

Systemic Connective Tissue Disease and Neuromyelitis Optica Spectrum Disorder Coexistence: A Systematic Review and Meta-Analysis

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Abstract

Background: Several results support the hypothesis that a group of pathologies falling within the Neuromyelitis Optica Spectrum Disorders (NMOSD) diagnostic criteria may coexist with Connective Tissue Diseases (CTD) in patients with a high susceptibility to autoimmune conditions. However, the relationship between NMOSD and rheumatologic diseases deserves further investigations to clarify all clinical aspects of this coexistence. We designed a systematic review and a proportional meta-analysis to estimate the association between CTD and NMOSD, with the aim of helping to plan the best strategy to achieve the most significant public health benefit for these conditions. **Methods:** We conducted a systematic review of the literature published until February 2023, searching in four databases: PubMed, Web of Science, EmBase, and OVID. Then, we conducted a random-effects proportional meta-analysis and assessed the risk of bias of the included studies using the Joanna Briggs Institute checklist. **Results:** The literature search yielded an overall result of 3176 publications (272 from PubMed, 880 from Web of Science, 634 from EmBase and 1390 from OVID). Of these, 29 were included in this systematic review. Analyzing studies that recruited unselected patients with Systemic Lupus Erythematosus (SLE) and Sjogren Syndrome (SjS), the pooled percentages of NMOSD overlapping were 0.6% (95% Confidence Interval [95% CI]: 0.1%–1.4%), and 6.5% (95% CI: 4.7–8.6), respectively. Studies enrolling rheumatologic patients with nervous system symptoms involvement reported higher percentage of NMOSD (i.e., among SjS patients, a pooled percentage of 26.5%, 95% CI: 5.5–54.6%, was found). Similarly, recruiting patients with NMOSD, we found pooled percentages of SjS or SLE respectively of 7.0% and 3.5%. **Conclusions:** Our research found that the coexistence of these two disorders was more frequent in female rheumatologic patients with a SjS diagnosis with neurological manifestations and in neurologic patients for whom a SjS diagnosis was suspected. Similarly, NMOSD are less frequently found in SLE and very rarely incident in Mixed Connective Tissue Disease (MCTD) patients. These considerations should be taken into account in clinical experience of rheumatologists and neurologists, since early diagnosis of both conditions may influence the timing of immunosuppressive therapy and the prevention of systemic disabilities.

Keywords: connective tissue disease; coexistence of autoimmune diseases; autoimmunity; neuromyelitis optica spectrum disorders

1. Introduction

Diseases classified as Neuromyelitis Optica Spectrum Disorders (NMOSD) are rare diseases characterized by clinical phenotypes that share some clinical and radiological features with Multiple Sclerosis (MS). The discovery of new pathogenic autoantibodies, including antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG) and aquaporin-4 antibodies (AQP4-IgG or NMO-IgG), in a subset of patients previously diagnosed with MS led to the consideration of NMOSD as an independent disease entity rather than one of the MS phenotypes [1,2].

The incidence of MS has increased over the years, and many advances in research have been made on this patho-

logical condition. For instance, awareness of its clinical characteristics has increased, and additional knowledge has been introduced to improve both the accuracy of diagnosis and the efficacy of therapeutic strategies. Nevertheless, although the widespread use of newly developed diagnostic tools, such as imaging, evoked potentials, cerebrospinal fluid studies, and autoantibodies research was introduced in clinical practice, a significant percentage of MS patients remains misdiagnosed [3]. Therefore, in recent years, several studies have confirmed that some MS diagnoses may be incorrect, and a significant number of patients may be put on inappropriate long-term MS treatments [4,5].



Several pathologies may mimic MS across the demyelinating spectrum: Acute Disseminated Encephalomyelitis (ADEM), Marburg Virus Disease (MVD), Baló Concentric Sclerosis (BCS), Tumefactive Demyelinating Lesion (TDL), Neuromyelitis Optica Spectrum Disorders (NMOSD), Myelin-Oligodendrocyte Glycoprotein Antibody-associated Disease (MOGAD), Progressive Multifocal Leukoencephalopathy (PML), and Guillain-Barré Syndrome (GBS). As neurological clinical symptoms overlap between MS and NMOSD, such as vision loss, motor deficits, sensory disturbances, and other symptoms localized to the brainstem, a large percentage of people with NMOSD are initially misdiagnosed with MS. For instance, recent published research from Smith *et al.* [6] reported that, following a cohort of NMOSD patients, 27% received a prior diagnosis of MS and 9% received a previous diagnosis of another disease. Accurately diagnosing NMOSD is crucial as the pathophysiology of NMOSD is characterized by a higher risk of relapses and disability, in comparison with MS. Finally, the presence of serum anti-AQP4 antibodies may specifically differentiate NMOSD from MS. MOGAD accounts for approximately 2–7% of all demyelinating syndromes in adults and may clinically mimic MS. The correct diagnosis of MOGAD is important because treatment and prognosis for this disease are different from those for MS or NMOSD. In spite of clinical phenotypic overlap between MOGAD, MS, and NMOSD associated with anti-aquaporin-4 (AQP4) antibodies (AQP4-NMOSD), biological, clinical, and neuropathological characteristics discriminate between these conditions. Thus, while NMOSD lesions are characterized by astrocytopathy, in MOGAD they are determined by inflammatory demyelination. Clinical criteria were emanated to specifically recognize MOGAD [7], and patients should not receive a diagnosis of MS or NMOSD when results are positive for a specific test for serum anti-myelin oligodendrocyte glycoprotein antibodies [8].

NMOSD includes all major clinical manifestations reported in association with AQP4-IgG. Among these, three main clinical features are recognized: various forms of brainstem encephalitis found in adults; a broad variety of cerebral symptoms mostly found in children; isolated longitudinally extensive transverse myelitis or isolated optic neuritis [1,2,9–11]. Over the years, scientific interest was focused onto this condition, since an early diagnosis may prevent debilitating recurrences. To date, to diagnose NMOSD, it has been recommended to use the revised criteria published by Wingerchuk *et al.* [9] in 2015. The laboratory detection of the NMO-IgG may be of valid support, but recognizing NMOSDs at first presentation remains a difficult task for physicians in their daily practice [9].

Interestingly, recent reports described that NMOSD conditions may be diagnosed in association with an autoimmune disease. Several groups of researchers recognized a strong association between NMOSD and systemic autoimmune diseases, such as Systemic Lupus Erythematosus

(SLE) or Sjögren Syndrome (SjS), or non-organ-specific autoantibodies (i.e., antinuclear antibody, extractable nuclear antigen) associated conditions [10,11]. Other authors found NMOSD correlated with Rheumatoid Arthritis (RA), Undifferentiated Connective Tissue Disease (UCTD), and vasculitis related to antineutrophil cytoplasmic antibodies (anti-ANCA) [12]. Moreover, Myasthenia Gravis (MG), and autoimmune thyroid diseases are the most reported autoimmune diseases associated with NMOSD in the literature among non-neurological organ-specific diseases [13]. These observations suggest that Neuromyelitis Optica (NMO) is the manifestation of the multifactorial susceptibility of some subjects to develop humoral autoimmunity and multiple autoimmune conditions. Many authors have tried to investigate the overlap between these two diseases; for instance, Wingerchuk and Weinshenker [14] wondered whether NMOSD may be a complication of an autoimmune disorders. However, many points remain unanswered, i.e., whether NMOSD antibodies in patients with a rheumatological disease are confined to patients with optic neuritis or myelitis, whether myelitis that occurs in the context of a connective tissue disease is clinically and pathologically similar to the myelitis seen in neuromyelitis optica, and what treatment strategy these patients should receive [14,15].

