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# Time to Disability Milestones and Annualized Relapse Rates in NMOSD and MOGAD

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**Objective:** To investigate accumulation of disability in neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein-antibody-associated disease (MOGAD) in a changing treatment landscape. We aimed to identify risk factors for the development of disability milestones in relation to disease duration, number of attacks, and age.

**Methods:** We analyzed data from individuals with NMOSD and MOGAD from the German Neuromyelitis Optica Study Group registry. Applying survival analyses, we estimated risk factors and computed time to disability milestones as defined by the Expanded Disability Status Score (EDSS).

**Results:** We included 483 patients: 298 AQP4-IgG<sup>+</sup> NMOSD, 52 AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD patients, and 133 patients with MOGAD. Despite comparable annualized attack rates, disability milestones occurred earlier and after less attacks in NMOSD patients than MOGAD patients (median time to EDSS 3: AQP4-IgG<sup>+</sup> NMOSD 7.7 (95% CI 6.6–9.6) years, AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD 8.7) years, MOGAD 14.1 (95% CI 10.4–27.6) years; EDSS 4: 11.9 (95% CI 9.7–14.7), 11.6 (95% lower CI 7.6) and 20.4 (95% lower CI 14.1) years; EDSS 6: 20.1 (95% CI 16.5–32.1), 20.7 (95% lower CI 11.6), and 37.3 (95% lower CI 29.4) years; and EDSS 7: 34.2 (95% lower CI 31.1) for AQP4-IgG<sup>+</sup> NMOSD). Higher age at onset increased the risk for all disability milestones, while risk of disability decreased over time.

**Interpretation:** AQP4-IgG<sup>+</sup> NMOSD, AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD, and MOGAD patients show distinctive relapse-associated disability progression, with MOGAD having a less severe disease course. Investigator-initiated research has led to increasing awareness and improved treatment strategies appearing to ameliorate disease outcomes for NMOSD and MOGAD.

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Neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) are rare and severe autoimmune diseases presenting with overlapping phenotypes of attack-related inflammation of optic nerve and spinal cord as well as other structures of the central nervous system.<sup>1,2</sup> In NMOSD, presence of pathognomonic aquaporin-4 antibodies (AQP4-IgG) in serum separates the predominant group of AQP4-IgG seropositive (AQP4-IgG<sup>+</sup>, up to 80%<sup>3</sup>) from (AQP4-IgG<sup>-</sup>) seronegative patients.<sup>4,5</sup> Antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG) have been described in numerous studies in subgroups of patients with seronegative NMOSD,<sup>6</sup> allowing to assign to these patients a diagnosis of MOG-IgG-associated disease (MOGAD), which is now regarded as a disease entity of its own.<sup>7,8</sup> AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD patients<sup>9</sup> remain a not yet conclusively understood, possibly heterogeneous, subgroup.

Individuals with NMOSD typically experience recurring attacks that are often severe, tend to recover poorly, if untreated, and lead to accumulation of substantial disability over the course of the disease. Thus, early and effective management of attacks as well as attack-preventive long-term treatment is crucial for disease control.<sup>2,10,11</sup> AQP4-IgG<sup>+</sup> NMOSD affects women more frequently,<sup>12</sup> and some studies suggest a higher attack-rate in women than in men.<sup>13,14</sup> MOGAD patients with NMOSD phenotype tend to be younger at manifestation than patients with NMOSD and exhibit a less pronounced female predominance.<sup>8,15</sup>

Over the past two decades, the treatment landscape for NMOSD has changed from a highly explorative phase through a period of established effective off-label treatments to the recent approval of therapies for (up to now exclusively) AQP4-IgG<sup>+</sup> NMOSD based on randomized clinical trials.<sup>16–18</sup> However, long-term data on safety and efficacy are missing and treatment for NMOSD and MOGAD patients still greatly relies on strategies using empirically effective off-label immunotherapy.<sup>19</sup> In 2014, the Neuromyelitis Optica Study Group (NEMOS) published diagnosis and treatment recommendations,<sup>20</sup> which among others facilitated adequate treatment decisions in Germany and possibly elsewhere. Concerning the ultimate treatment goal, the prevention of long-term disability, our current knowledge remains sparse. Effective treatment in AQP4-IgG<sup>+</sup> NMOSD reduces the risk of attacks, but has not unequivocally proven to lower the risk of sustained disability accumulation in short-term prospective clinical trials.<sup>21,22</sup> Cohort studies identified additional risk factors for long-term disability in NMOSD such as age above 50, a severe first attack and a long interval to correct diagnosis, which can be considered a proxy for delayed treatment initiation.<sup>21,23</sup> However, results are often limited by small sample sizes and/or short follow-up times and often restricted to the early disease phase. Data on patients with MOGAD or those with a NMOSD phenotype but without AQP4- or MOG-IgG antibodies are even more rare.<sup>24,25</sup> A comparison of reliable long-term data

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on disability risks in AQP4-IgG<sup>+</sup> NMOSD, AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD, and MOGAD patients is still lacking but are essential for personalized counselling and treatment decision in these rare diseases.

This study investigated the accumulation of disability in AQP4-IgG<sup>+</sup> and AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD and MOGAD patients in a changing treatment landscape. To this regard, we analyzed the time to and risk factors for reaching disability milestones in the nationwide German NEMOS cohort.

## Methods

### Study Setting and Data Collection

Clinical data of NMOSD patients and patients with serum MOG-IgG were collected from 25 centers of the NEMOS registry in Germany ([www.nemos-net.de](http://www.nemos-net.de)). Participating NEMOS centers include university hospitals, regional hospitals, specialized outpatient clinics, and a rehabilitation center that contribute clinically and scientifically to the care of NMOSD patients. The current study combines retrospective and (since 2016) prospective longitudinal data. Clinical data were documented at visits that were typically scheduled on an annual basis. Data were then exported, reviewed, and validated with database closure in September 2021 to ensure data consistency. The collected data included basic demographic information (sex, age at first manifestation) and important disease characteristics (AQP4-IgG and MOG-IgG status, type of first manifestation, year of diagnosis, diagnostic criteria, Expanded Disability Status Score (EDSS), number and type of attacks, type of attack, preventing immunotherapies used).

