34 Search strategy [#10](#) Present draft of search strategy to be used for at least one Page 7
35 electronic database, including planned limits, such that it
36 could be repeated
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41 Study records - [#11a](#) Describe the mechanism(s) that will be used to manage Page 8
42 data management records and data throughout the review
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47 Study records - [#11b](#) State the process that will be used for selecting studies Page 8
48 selection process (such as two independent reviewers) through each phase
49 of the review (that is, screening, eligibility and inclusion in
50 meta-analysis)
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57 Study records - [#11c](#) Describe planned method of extracting data from reports Page 8,9
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1	data collection		(such as piloting forms, done independently, in duplicate),	
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3	process		any processes for obtaining and confirming data from	
4				
5			investigators	
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7				
8	Data items	#12	List and define all variables for which data will be sought	Page 8
9				
10			(such as PICO items, funding sources), any pre-planned	
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12			data assumptions and simplifications	
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14				
15	Outcomes and	#13	List and define all outcomes for which data will be sought,	Page 6,7
16				
17	prioritization		including prioritization of main and additional outcomes,	
18				
19			with rationale	
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23	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	Page 8
24				
25	individual studies		individual studies, including whether this will be done at	
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27			the outcome or study level, or both; state how this	
28				
29			information will be used in data synthesis	
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33	Data synthesis	#15a	Describe criteria under which study data will be	Page 9
34				
35			quantitatively synthesised	
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38	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe	Page 9
39				
40			planned summary measures, methods of handling data	
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42			and methods of combining data from studies, including any	
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44			planned exploration of consistency (such as I ² , Kendall's	
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46			τ)	
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50	Data synthesis	#15c	Describe any proposed additional analyses (such as	Page 9,10
51				
52			sensitivity or subgroup analyses, meta-regression)	
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56	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the	Page 9
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1 type of summary planned

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4 Meta-bias(es) [#16](#) Specify any planned assessment of meta-bias(es) (such Page 8,9,10
5 as publication bias across studies, selective reporting
6 within studies)
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11 Confidence in [#17](#) Describe how the strength of the body of evidence will be Page 9
12 cumulative assessed (such as GRADE)
13 evidence
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18 None The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution
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20 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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