With this review, we aimed to integrate updated published data in the literature, providing an exhaustive overview of the estimation of the association between Connective Tissue Diseases (CTD) and MNOSD, using a proportional meta-analysis. Our results provide additional evidence-based information to help plan the best strategy to achieve the most significant public health benefit for these conditions.

2. Materials and Methods

2.1 Data Sources and Searches

We conducted a systematic review regarding the association between NMOSD and CTD, that has been published in the English language before February 2023. We systematically searched four databases: PubMed, Web of Science, EmBase, and OVID. The search strategy and terms used are shown in Table 1.

2.2 Inclusion and Exclusion Criteria

Publications on the association between NMOSD and CTD were eligible if they met the following inclusion criteria: case reports, studies, or trials involving aquaporin-4 antibody (AQP4-Ab) positive patients with a diagnosis of SLE, SjS, Systemic Sclerosis (SSc), or Mixed Connective Tissue Disease (MCTD). All the articles involving AQP4-Ab negative patients or with unknown serum antibodies status were excluded. Duplicate results were considered only once. Abstracts, posters, editorials, commentary, reviews, background articles, and guidelines were excluded. Surveys and studies involving cells (*in vitro*) or animals (*in*

Table 1. Keywords used for the literature search.

Database	
PubMed	("Neuromyelitis Optica Spectrum Disorder" [tiab] OR "NMOSD" [tiab] OR "Neuromyelitis Optica" [tiab] OR "NMO" [tiab] OR "Neuromyelitis" [tiab] OR "Devic's Syndrome" OR "Longitudinal Extensive Transverse Myelitis" OR "LETM") AND ("Mixed Connective Tissue Diseases" OR "MCTD" OR "Connective Tissue Disease" OR "CTD" OR "Systemic lupus erythematosus" OR "SLE" OR "Systemic Sclerosis*" OR "Scleroderma systemic" OR "SSc" OR "Sjögren's syndrome") NOT ("review" [pt] OR "systematic review" [pt] OR "meta-analysis" [pt])
Web Science	myelo optic neuropathy OR neuromyelitis optica spectrum disorder OR nmosd OR neuromyelitis optica OR nmo OR neuromyelitis OR devic syndrome OR longitudinal extensive transverse myelitis OR letm and mixed connective tissue diseases OR mctd OR connective tissue disease OR ctd OR systemic lupus erythematosus OR sle OR systemic sclerosis OR scleroderma systemic OR ssc OR sjogren syndrome not review OR systematic review OR meta-analysis
EmBase	('myelo optic neuropathy' OR 'neuromyelitis optica spectrum disorder' OR nmosd OR 'neuromyelitis optica' OR nmo OR neuromyelitis OR 'devic syndrome' OR 'longitudinal extensive transverse myelitis' OR 'letm') AND ('mixed connective tissue diseases' OR mctd OR 'connective tissue disease' OR ctd OR 'systemic lupus erythematosus' OR sle OR 'systemic sclerosis' OR 'scleroderma systemic' OR ssc OR 'sjögren syndrome') NOT (review OR 'systematic review' OR 'meta analysis')
OVID	((myelo optic neuropathy or neuromyelitis optica spectrum disorder or nmosd or neuromyelitis optica or nmo or neuromyelitis or devic syndrome or longitudinal extensive transverse myelitis or letm) and (mixed connective tissue diseases or mctd or connective tissue disease or ctd or systemic lupus erythematosus or sle or systemic sclerosis or scleroderma systemic or ssc or sjogren syndrome)).tw. not (review or systematic review or meta analysis).pt.

NMOSD, Neuromyelitis Optica Spectrum Disorders; NMO, Neuromyelitis Optica; LETM, Longitudinally Extensive Transverse Myelitis; MCTD, Mixed Connective Tissue Disease; CTD, Connective Tissue Diseases; SLE, Systemic Lupus Erythematosus; SSc, Systemic Sclerosis.

vivo) and studies reporting only antibodies frequency were excluded as inappropriate study design. Articles published in languages other than English and articles judged out of topic for the purpose of this review were also excluded. Inclusion and exclusion criteria are summarized in Table 2.

2.3 Data Collection and Extraction

After importing the initial search results from four databases into Zotero, duplicates were removed. Retrieved results were then imported into Rayaan [16]. Based on the eligible criteria, two reviewers independently screened titles and abstracts and excluded irrelevant searches. Discrepancies during this screening process were extensively discussed until a consensus was reached. The full text of the remaining searches was retrieved and examined to select the included articles.

2.4 Risk of Bias and Quality Assessment

The quality of each included article was assessed using the Joanna Briggs Institute's critical appraisal checklist [17–19]. Bias was addressed through an appropriate sample frame, appropriate sampling of the study participants, adequate sample size, a detailed description of the study subjects and setting, sufficient coverage of the identified samples for the data analysis, a valid method used for the identification of the condition, a condition measured in a standard and reliable way for all participants, an appropriate statistical analysis, an adequate response rate, or an appropriately managed low response rate.

2.5 Statistical Analysis

All meta-analyses were conducted in R version 4.1.1 (2021-08-10, R Foundation, Boston, MA, USA) [20] using the "meta" package. The proportion estimates were pooled from the included studies using a random-effects meta-analysis model with the Der Simonian and Laird variance estimator. The variance of each outcome measure was stabilized using the Freeman-Tukey arcsine square-root transformation.

We assessed heterogeneity with the I^2 measure and according to the Cochrane manual $I^2 > 50\%$ was considered heterogeneity. I^2 was commonly applied to estimate heterogeneity for proportional meta-analysis [21,22]. In this type of analysis, proportional data are frequently found in studies with smaller samples. The chi squared test and Tau squared were also used to investigate heterogeneity. Finally, we performed a proportional subgroup meta-analysis selecting groups of studies based on different patient populations. Differences between subgroups were compared using the chi-square test.

3. Results

The literature search across four databases yielded an overall result of 3176 total publications (272 from PubMed, 880 from Web of Science, 634 from EmBase, and 1390 from OVID). After removing all duplicates, 970 publications were excluded. Based on titles and abstracts, 1973 publications were excluded. Two-hundred-thirty-three publications were retrieved and examined in full text; 120 publications were excluded for not meeting the inclu-

Table 2. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
AQP4-Ab positive NMOSD patients with a diagnosis of SLE, SjS, SSc or MCTD	AQP4-Ab negative patients or with unknown serum antibodies status
Case reports, studies or trials	Patients without diagnosis of CTD, even if they were positive for related autoantibodies
English articles	Duplicate
	Wrong publication type
	Surveys, <i>in vitro</i> and <i>in vivo</i> studies
	Studies reporting only antibodies frequency
	Articles published in foreign language
	Out of topic articles

CTD, Connective Tissue Diseases; MCTD, Mixed Connective Tissue Disease; SLE, Systemic Lupus Erythematosus; SjS, Sjogren Syndrome; SSc, Systemic Sclerosis; NMOSD, Neuromyelitis Optica Spectrum Disorders; AQP4-Ab, aquaporin-4 antibody.

sion criteria. One hundred thirteen publications, including 41 population studies and 72 case reports, were assessed for eligibility. Among the population studies, 12 were excluded for incomplete data, and one was excluded due to a small sample size. A population study was retrieved by another source, so that 29 publications were finally included in this systematic review. The selection process for the studies is schematically shown by the PRISMA flow diagram. The PRISMA checklist was included in **Supplementary Material [23]** (Fig. 1).