Inclusion criteria were diagnosis of NMOSD with or without AQP4-IgG according to the 2015 diagnostic criteria of the International Panel for NMO Diagnosis (IPND)<sup>9</sup> or diagnosis of MOGAD with a typical clinical syndrome according to the clinical judgement of an expert in the neuroimmunological field and presence of serum MOG-IgG. Patients that were documented to fulfill the 2006 Wingerchuk diagnostic criteria for NMOSD<sup>26</sup> were checked manually for fulfillment of the 2015 IPND criteria. A diagnosis of NMOSD without AQP4-IgG additionally required documented negative testing for MOG-IgG (AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD). Standard testing for AQP4-IgG and MOG-IgG was performed with cell-based assays<sup>27,28</sup> in the majority of the patients (at least 70% in AQP4-IgG<sup>+</sup> NMOSD and 82% in MOGAD, for the rest no documentation of assay available). Patients were excluded in case of incomplete core data sets or absence of at least one documented EDSS

examination in stable disease phase without relation to an attack.

### Measurement of Disability

Neurologic disability was assessed via EDSS<sup>29</sup> by the treating physicians. For EDSS calculation, scores from 0 (no neurologic disability) to 10 (death due to the disease) are given according to a combination of subscores in eight functional systems (visual, brainstem, cerebellar, pyramidal, sensory, bowel and bladder, and cerebral functions, as well as an ambulation index indicating walking ability). We selected a set of four EDSS scores as disability milestones over the disease course to cover a comprehensible range of severity grades from moderate disability to substantial impairment. An EDSS score of 3 describes moderate disability in at least one functional system; at EDSS 4 the walking ability is reduced while the patient is still able to walk 500 m or more without rest or assistance; at EDSS 6 unilateral assistance is needed to walk at least 100 m; and at EDSS 7 patients are not able to walk 5 m without assistance and are mostly wheelchair dependent. As covariates we set diagnosis, sex, type of first manifestation, and age at initial presentation. An additional covariate was implemented to reflect the major changes in knowledge and treatment routine for NMOSD over time. To do so, we included the epoch of reaching the EDSS outcome before or after 2014 (10 years after the discovery of AQP4-IgG-antibodies) as an arbitrary cutoff. We further exploratively checked the registry for time until death for patients who died due to complications of NMOSD or MOGAD (equals an EDSS of 10).

### Statistical Analysis

We summarized descriptive data either as mean with standard deviation (SD) or as frequency according to the nature of the data. Assuming that attack occurrence follows a negative binomial distribution,<sup>30</sup> we estimated unadjusted annualized attack rates (AAR, mean number of attacks per year) with 95% confidence intervals (CI). Statistical significance for the demographic parameters and AAR between the different disease types were tested by Kruskal-Wallis, chi-squared test or analysis of variance (ANOVA). Median time to reach an EDSS milestone was calculated by Kaplan–Meier method. An explorative post-hoc analysis included the number of attacks as a pseudo-time variable to explore the association between number of attacks and disability milestones. We implemented multivariate Cox proportional hazard regression stratified by diagnosis to explore the impact of covariates on disability evolution; hazard ratios and their 95% CI were computed. The *p* values <0.05 were considered statistically

significant. All analyses were performed in R (V.3.2.3), including the survival package.

**Ethics**

Following the lead vote from the Technical University of Munich, ethics committees of all participating NEMOS centers approved the data collection in the registry for this purpose. Written informed consent was obtained from all patients before entering the registry.

**Results**

**Individuals Included**

We screened 744 patients in the NEMOS registry for eligibility (see patient flow chart, Fig. 1). Due to insufficient core data as defined above 208 patients were excluded. Two patients with suspected NMOSD did not fulfill the IPND diagnostic criteria for AQP4-IgG<sup>+</sup> or AQP4-IgG<sup>-</sup> NMOSD,<sup>9</sup> nor had evidence of MOG-IgG and 51 patients had no documented or only attack-related EDSS examination available. This leads to a final sample size of 483 patients: 298 patients with AQP4-IgG<sup>+</sup> NMOSD, 52 patients with AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD, and 133 patients with MOGAD.

**Demographic and Clinical Characteristics Indicate Representativeness of Our Cohort**

Demographic and clinical data are summarized in Table 1. The mean follow-up time was 10 years (SD 8.9) for AQP4-IgG<sup>+</sup> patients, 9.1 years (SD 5.9) for AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> patients and 7.4 years (SD 8.6) for MOGAD patients.

The sex distribution among the cohorts differed significantly (Table 1): In the AQP4-IgG<sup>+</sup> subgroup the vast majority (90.6%) were women, as opposed to a more balanced sex distribution for the subgroup of AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> patients (42.3%). In the MOGAD subgroup 57.1% were female.

On average, AQP4-IgG<sup>+</sup> NMOSD patients were older at onset than AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD and MOGAD patients (mean age 43.1 (SD 16.3) versus 35.7 (SD 12.4) versus 33.6 (SD 13.6) years) and age at onset was evenly distributed across age groups (30–35% in each group under 35 years, 35–50 years and over 50 years). In contrast, more than half of AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD and MOGAD patients (51.9% and 54.1%, respectively) first developed symptoms below the age of 35 and only rarely above the age of 50 (*p* < 0.001). Of note, 4 (3.0%) of the