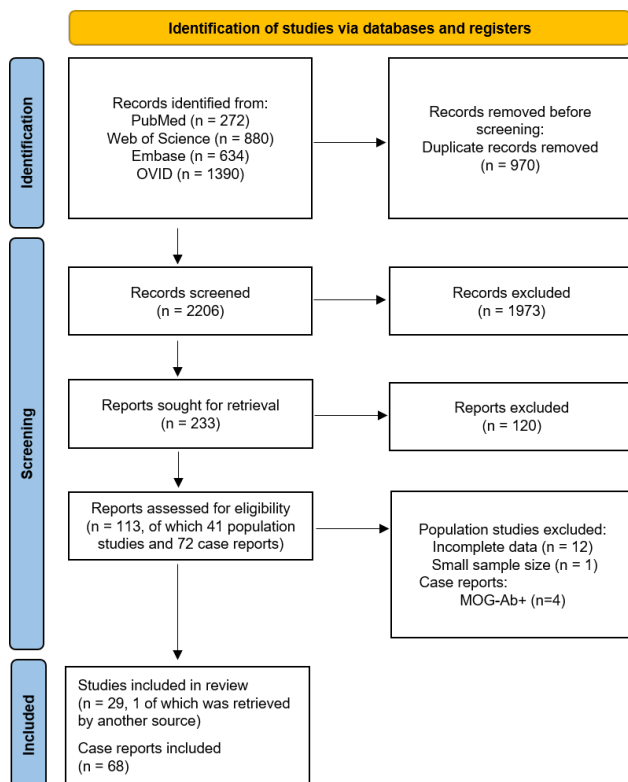


Fig. 1. PRISMA flow-diagram. MOG, myelin oligodendrocyte glycoprotein.

Among the case reports included, most of the AQP4-IgG positive patients were associated with SLE, followed by SjS. Only 4 AQP4-IgG positive patients were associated with SSc and only 2 case reports described 3 AQP4-IgG positive patients associated with MCTD. Finally, 2 AQP4-IgG positive patients had an overlap of two different autoimmune diseases: Systemic Lupus Erythematosus and Myasthenia Gravis (SLE-MG), and (Systemic Lupus Erythematosus and Sjogren Syndrome (SLE-SjS) (Table 3, Ref. [24–52]).

Table 3 summarize the main features of the population studies included in the meta-analysis.

We performed a proportional meta-analysis [53] including publications investigating CTD rates among the NMOSD cohort and NMOSD rates in patients with CTD (i.e., SjS and SLE). As previously described, we reviewed studies to investigate the percentage of NMOSD in groups of patients with a diagnosis of connective tissue disease, including SjS and SLE, that are frequently correlated with NMSOD.

Considering all the retrieved studies, a total of 5941 CTD patients were included (Fig. 2). According to their clinical characteristics, CTD patients were divided into 5 subgroups, on the basis of the different diseases considered (SjS, SLE or a heterogeneous group of CTDs) and the presence of nervous system involvement. In this analysis, we found a single study that, recruiting SLE patients with transverse myelitis, showed a high SLE frequency rate of 48.9% (95% CI: 33.7–64.2%, Fig. 2 subgroup a) [27]. The second group included studies recruiting unselected SLE patients and showed a pooled percentage of 0.6% (95% Confidence Interval [95% CI]: 0.1%–1.4%, $I^2 = 79\%$, $t^2 = 0.0014$). In the third subgroup, studies enrolling SjS patients with nervous system symptoms were analyzed and reported a pooled percentage of 26.5%, (95% CI: 5.5–54.6%, $I^2 = 85\%$, $t^2 = 0.0501$). Studies with unselected SjS diseases were analyzed in the fourth group and reported a pooled NMOSD percentage of 6.5% (95% CI: 4.7–8.6%, $I^2 = 0\%$, $t^2 = 0$). Finally, in the fifth subgroup, two studies including

Table 3. Characteristics of the included studies.

References	Number of Cohort patients		Females (%)	Age at onset of neurological symptoms	Study design	NMOSD	SjS	SLE	JB	Quality Assessment
Huang <i>et al.</i> (2022) [24]	502	AQP4-IgG-positive NMOSD	88.8	37.3 ± 15.0	Retrospective		54	10	9	
Kunchok <i>et al.</i> (2021) [25]	28	Pediatric AQP4-IgG-positive NMOSD	89.3	14.5 (12.5–16.0)	Retrospective		0	2	8	
Kunchok <i>et al.</i> (2021) [25]	352	Adult AQP4-IgG-positive NMOSD	84.1	46.0 (30.0–53.5)	Retrospective		18	25		
Akaishi <i>et al.</i> (2021) [26]	1651	AQP4-IgG-positive NMOSD	89.5	46.1 ± 15.9	Retrospective		105		9	
Zhong <i>et al.</i> (2017) [27]	65	NMO	87.7		Retrospective		23		8	
Yao <i>et al.</i> (2022) [28]	113	First onset AQP4-IgG-positive NMOSD	68.1		Retrospective		16	7	7	
Pittock <i>et al.</i> (2008) [29]	153	NMO and 75 (49.0%) had LETM (recurrent in 44 patients)	-	-	Retrospective		3	3	7	
Pereira <i>et al.</i> (2017) [30]	22	NMO	95.5	43.0 ± 13.5	Retrospective		0	1	8	
Park <i>et al.</i> (2015) [31]	106	NMOSD	67.0		Retrospective		21	2	8	
Masuda <i>et al.</i> (2016) [32]	75	NMO	93.3	38.7 ± 24.5	Retrospective		8	0	8	
Lavanya <i>et al.</i> (2021) [33]	28	NMOSD	75.0	9.5 (9–46)	Retrospective		0	1	6	
Gkaniatsou <i>et al.</i> (2020) [34]	53	37 QP4-IgG and 16 MOG-IgG seropositive patients	83.0 ^a		Retrospective		0	6	7	
Nakamura <i>et al.</i> (2007) [35]	23	NMOSD	95.7		Retrospective		2	0	6	
Yang <i>et al.</i> (2018) [36]	57	NMOSD	96.5	42.33 ± 11.29 ^b	Retrospective		7	3	8	
Contentti <i>et al.</i> (2023) [37]	140	NMOSD	86.4	40.8 ± 15.5 ^c	Retrospective		6	7	8	
Nagaishi <i>et al.</i> (2011) [38]	212	AQP4-IgG-positive NMOSD	91.4	42.9 ± 15.9 ^d	Retrospective		42		9	
Zhang <i>et al.</i> (2020) [39]	45	SLE with transverse myelitis	97.8	36.6 ± 12.2	Retrospective	22			7	
Mehta <i>et al.</i> (2021) [40]	1768	SLE	100.0	21 ^e	Retrospective	5			7	
Asgari <i>et al.</i> (2018) [41]	208	SLE	-	-	Retrospective	2			7	
Moraitis <i>et al.</i> (2019) [42]	90	jSLE	87.8	15 (11–17.5) ^f	Retrospective	5			9	
Birnbaum <i>et al.</i> (2017) [43]	109	SjS with 82% of patients with neurologic syndromes	89.0		Cross-sectional	11			9	
Williams <i>et al.</i> (2019) [44]	2297	SLE	86.7 ^g		Retrospective	3			8	
Alexopoulos <i>et al.</i> (2015) [45]	89	SLE without neurological disease	-	-	Retrospective	2			8	
Qiao <i>et al.</i> (2015) [46]	616	SjS	91.2	-	Retrospective	43			8	
Jarius <i>et al.</i> (2011) [47]	54	CTD with SN involvement	m:f 1:20	46 (16–75)	Retrospective	16			8	
Min <i>et al.</i> (2009) [48]	12	SjS with SN involvement	100.0	37.3 ± 13.5	Retrospective	6			6	
Katsumata <i>et al.</i> (2012) [49]	556	SLE	-	-	Retrospective	3			8	
Katsumata <i>et al.</i> (2012) [49]	60	SjS	-	-	Retrospective	3				
Kolfenbach <i>et al.</i> (2011) [50]	15	Acute myelitis and suspected CTD	88.2 ^a	38.3 (16.2–72.0)	Retrospective	8			8	
Estiasari <i>et al.</i> (2012) [51]	22	CNS manifestations associated with SjS	90.9	36.72 ± 13.57	Retrospective	7			9	
Jarius <i>et al.</i> (2012) [52]	175	NMOSD in Caucasians patients	85.7	39 (10–81)	Retrospective		1	8	9	