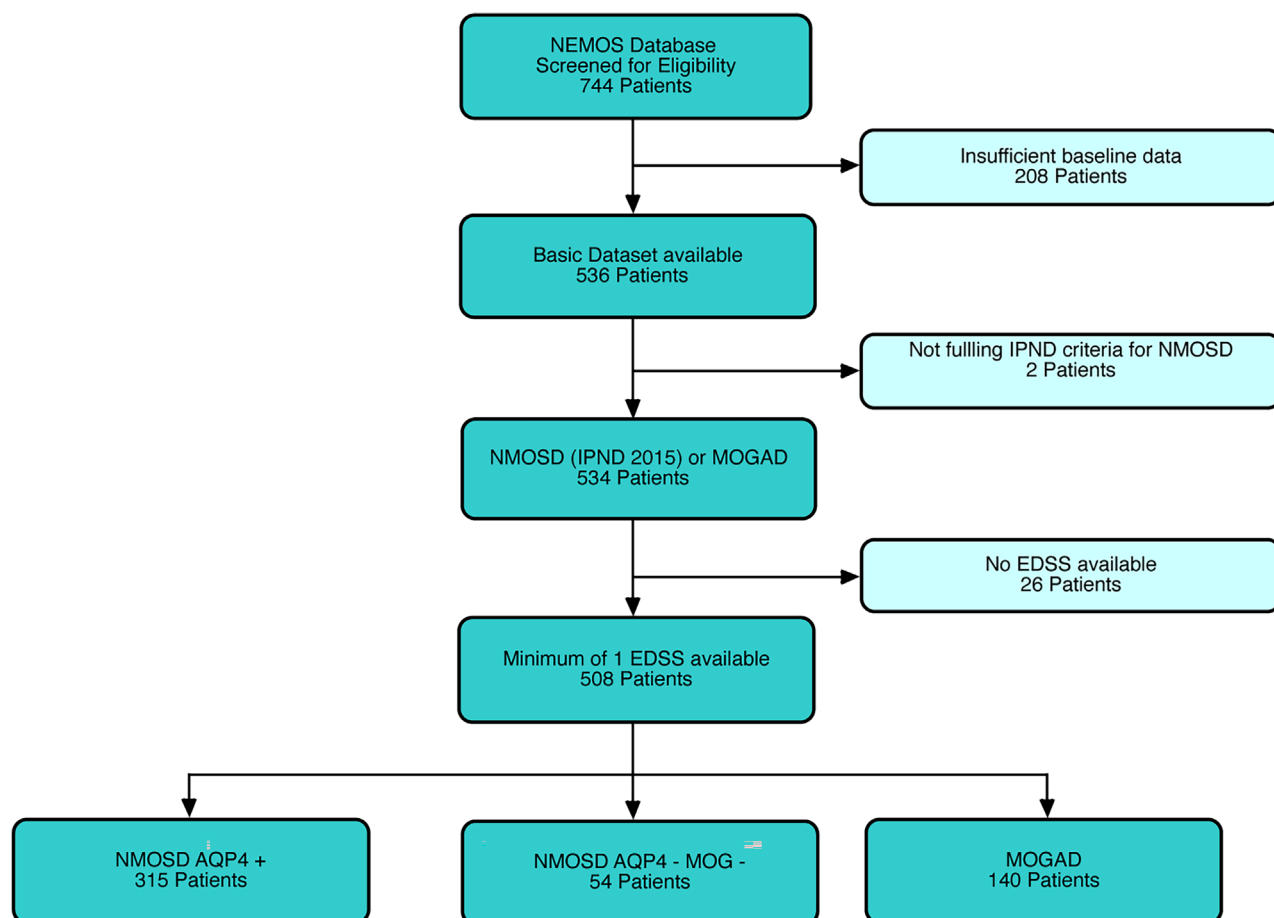


FIGURE 1: Flow chart of inclusion process. [Color figure can be viewed at [www.annalsofneurology.org](http://www.annalsofneurology.org)]

**TABLE 1. Demography and Clinical Basic Data Set, Subgroup Specific for AQP4-IgG<sup>+</sup> and AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD and MOGAD**

		AQP4-IgG <sup>+</sup> NMOSD	AQP4-IgG <sup>-</sup> / MOG- IgG <sup>-</sup> NMOSD	MOGAD	<i>p</i> -value
Total number of patients	n	298	52	133	
Age at onset (YR)	Mean (SD)	43.1 (16.3)	35.7 (12.4)	33.6 (13.7)	<0.001 <sup>a</sup>
Age group at onset (YR)					<0.001 <sup>b</sup>
<35	n (%)	93 (31.2)	27 (51.9)	72 (54.1)	
35–50	n (%)	105 (35.2)	18 (34.6)	44 (33.1)	
>50	n (%)	100 (33.6)	7 (13.5)	17 (12.8)	
Sex					<0.001 <sup>b</sup>
Male	n (%)	28 (9.4)	30 (57.7)	57 (42.9)	
Female	n (%)	270 (90.6)	22 (42.3)	76 (57.1)	
Attack type at first manifestation					0.003 <sup>b</sup>
Optic neuritis	n (%)	106 (35.6)	18 (34.6)	64 (48.1)	
Transverse myelitis	n (%)	131 (44)	20 (38.5)	33 (24.8)	
Optic neuritis and myelitis	n (%)	11 (3.7)	3 (5.8)	9 (6.8)	
Brainstem symptoms	n (%)	14 (4.7)	3 (5.8)	3 (2.3)	
Cerebral symptoms	n (%)	1 (0.3)	0 (0)	4 (3)	
Other	n (%)	28 (9.4)	6 (11.5)	20 (15)	
Number of patients with documented attacks	n (%)	262 (87.9)	42 (80.8)	118 (88.72)	0.308 <sup>b</sup>
Number of attacks per patient	Mean [range]	4.7 [1, 30]	4.0 [1, 12]	3.9 [1, 27]	0.052 <sup>a</sup>
Annualized attack rate	Mean (95% CI)	0.54 (0.49–0.60)	0.52 (0.42–0.66)	0.80 (0.66–0.97)	0.006 <sup>c</sup>
Patients with monophasic disease	n (%)	57 (21.8)	8 (19.0)	39 (33.1)	<0.001 <sup>b</sup>
Number of patients with treatment information	n (%)	256 (97.3)	40 (93.0)	110 (84.6)	
Treatment episodes <sup>d</sup>					0.001 <sup>b</sup>
Rituximab	n (%)	285 (34.3)	38 (35.5)	81 (24.3)	
Azathioprine	n (%)	151 (18.2)	16 (15.0)	91 (27.3)	
Other <sup>e</sup>	n (%)	395 (47.5)	53 (49.5)	162 (48.5)	
Follow-up time (YR)	Mean (SD)	10.2 (9.0)	8.5 (5.7)	7.2 (8.4)	<0.001 <sup>a</sup>

<sup>a</sup>Kruskal-Wallis test.<sup>b</sup>Chi-squared.<sup>c</sup>ANOVA.<sup>d</sup>Treatment episodes: lines of treatment, multiple treatment episodes of the same agent per patient are recorded, if initiated at different timepoints or subject to relevant dosage changes.<sup>e</sup>Other treatment (alphabetical order): alemtuzumab, ciclosporin A, cyclophosphamide, dimethyl fumarate, eculizumab, glatiramer acetate, interferon beta, intravenous immunoglobulins, methotrexate, mitoxantrone, mycophenolate mofetil, natalizumab, oral steroids, intermittent immunoadsorption, regular intravenous steroid treatment, regular plasma exchange, teriflunomide, tocilizumab, or study medication. CI: 95% confidence interval. SD: standard deviation.

**Table 2. Annualized Attack Rates (AAR) over the course of disease**

Years since first symptoms	AQP4-IgG+ NMOSD	AQP4-IgG-/MOG-IgG-NMOSD	MOGAD	p-value
0–2	1.06 (0.97–1.16)	0.91 (0.72–1.14)	1.26 (1.07–1.49)	0.08
2–4	0.33 (0.26–0.43)	0.29 (0.17–0.48)	0.41 (0.30–0.57)	0.52
4–6	0.36 (0.28–0.47)	0.29 (0.15–0.55)	0.33 (0.21–0.51)	0.81
6–8	0.32 (0.24–0.44)	0.26 (0.12–0.57)	0.28 (0.16–0.47)	0.82
8–10	0.33 (0.23–0.47)	0.41 (0.18–1.00)	0.28 (0.13–0.67)	0.80

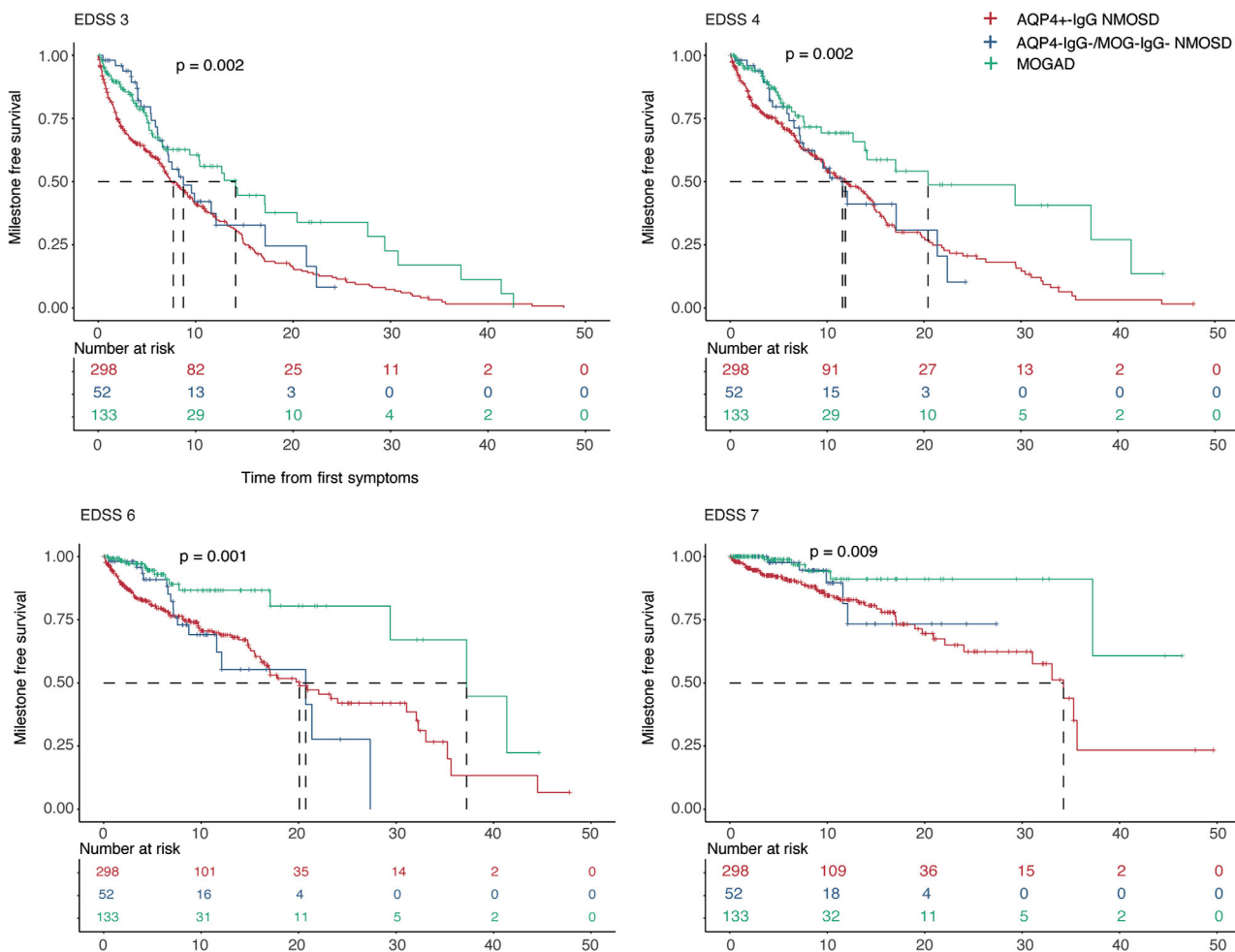
Note: Confidence interval is based on negative binomial regression. Differences between groups were analyzed by ANOVA.

MOGAD patients manifested before adolescence (<10 years of age).

**Manifestation, Relapse Rates, and Treatment Differ between Cohorts**

Optic neuritis (ON) and transverse myelitis (TM) constituted around 80% of first manifestations in all three groups.