^aFemale rate of the whole cohort; ^{b,c} mean age at onset of NMOSD group with CTD and AD, respectively; ^dmedian age at onset of the whole cohort; ^emean age at onset of ten patients with myelitis;

^f median age at onset of five AQP4-positive patients; ^gFemale rate of fifteen SLE patients.

SjS, Sjogren Syndrome; SLE, Systemic Lupus Erythematosus; jSLE, juvenile Systemic Lupus Erythematosus; JBI, Joanna Briggs Institute; AQP4, aquaporin-4; LETM, Longitudinal Extensive Transverse Myelitis; MOG, Myelin-oligodendrocyte glycoprotein; CNS, Central Nervous System.

patients with different CTDs were recruited. Jarius *et al.* [47], recruited a group of patients with SLE, SjS, Systemic Scleroderma, polymyositis/dermatomyositis, Sharp Syndrome, or vasculitis at the time of neurological presentation, and found a proportion of NMOSD of 29.6% (95% CI: 18.0–43.6%). Kolfenbach *et al.* [50] recruited a sample of 15 SjS and/or SLE patients with myelitis, and reported 8 cases of NMOSD (Fig. 2).

Among neurologic patients with NMOSD, we first examined the proportions of SjS plus SLE cases in the same analysis. We then performed a proportional meta-analysis considering them as independent groups. Unfortunately, up to now there are no epidemiological structured studies in this field, and studies published so far with the aim of describing the coexistence between NMOSD and CTD may differ for many reasons, among which the main is the patient inclusion criteria. For instance, some authors included patients with NMO according to the diagnostic criteria as described by Wingerchuk *et al.* [9]; Huang *et al.* [24] and Akaishi *et al.* [26] restricted the entry criteria only to AQP4-IgG-positive NMOSD individuals. Kolfenbach *et al.* [50] and Jarius *et al.* [47] included in their analysis several CTDs, whereas other authors preferred to restrict their analysis to a single CTD, such as SjS or SLE.

The pooled proportion of patients with overlapping NMOSD and SjS plus SLE diseases was 10.5% (95% CI: 7.7–13.6%, $I^2 = 68\%$, $t^2 = 0.0045$, Fig. 3). A high percentage was reported by Park *et al.* [31], who published a value of 21.7% (95% CI: 14.3–30.8%) with a weight of 8.1%. In this retrospective analysis of 5-year data collected in Korea, they enrolled 106 consecutive patients with NMOSD; 21 of which met SjS criteria and 2 met the SLE criteria [31]. Studies showing lower rates were published by Pereira *et al.* [30] and Contentti *et al.* [37], which also reported low and intermediate weight values: 3.5% and 8.8%, respectively. Pereira *et al.* [30] conducted a retrospective study that enrolled 22 consecutive patients attending the Neurology Outpatient Department in Brazil, with the aim of reporting the frequency of autoimmune disorders and seropositivity for autoantibodies. Contentti *et al.* [37] retrospectively reviewed medical records which included patients with first-onset NMOSD according to the 2015 diagnostic criteria from Argentina, Brazil, and Venezuela. The aim of this study was to determine the frequency of the association between NMOSD and autoimmune disease (AD), and then compare the characteristics of NMOSD patients with and without associated AD. In their sample, the 23.5% of NMOSD patients were associated with an AD, of which Hashimoto disease was the most frequently reported [37].

Finally, the highest weight value was reported by Huang *et al.* in 2022 [24]. They retrospectively enrolled a sample of 711 consecutive NMOSD patients in China, but only those positive for serum AQP4-Abs (502) were included in the analysis. Retrospectively reviewing their medical registry over the last 3 years, they found 54 patients with SjS and 10 with SLE (Fig. 3) [24].

Seventeen studies enrolling a total of 3745 patients were analyzed to investigate the association between Sjogren diseases and NMOSD. The pooled percentage of this coexistence was 7.0% (95% CI: 4.2–10.5%, $I^2 = 90\%$, $t^2 = 0.0120$). Zhong *et al.* [27] enrolled 65 patients in China and reported the highest value with a percentage of 35.4% (95% CI: 23.9–48.2%). However, studies with higher weight reported similar percentages of approximately at 7–10%, whereas Pereira *et al.* [30], Lavanya *et al.* [33], and Gkaniatsou *et al.* [34] did not report any patients with SjS (Fig. 4).

Among the included studies, the largest sample was recruited by Akaishi *et al.* [26]. In their retrospective study, they retrieved data from 1651 patients who were positive for serum AQP4-IgG. Only 1139 of these 1651 patients had complete clinical information on serum anti-Sjögren's Syndrome antigen A (SSA)/Ro antibodies, dry eye, and dry mouth. Among an overall total of 1139 patients, 105 cases of SjS should be considered, with a real rate of 7.4% [26]. Finally, lower percentages were reported by Contentti *et al.* [37] in their recent study that included AQP4-IgG positive first-onset NMOSD patients (4.3%, 95% CI: 1.6–9.1%).

In Fig. 5, we showed the percentage of SLE overlapping with NMOSD in studies that enrolled NMOSD patients (3.5%, 95% CI: 2.0–5.4, $I^2 = 60\%$, $t^2 = 0.0031$).

4. Discussion

The association between connective tissue disease and a number of pathologies regrouped under the definition of NMOSD has so far been poorly investigated. In this investigation, we have systematically reviewed the available literature retrieved from important databases, as described in methods. We collected mainly clinical cases and some retrospective studies that investigated this topic. No prospective study has so far been published.

A recent published systemic review retrieved available literature from PubMed on the coexistence between NMOSD and all types of autoimmune morbidity. Shahmohammadi *et al.* [13] found that among systemic autoimmune disease, Sjogren's Syndrome (SS) and Systemic Lupus Erythematosus (SLE) were the most frequently reported diseases associated with NMOSD. Less frequently reported systemic autoimmune diseases were Systemic Sclerosis (SSc) and Mixed Connective Tissue Diseases (MCTD) [13]. On the basis of these results and in the absence of precise information about the prevalence and incidence of these autoimmune diseases with NMOSD, we performed a systemic literature review of the association of NMOSD and SjS, SLE, SSc, or MCTD. We then conducted a first proportional meta-analysis to investigate the burden of the association between SLE or SjS in NMOSD patients and NMOSD in SLE or SjS patients. Among all the studies, it was evident that patients with these conditions require early identification of both diseases and an accurate clinical evaluation to tailor effective therapy. Identifying the coexistence of both diseases may reduce the risk of recurrence and clinical progression.