Brainstem (including area postrema syndrome) and cerebral manifestations and other or multiple syndromes were less frequent. TM as first attack occurred more often in AQP4-IgG+ patients (TM: 44.0%, n = 131; ON 35.6%, n = 106; combined: 3.7%, n = 11), ON more often in MOGAD patients (ON: 48.1%, n = 64; TM 24.8%, n = 33; combined 6.8%, n = 9) (p = 0.012). Among



**FIGURE 2: Disease duration and disability milestones.** Kaplan–Meier estimates for time (in years) to reach an assigned EDSS of 3, 4, 6, and 7 since onset of first symptoms for patients with AQP4-IgG+ NMOSD (red line), AQP4-IgG-/MOG-IgG- NMOSD (blue line), and MOGAD (green line). [Color figure can be viewed at [www.annalsofneurology.org](http://www.annalsofneurology.org)]

**Table 3. Estimated Time to EDSS Disability Milestones**

	AQP4-IgG+ NMOSD	AQP4-IgG-/MOG-IgG- NMOSD	MOGAD	p-Value
EDSS 3	10.6 [7.7] (6.7–9.7)	11.5 [8.7] (7.2–21.4)	17.3 [14.1] (10.4–27.7)	0.006 <sup>a</sup>
EDSS 4	14.3 [11.9] (9.7–14.7)	12.8 [11.6] (7.6 – NA)	23.9 [20.4] (14.1 – NA)	0.003 <sup>a</sup>
EDSS 6	22.0 [20.1] (16.5–32.1)	16.9 [20.7] (11.6 – NA)	33.2 [37.2] (29.4 – NA)	<0.001 <sup>a</sup>
EDSS 7	29.7 [34.2] (31.1 – NA)	22.8 [NA] (NA– NA)	40.2 [NA] (37.2, NA)	<0.001 <sup>a</sup>

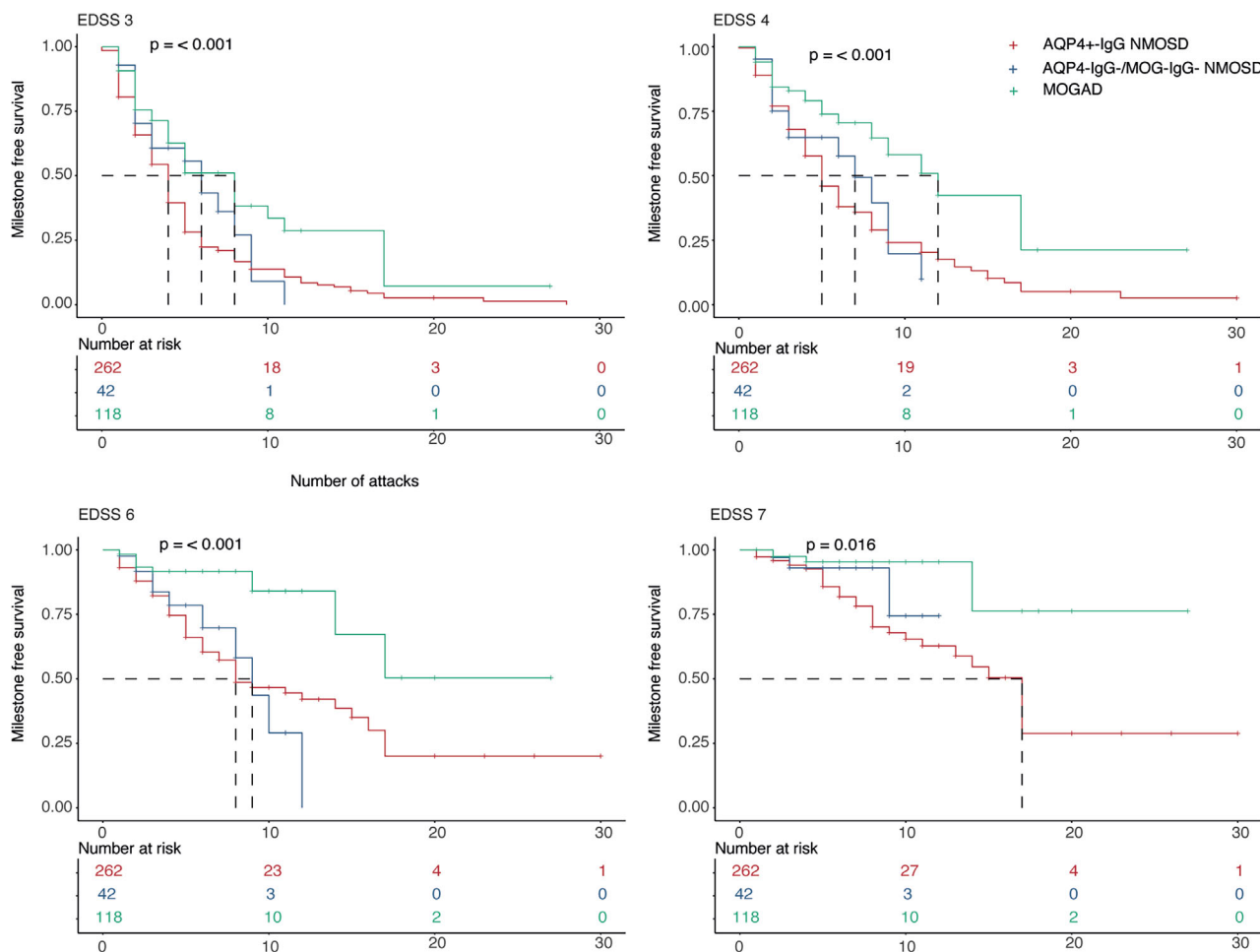
Note: Mean [Median] time in years and 95% CI from onset of first symptoms to reaching an EDSS of 3, 4, 6, and 7 for AQP4-IgG+ and AQP4-IgG-/MOG-IgG- NMOSD and MOGAD patients. NA: Calculation not possible due to insufficient patient numbers.

<sup>a</sup>Log-rank test.

AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD patients TM and ON were almost equally distributed as first manifestations (TM: 38.5%, n = 20; ON: 34.6%, n = 18).

Complete attack documentation for the entire course of disease was available for 87.9% (n = 262) of AQP4-IgG<sup>+</sup> NMOSD patients, 80.8% (n = 42)

of AQP4<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD patients and 88.7% (n = 118) of MOGAD patients. Monophasic disease was observed in 57 (21.8%) of AQP4-IgG<sup>+</sup> NMOSD patients, 8 (19.0%) of AQP4<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD patients, and 39 (33.1%) of the MOGAD patients. Annualized attack rates (AAR) was higher in



**FIGURE 3: Number of attacks and disability milestones.** Kaplan–Meier estimates for number of attacks before reaching an EDSS of 3, 4, 6, and 7 for patients with AQP4-IgG<sup>+</sup> NMOSD (red line), AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD (blue line), and MOGAD (green line). [Color figure can be viewed at [www.annalsofneurology.org](http://www.annalsofneurology.org)]



**Table 4. Estimated Number of Attacks to EDSS Disability Milestones**

	AQP4-IgG+ NMOSD	AQP4-IgG-/MOG-IgG- NMOSD	MOGAD	p-Value
EDSS 3	5.2 [4] (3 – 4)	5.6 [6] (3 – NA)	9.1 [8] (5 – 17)	<0.001 <sup>a</sup>
EDSS 4	7.2 [5] (5 – 6)	6.5 [7] (6 – NA)	13.1 [12] (9, NA)	<0.001 <sup>a</sup>
EDSS 6	12.6 [8] (7 – 16)	8.3 [9] (8 – NA)	19.7 [NA] (14 – NA)	<0.001 <sup>a</sup>
EDSS 7	16.4 [17] (13 – NA)	10.8 [NA] (9 – NA)	23.4 [NA] (14, NA)	0.016 <sup>a</sup>

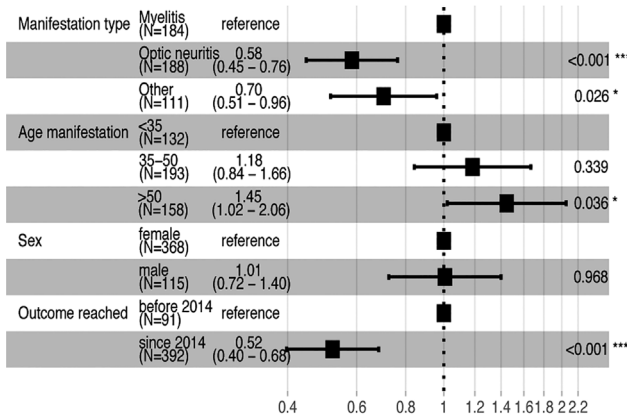
Note: Mean [median] number of attacks and (95% CI) until reaching an EDSS of 3, 4, 6, and 7 for AQP4-IgG+ and AQP4-IgG-/MOG-IgG- NMOSD, and MOGAD patients. NA: Calculation not possible due to insufficient patient numbers.

<sup>a</sup>Log-rank test.

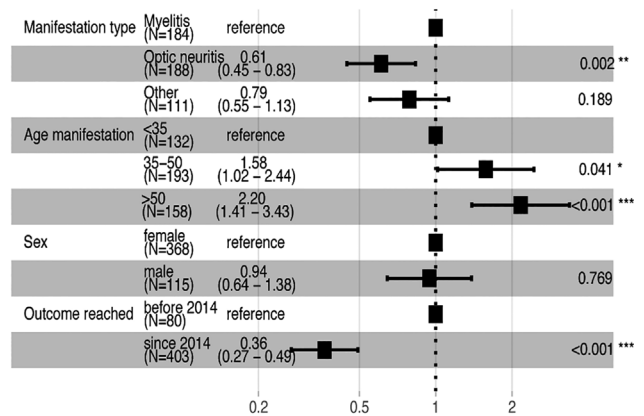
MOGAD (AQP4-IgG<sup>+</sup> NMOSD: AAR = 0.54 [95% CI = 0.49–0.60]; AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD: AAR 0.52 [95% CI 0.42–0.66]; MOGAD: AAR 0.80 [95% CI 0.66–0.97], *p* = 0.006). When looking at the AAR in more detail at 2-year intervals (Table 2), an initially lower relapse rate was observed for AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD patients (AAR 0.91 [0.72–1.14]) than for AQP4-IgG<sup>+</sup> NMOSD patients (AAR: 1.06

[0.97–1.16]) and MOGAD (AAR 1.26 [1.07–1.49]) patients. Not taking treatment effects into account, AAR declined over the years for all patients, but most markedly for patients with MOGAD (AAR 0.28 [0.13–0.67] at 10 years compared to onset of disease). However, in the AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD group a later increase was noted (AAR: 0.41 [0.18–1.00] at year 8–10). The vast majority of patients (AQP4-IgG<sup>+</sup> NMOSD: 97.3%;