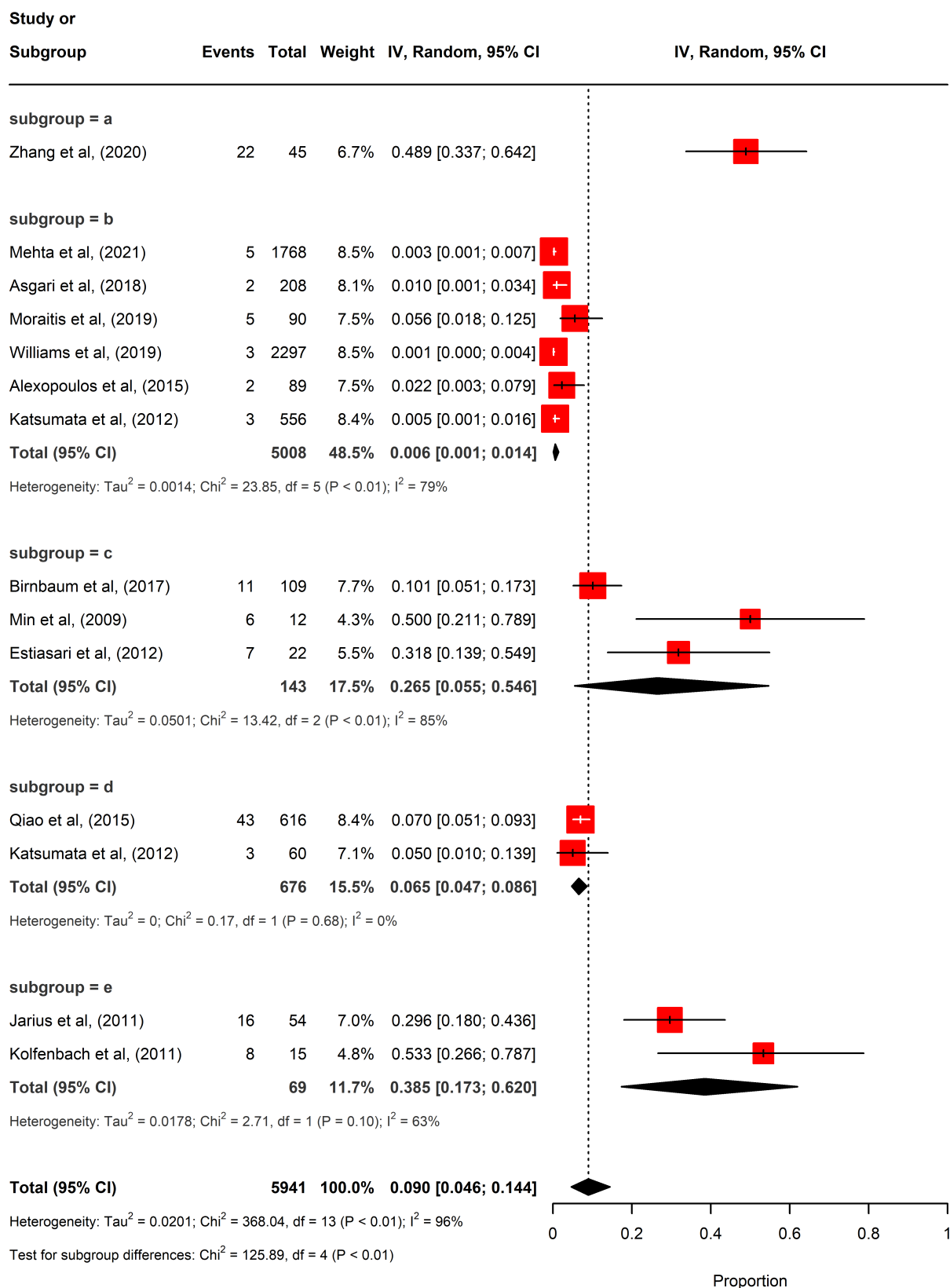


Fig. 2. Forest plot of the meta-analysis showing the proportion of NMOSD cases in rheumatologic patients. Studies were allocated in the following subgroups: a. SLE patients with transverse myelitis; b. unselected SLE patients; c. SjS patients with nervous system involvement; d. unselected SjS patients; e. CTD patients with nervous system involvement. 95% CI, 95% Confidence Interval; IV, Inverse Variance.

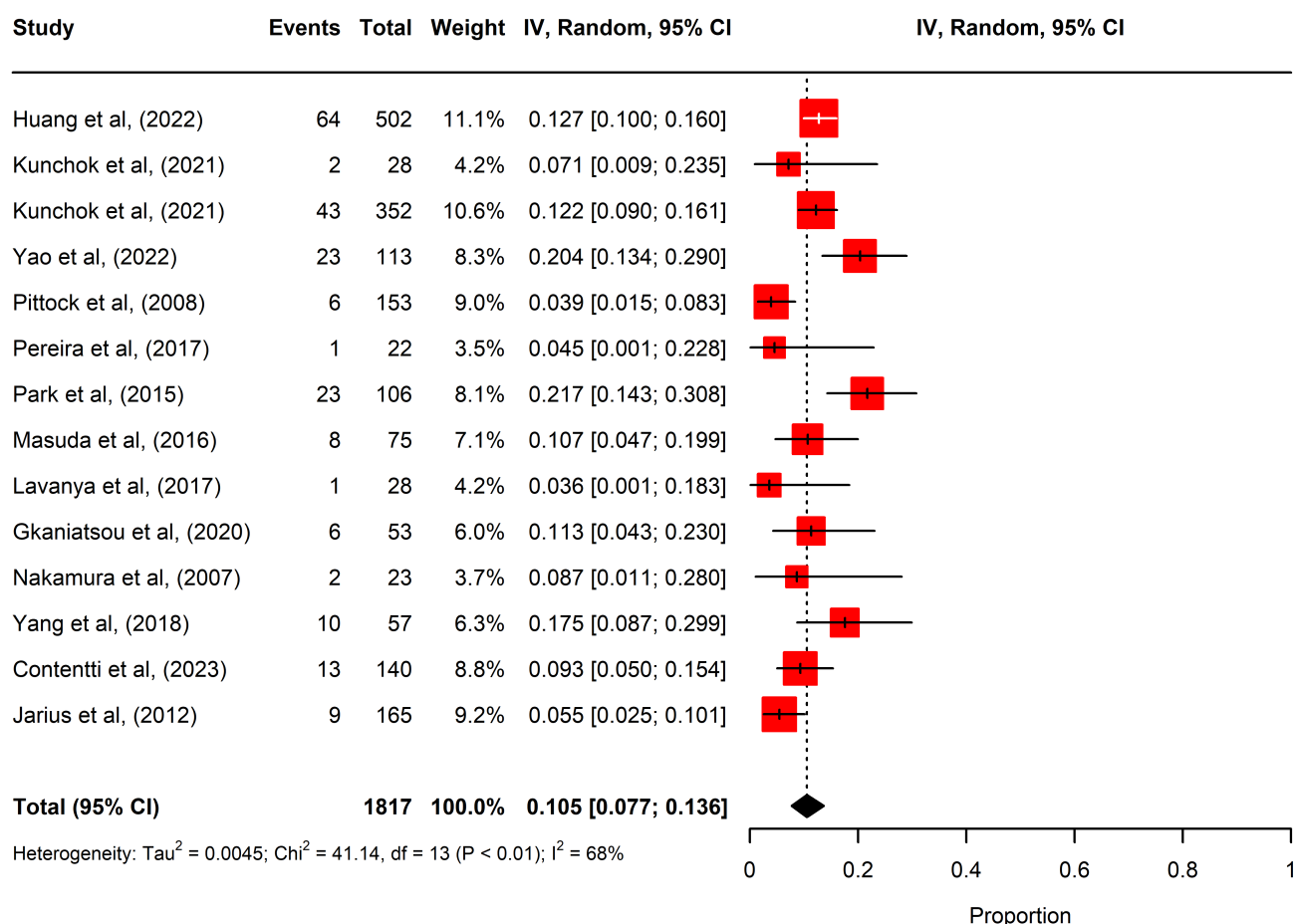


Fig. 3. Forest plot of the meta-analysis showing the proportion of combined cases of SjS and SLE in NMOSD patients.