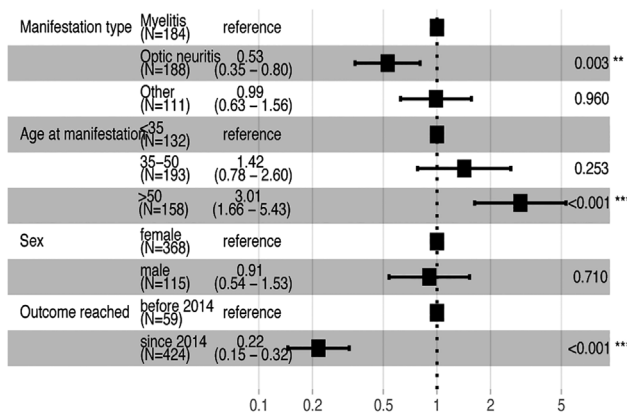
**A EDSS 3**



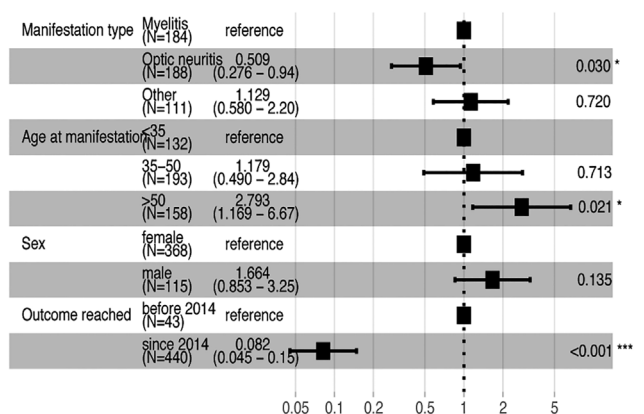
**B EDSS 4**



**C EDSS 6**



**D EDSS 7**



**FIGURE 4: Risk factors for disability milestones. Hazard ratios for the effects of type of first manifestation (acute myelitis, acute optic neuritis, other), age at first manifestation, sex, and epoch of reaching the outcome (before/after 2014) of (A) EDSS 3, (B) EDSS 4, (C) EDSS 6, and (D) EDSS 7 in all 3 groups.**

AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD: 93.0%; MOGAD: 84.6%) received at least once an immunosuppressive or immunomodulating attack-preventing treatment, most commonly rituximab or azathioprine. Approximately half of all recorded treatment episodes consisted of other medications than rituximab or azathioprine (Table 1). These include MS medications, medications previously used to treat NMOSD (or administered before the correct diagnosis was made), as well as other immunosuppressive agents and, in rarer cases, extracorporeal treatment methods. A few patients received eculizumab, which was approved in Germany for the treatment of recurrent AQP4-IgG<sup>+</sup> NMOSD in 2019.

#### Disability Milestones: Median Time until Development of an EDSS Score of 3, 4, 6, and 7

Kaplan–Meier estimates for the probability to develop EDSS 3, 4, 6, and 7 over time since the onset of first symptoms are depicted in Figure 2. We observed a shorter median time to reach the different disability milestones in AQP4-IgG<sup>+</sup> as well as AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD patients compared to the MOGAD patients. For example, MOGAD patients reached an EDSS of 4 about 10 years later than NMOSD patients with a median time of 20.4 years (MOGAD, CI above 14.11 without upper limit) vs. 11.9 years (AQP4-IgG<sup>+</sup>, CI 9.7–14.7) and 11.6 years (AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup>, CI above 7.6 without upper limit). For other EDSS steps see also Table 3. AQP4-IgG<sup>+</sup> NMOSD patients had a faster accumulation of disability in the first 5–10 years, while over time the development of the disability milestones in AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD appeared to become faster (Fig. 2). To reach the EDSS scores of 6 and 7, the median time for AQP4-IgG<sup>+</sup> NMOSD patients was 20.1 years (CI 16.5–32.1) and 34.3 years (95% CI above 31.1 without upper limit). The calculation for AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD patients yielded 16.8 years for EDSS 6 (95% CI above 11.6 without upper limit), although it must be noted that the number at-risk patients is low in this group and no statements can be made for EDSS 7. For MOGAD estimates for EDSS steps 6 and 7 could not be calculated due to a lack of data.

#### Accumulation of Disability with Attacks

Overall, accrual of disability in MOGAD occurred after more attacks than in both NMOSD subgroups, and AQP4-IgG<sup>+</sup> NMOSD needed more attacks than AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD (Fig. 3): AQP4-IgG<sup>+</sup> NMOSD patients experienced a median of 4 attacks (95% CI 3–4) before reaching an EDSS of 3 (AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD: 6 attacks, CI

3–NA). In AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD patients, EDSS steps 4 and 6 were reached after fewer attacks than in AQP4-IgG<sup>+</sup> NMOSD (see also Table 4). In MOGAD patients, a median of 8 attacks (95% CI 5–17) occurred before developing an EDSS of 3, and 12 attacks (95% CI >9 without upper limit) before reaching an EDSS of 4. The number of attacks to EDSS 6 and EDSS 7 could not be determined in this subgroup due to insufficient data.

#### Risk Factors for Disability Progression

Next, we were interested in demographic variables modulating the risk to reach an EDSS milestone. We explored different models regarding the interaction of predictors, and apart from sex found no evidence of a relevant interaction with the three diagnostic groups. We therefore used a simplified model stratified for the diagnoses of AQP4-IgG<sup>+</sup> NMOSD, AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD, and MOGAD for subsequent analyses. Covariates and their hazard ratios (HRs) on reaching the disability milestones are outlined in Figure 4. Patients with optic neuritis as first manifestation have a reduced risk of developing all EDSS milestones compared to patients with myelitis as first manifestation. Patients who developed their first attack after the age of 50 years had an overall elevated risk to develop all milestones, and an over 2-fold elevated risk to develop the higher EDSS steps 6 and 7 (EDSS 6: HR 3.01, CI 1.66–5.43,  $p < 0.001$ ; EDSS 7: HR 2.79, CI 1.17–6.67,  $p = 0.021$ ). Comparing the timepoint of outcome assessment, the risk of reaching a disability milestone decreased substantially after 2014 with hazard ratios ranging from 0.52 (CI 0.40–0.68,  $p < 0.001$ ) for EDSS 3 to 0.08 (CI 0.045–0.15,  $p < 0.001$ ) for EDSS 7 compared to before 2014.

#### Mortality in the NEMOS Cohort

Death was documented in 18 of 483 patients (AQP4-IgG<sup>+</sup> NMOSD: 15 of 298, AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD: 2 of 52, MOGAD: 1 of 133) after a mean disease duration of 9.0 years (median 8.2, range 1.2–27.6 and a mean number of 7.9 attacks (median 7, range 2–24). Apart from three patients being six, 14 and 28 years old at the time of first manifestation, all deceased patients were >40 years of age at diagnosis. The mean age was 49.1 years (median 51.5, range 6–76). All of them had received at least one immunosuppressive medication over the course of the disease. The exact cause of death was difficult to analyze in retrospect, as for 6 cases no further information was available. For the remaining patients, the available evidence suggests that they more likely died from complications of accrued neurological

disability and/or immunosuppressive therapy than from an acute attack.