Many findings evaluating the disease severity in patients with both NMOSD and CTD come from studies comparing patients with NMOSD alone and patients with NMOSD+CTD. Recently, Yao *et al.* [28] found that, while demographic data were not associated with outcomes among these groups, the only variables significantly linked were those strictly related to some clinical aspects. Therefore, a Kaplan-Meier survival analysis showed that the first recurrence in NMOSD patients was complicated by an overlapping CTD onset significantly earlier than in patients without CTD. Hence, the number of recurrences was more frequently found among patients with NMOSD+CTD when compared to those with NMOSD alone. Similarly, the presence of anti-SSA/Ro antibodies was correlated with disease activity and severe disability in NMOSD [28].

However, there are few studies comparing groups of NMOSD patients with and without CTD, and most of them have a monocentric design, recruiting a limited number of patients [28]. All studies concluded that there were few differences between considered groups. For instance, Zhang *et al.* [39] found that patients with associations between NMOSD and CTD were more frequently female, had high percentages of cerebrospinal fluid (CSF) restricted oligoclonal bands, and fewer nonspecific lesions on the brain. Yang *et al.* [36] found that patients with NMOSD and CTD

had higher serum Immunoglobulin G (IgG), longer spinal cord lesions, and frequent short transverse myelitis. Recently, Yao *et al.* [28] compared hematochemical results among patients with and without CTD at their first NMOSD attack. In this study, mean values of lymphocyte to monocyte ratio (LMR) and C-reactive protein (CRP) were significantly associated with the presence of CTD. Thus, these groups of patients appear to be different, as patients with an overlapping CTD demonstrated an enhanced level of systemic uninflammatory reactions [28].

In the past, many researchers have questioned whether NMOSD could be considered a complication of a connective tissue disease. The last findings led to the consideration that this association is the coexistence of two diseases rather than one being a consequence of the other [54]. Given that different case reports highlight that optic neuritis and myelitis may occur in systemic rheumatologic diseases, particularly in SLE and SjS, and taking into account that systemic rheumatologic diseases and NMOSD occur together frequently in these two systemic autoimmune conditions, a variety of hypotheses have been delivered to explain these correlations. Systemic autoimmune diseases may be the cause of Neuromyelitis Optica in some patients, or they may coexist as two independent diseases in the same condition, leading to a variety of clinical presentations in patients

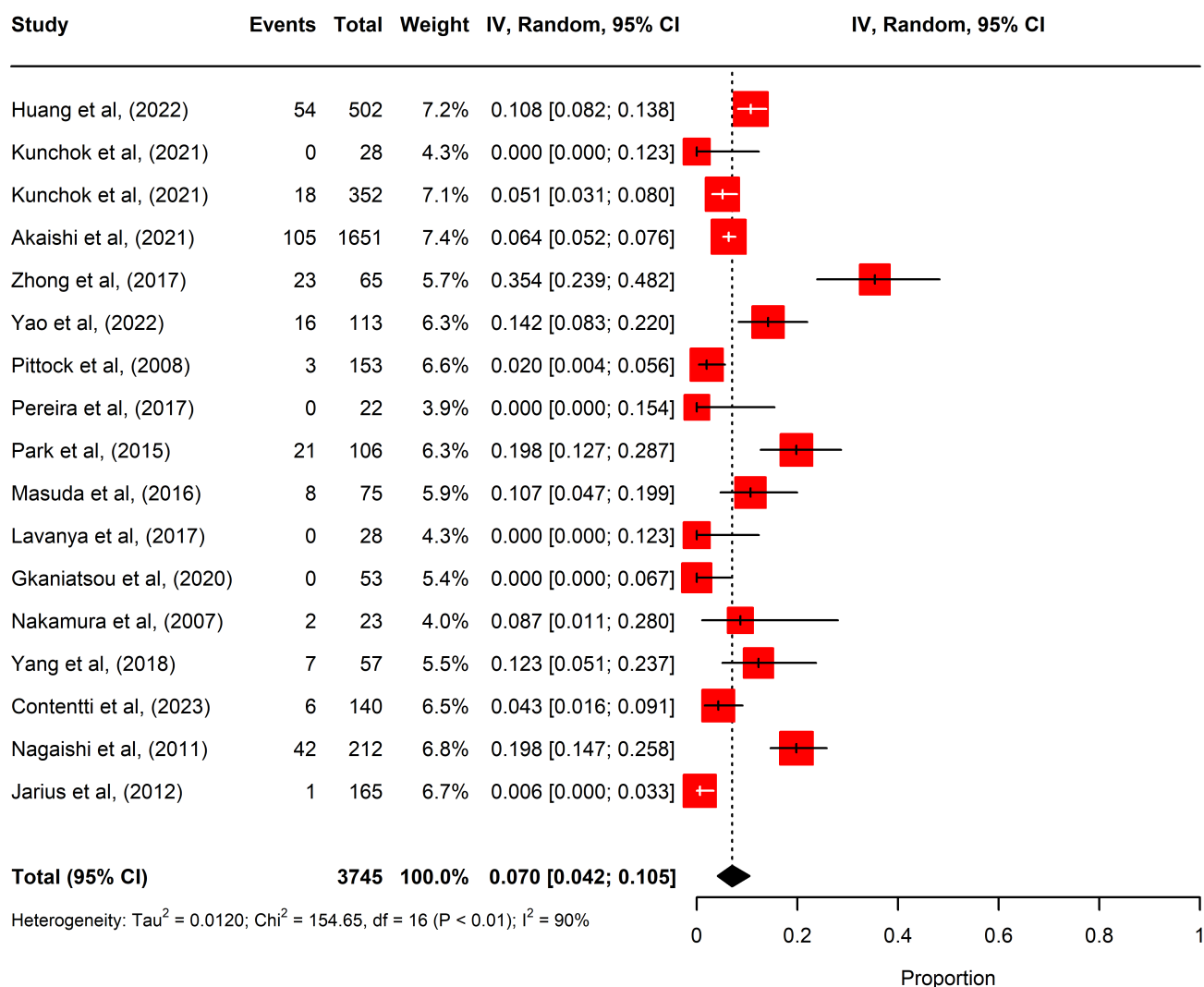


Fig. 4. Forest plot of the meta-analysis showing the proportion of SjS cases in NMOSD patients.

[14]. Over the years, some authors have investigated this topic and enrolled patients with concomitant NMO, transverse myelitis, and systemic autoimmune diseases [14,15,47,55]. All studies seem to suggest that the two pathologies may coexist. A high proportion of patients with only NMO and NMO with CTD were positive for AQP4 autoantibodies, with the same frequency in both groups. Anti AQP4-IgG antibodies were found to be exclusively linked to pathologies associated with the NMOSD, and were never detected in their absence [14,15,47,55]. These results are in line with the observation that in all clinical cases described until now, the onset of NMSOD may occur after a pre-existing CTD condition and vice versa. Thus, this evidence implies some considerations in the diagnostic and therapeutic phases. From a diagnostic standpoint, rheumatologists and neurologists may consider starting a work up for the diagnosis of coexisting conditions in their patients in high risk cases. For these cases, clinicians have to consider that patients should be monitored by a multidisciplinary team in order to prevent further relapses.

Several authors have noted that many cases of connective tissue diseases have been documented with the association of longitudinal extensive transverse myelitis (LETM), optic neuritis (ON), and brain lesions [14,15,31,37,39,50]. Consequently, we have investigated the published reported proportions of NMOSD among SjS and SLE patients. Our results showed that the pooled proportions of SjS and SLE patients that had an additional diagnosis of NMOSD were approximately 6.5% and 0.6%, respectively. However, when NMOSD screening was restricted to a population of rheumatologic patients with nervous system involvement, the probability of finding positive cases may increase. For instance, Zhang *et al.* [39] enrolled only SLE patients with coexistent transverse myelitis, which increased the risk of finding NMOSD. Hence, while Zhang *et al.* [39] revealed a higher percentage of NMOSD (48.9%, 95% CI: 33.7–64.2%), a major number of studies conducted on unselected SLE patients reported an approximately percentage <1%. Among these, only Moraitis *et al.* [42] showed a percentage of 5.6% (95% CI: 1.8–12.5%). They screened a large group

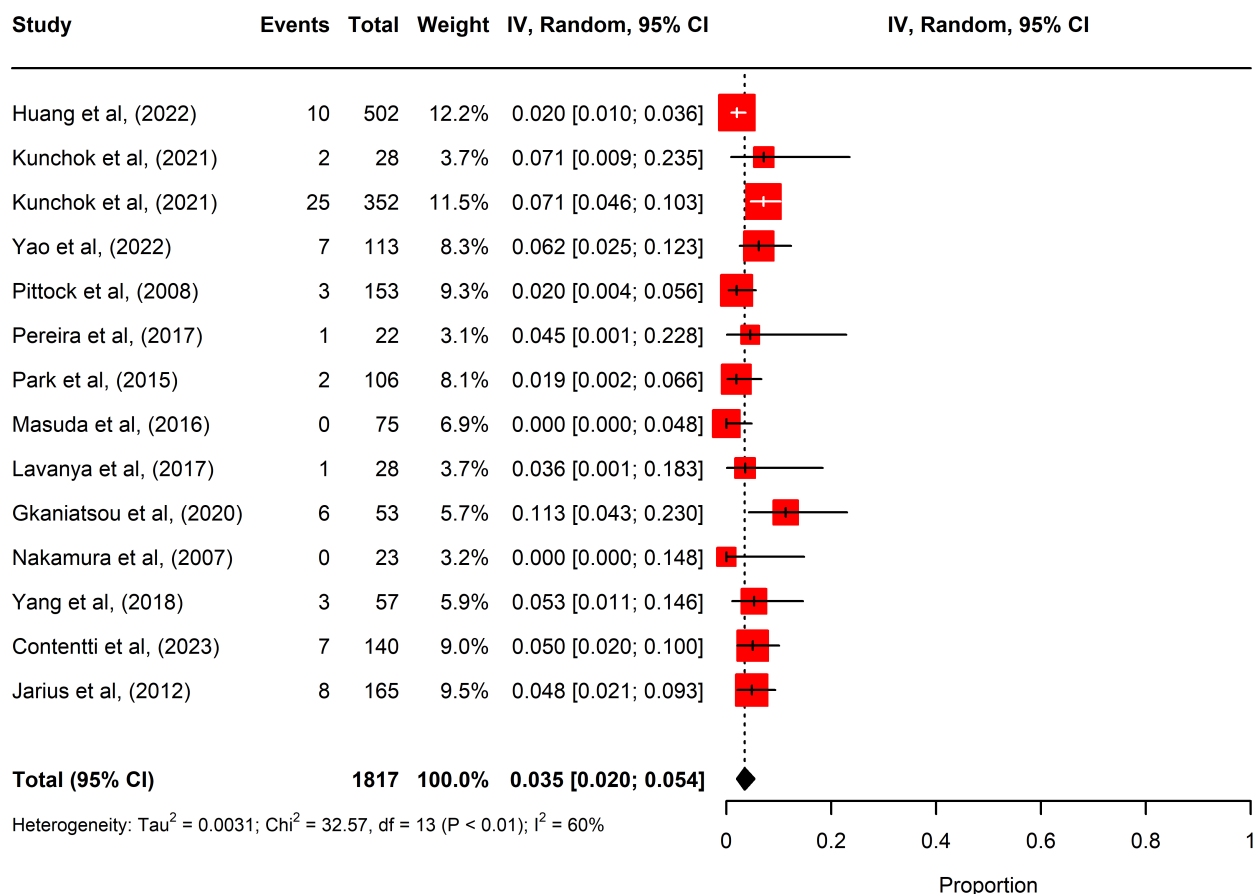


Fig. 5. Forest plot of the meta-analysis showing the proportion SLE cases in NMOSD patients.

of unselected patients with juvenile SLE for anti-aquaporin 4 antibodies (AQP4-Ab) and found an unexpected high proportion. This latter finding may suggest that some patients with juvenile Systemic Lupus Erythematosus may develop antibodies against aquaporin-4, exposing them to the risk of developing a neurological disease, and that they probably should be systematically screened for the presence of an additional neurological disease [42]. Many studies are warranted for this group of patients.

We retrieved five publications that investigate the rate of NMOSD among SjS patients. The pooled proportion obtained from unselected individuals was 6.5% (95% CI: 4.7–8.6%). As expected, the pooled proportion increased significantly when SjS studies recruiting patients with an associated nervous system disease were included in the analysis (Fig. 2).

From the point of view of rheumatologists, taking into account our data and those reported in the literature, it is reasonable to suggest that screening asymptomatic patients for NMOSD should not be recommended and that rheumatologic patients should begin a work up for NMOSD, especially in the presence of ON, NMO, longitudinal myelitis, or specific clinical signs of involvement of the following areas of the nervous system: brain, area postrema, diencephalon, or brainstem [56]. For instance, it is plausible to screen all

patients with a history of CTD presenting with optic neuritis of any degree. As mentioned in the last guideline published recently by Jarius *et al.* [11] in 2023, six clinical phenotypes are now associated with a NMOSD, and all patients with these clinical conditions are now indicated to begin a work up with clinical evaluation for the diagnosis of NMOSD, including MRI investigation and AQP4-IgG or MOG-IgG research.

However, the AQP4-IgG is highly specific for the NMOSD definition, and even in the presence of a systemic rheumatologic disease, a positive test result ensures an additional diagnosis of NMO. Nevertheless, 25% of patients with NMOSD came back negative for both AQP4-IgG and MOG-IgG. Many clinical and retrospective studies stated this finding in our systematic literature review. In spite of the high specificity, a negative result of antibody research for NMO targeting antigens may be attributed to two factors. First, the sensitivity of the procedure used to test AQP4-IgG. The cell-based assay is the most recommended test to detect anti-aquaporin-4 antibodies, and has a sensitivity of 76%. Hence, lower concentrations may be undetectable with the currently used tests. Second, the heterogeneity of the target antigen may yield a missed reactivity of tests. As a consequence, the absence of serum AQP4-Ab in patients may be interpreted by considering the exis-

tence of another potential AQP4 peptide sequence or non-AQP4 antigens as the antibody target [57]. Therefore, given the possibility that some NMOSD patients may be antibody negative, a strict clinical follow-up is required for suspected cases.

A negative patient for anti-AQP4 may be found positive for anti-MOG-IgG. Moreover, anti-MOG-IgG-positive patients matching MOGAD criteria show a diverse clinical phenotype in NMOSD and MS. In rare cases (<3%), we can find anti-MOG positivity in adults with MS, suggesting that this finding could be suitable for discriminating MS from other demyelinating syndromes [58].

Due to high specificity, the discovery of anti-AQP4 facilitates the clinical and radiological distinction of NMOSD from classical Multiple Sclerosis, and initial misdiagnosis of MS became less frequent once NMO-IgG/AQP4-Ab testing became commercially available [52]. Misdiagnosed NMOSD with MS may lead to ineffective treatment, as medications effective in Multiple Sclerosis are, in some instances, ineffective or possibly deleterious in NMOSD patients. Thus, the importance of having a sensitive and specific assay to detect AQP4-IgG cannot be overlooked [59]. Several methods (e.g., enzyme-linked immunosorbent assay [ELISA], western blot, and radioimmunoassay [RIA]) have become commercially available for anti-AQP4 and anti-MOG IgG research in clinical practice, however most of them are associated with inaccurate results [59,60]. Recently, a new method using immunofluorescence and a transfected cell assay (cell-based assay [CBA]) was introduced in clinical practice. Currently CBA with live cells is considered the most specific method for anti-AQP4 testing [59,60]. Similarly, CBA methods are considered the most accurate laboratory assay to test patients for anti-MOG. Thus, CBA assays transfected with the full-length human MOG (FL-MOG) and using IgG1-specific secondary antibodies improved further the specificity of the test for non-MS demyelinating diseases: Optic Neuritis (ON), transverse myelitis (TM), AQP4-Ab-negative NMO, or ADEM [8]. Finally, taking into account all the findings discussed above, retesting with specific and sensible assay samples with a previously negative result obtained with a less accurate method may be a suitable way to avoid a wrong diagnosis.

Studies analyzing the proportions of SjS or SLE occurrences among patients with a confirmed diagnosis of NMOSD in our research are shown in Figs. 3,4,5. Among neurologic patients, the percentage of SLE diagnosis range from 0% to 7% (Fig. 5), whereas the percentage of SjS range from 0% to 35% (Fig. 4). In general, being positive for one of the entities defined as NMOSD is more frequently observed among patients with SjS than SLE. Additionally, when we analyzed in the same meta-analysis, the SjS+SLE frequency in NMOSD patients pooled percentage increased significantly (Fig. 3). Nevertheless, larger studies, especially those with a prospective design, are needed to confirm these suggestions.

These data did not clarify whether neurologists should begin a work-up for the diagnosis of a connective tissue disease in their clinical experience evaluating NMOSD patients. Expert consensus suggests that neurologists should test for CTD only in cases where clinical symptoms are suggestive of a contextual rheumatologic complication [28]. Many authors have suggested that the CTD screening may be considered only in cases of suspicion, but the percentages that we found may suggest that asymptomatic patients with rheumatologic disease or patients with symptoms that overlap with NMOSD may remain unaware of their real serological status for a long time [28]. To date, as expected, the frequency of Antinuclear Antibodies (ANA) was significantly higher in NMOSD patients with CTD than in those without, but the photogenetic role of the presence of CTD antibodies in NMOSD with asymptomatic rheumatologic diseases is still unknown, and many research questions should be addressed to deepen our knowledge in these serologic conditions [36].

Recently, a group of researchers reported relevant findings on this regard. Measuring homocysteine (Hcy) may be very important in inflammatory demyelinating disorders, as its results appear to be independently correlated with AQP4-IgG-active NMOSD. These measurements may be useful to predict relapse and prognosis in patients with their first NMOSD attack, given that Hcy levels were found to be associated with the Expanded Disability Status Scale (EDSS) in these patients [28]. Although the mechanism by which Hcy may lead to central nervous system (CNS) damage is still unknown, patients with NMOSD may benefit from low serum Hcy concentration. Yao *et al.* [28] showed that patients with first attack NMOSD with CTD had significantly higher median values of Hcy than those without CTD and showed that, among other considered laboratory parameters, Hcy was the only variable independently associated with first NMOSD attack in patients with CTD. Thus, they suggested that serum Hcy level above 14 $\mu\text{mol/L}$ may help to predict coexistence in the first attack of NMOSD in patients unaware of their CTD overlap condition [28]. Hcy is easily measured by a simple venous sampling, using different analytical techniques. Enzyme immunoassay (EIA), fluorescence polarization immunoassay (FPIA), and chemiluminescence immunoassay (CLIA) are the most suitable methods in clinical practice. However, interest in the use of chromatographic methods has recently increased [61].

Similar to Hcy, emerging investigations indicate that glial fibrillary acidic protein (GFAP) is a strong candidate for predicting NMOSD relapse. GFAP is a type III intermediate filament protein that constitutes the cytoskeleton of astrocytes [62]. NMOSD is an astrocytopathy that cause the release of GFAP from astrocytes into the interstitial fluid, cerebrospinal fluid (CSF), and blood. As a consequence, several studies have suggested that serum measurements of GFAP may be a useful method for predicting a NMOSD acute phase. Both CSF GFAP and serum GFAP correlated with EDSS scores and the length of spinal cord

injury. GFAP concentrations increase during NMOSD attack and decrease after the start of corticosteroid treatment. CSF GFAP testing is unfeasible for frequent sampling, and convectional ELISA is not sensitive enough to detect low concentrations of GFAP (0.5–5000 pg/mL) in the serum. Thus, an ultrasensitive single-molecule array technology was used to develop peripheral blood-based assays to monitor NMOSD patients [63,64].

Our analysis had some limitations. It involved a small number of studies, with a low number of patients. The recruiting criteria among studies was different, and this may have caused significantly different results among studies. We included studies with a retrospective design, of which only one was a cross-sectional design; large prospective studies are warranted to increase the accuracy of data and confirm the implications of our results.

5. Conclusions

We have conducted, for the first time, a meta-analysis to estimate the burden associated with the coexistence of NMOSD and CTD and we have discussed the main implications of these aspects for diagnosis. This condition was more frequently found in female rheumatologic patients, mainly in those with a SjS diagnosis and nervous system involvement, and in neurologic patients where a SjS diagnosis was suspected. These considerations should be taken into account in the clinical experience of rheumatologists and neurologists, since early diagnosis of both conditions may influence the timing and selection of immunosuppressive therapy.

Availability of Data and Materials

The datasets analyzed in this article are available upon request to: en.polilli@gmail.com.

Author Contributions

EP: Conceptualization, Data curation, formal analysis, investigation, methodology, supervision, validation, visualization, writing. JEE, EP, GAnn, MDA, AG, FT, ADR, GAng, CC, PT, PV, GDI: Data curation, formal analysis, investigation, methodology, and supervised the procedures, wrote the manuscript. GP: Supervision, Validation, revision the language. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/j.jin2302035>.

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