## Discussion

Patients with NMOSD or MOGAD carry the risk of acquiring substantial disability over the course of the disease due to recurrent attacks with a high risk for poor recovery. Here, we analyzed a unique longitudinal dataset to explore time course and risk factors for long-term disability accumulation in the German NEMOS registry in a changing and complex treatment landscape. We found that MOGAD takes a less aggressive overall disease course than NMOSD despite the lack of established treatment concepts. Interestingly, the subgroups of patients with AQP4-IgG<sup>+</sup> and AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD had a very similar treatment profile, with Rituximab and Azathioprine being used most frequently, but showed some differences in disability accumulation. Despite a similar average time to reach disability milestones, AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD patients reached them with a larger number of attacks suggesting either less severe attacks or a better recovery in these patients. Moreover, we were able to extend the knowledge on the risk factors age and syndrome at manifestation, and to provide important evidence about the success of the scientific community to establish effective off-label treatment strategies in a rare disease.

### Demographic Data Indicate Generalizability

In line with previous studies, our findings indicate a later disease onset in AQP4-IgG<sup>+</sup> NMOSD than in MOGAD. Interestingly, with an average age of 35 years at first manifestation, AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD patients appear more similar to the MOGAD group.<sup>8</sup> Another significant difference between AQP4-IgG<sup>+</sup> and AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD patients in our cohort regards the sex distribution, with 91% females in the AQP4-IgG<sup>+</sup> NMOSD group compared to 42% in AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD patients and 57% in MOGAD. Overall, these demographic cohort characteristics are very similar to those of other cohorts, indicating a high representativeness of our cohort.<sup>3</sup>

### Time-to-Disability Milestones Was Longer Than in Historic NMOSD Studies

Regarding the development of disability in NMOSD, several studies have described an increase in the EDSS, a disability scale originally developed for patients with MS, over the course of the disease in both NMOSD and MOGAD.<sup>14,31–34</sup> For example, in a 2010 French cohort of 125 patients (AQP4-IgG<sup>+</sup> and AQP4-IgG<sup>-</sup> NMOSD patients, diagnosed according to the 2006 revised

diagnostic criteria<sup>26</sup>) a median time of 7 years to reach an EDSS score of 4 was found, and 10 and 21 years to reach EDSS scores of 6 and 7, respectively.<sup>31</sup> An analysis of patients seen at the Mayo Clinic until 2011 reported a median time of 17 years to an EDSS of 6 in 162 NMOSD patients (88% AQP4-IgG<sup>+</sup>), without significant differences between seropositive and negative patients.<sup>33</sup> In our cohort, we observed a longer time to EDSS milestones 3, 4, 6, and 7 than in those historic NMOSD cohorts, which might indicate a more effective disease management over time. In comparison, the median time from disease onset to an EDSS score of 4 was 11.4 years, 23.1 years for EDSS 6, and 33.1 years for EDSS 7 in 1562 patients with relapsing–remitting MS.<sup>35</sup>

### MOGAD and NMOSD Show Distinctive Long-Term Profiles

Our data reflect a diverging disease course regarding the development of disability in MOGAD compared to NMOSD: Disability milestones occur significantly later in MOGAD than in NMOSD; substantially more attacks pass before developing EDSS scores of 3 and 4; and the likelihood to develop more severe disability is lower. AQP4-IgG<sup>+</sup> NMOSD patients were older than AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD patients and MOGAD patients at disease onset and when reaching the disability milestones of EDSS 3 and 4 (median 56 and 62 years vs 47 and 53 years vs 53 and 58 years, respectively). But due to the faster disability development in NMOSD, age at reaching milestone 6 and 7 was almost equal for AQP4-IgG<sup>+</sup> NMOSD and MOGAD (median 70 and 79 years vs 72 and 72 years). AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD patients generally showed a comparable disease progression to AQP4-IgG<sup>+</sup> NMOSD patients but have a higher long-term risk of developing severe disability due to their first manifestation at an earlier age (EDSS 6: median 59 years, EDSS 7: no sufficient data). MOGAD patients exhibited a lower median age of onset and may develop severe disability at an older age than NMOSD patients.

### A Late Disease Onset Is a Risk Factor for the Development of Disability

A late (above the age of 50) or very late (over the age of 70) onset reportedly predicts a significantly worse outcome in terms of motor disability and mortality.<sup>32,36–38</sup> In accordance with these data, our study indicates that onset at an older age (which is seen more frequently in AQP4-IgG<sup>+</sup> than AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD or MOGAD patients) is a risk factor for the early development of higher EDSS scores. The fact that this was observed not only in AQP4-IgG<sup>+</sup> NMOSD suggests that

this may be a fundamental underlying reduction of neuronal repair associated with aging rather than a disease specific mechanism.<sup>39</sup> At the same time, a later disease manifestation (e.g., in the 40s) less probably interferes with formative life events, e.g., in terms of professional orientation and family planning. This in turn might add to the burden of disease for the initially younger MOGAD and AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD patients.

### **Treatment Strategies Developed by the Scientific Community May Have Improved Disease Outcomes for NMOSD and MOGAD Patients in the Past 20 Years**

The growing knowledge and optimized use of in particular off-label therapies seem to have lowered the risk for disability within the past decade. This study did not evaluate directly the impact of different acute or long-term treatment regimens in our cohort. Instead, we analyzed changes in the development of disability in our cohort in relation to the rapidly expanding knowledge on therapeutic options in NMOSD and MOGAD. During the 2010 decade, numerous publications reported insufficient efficacy of classical MS medications in NMOSD patients, with some even causing disease exacerbation.<sup>19,40–42</sup> On the other hand, retrospective studies suggested efficacy of rituximab, azathioprine and other immunosuppressants in the treatment of NMOSD. Moreover, more stringent treatment strategies for acute relapse were proposed, including escalatory therapy with (early) plasma exchange or immunoadsorption. We chose the year 2014, in which NEMOS published therapy guidelines and also the antibody against AQP4-IgG was known for 10 years as an arbitrary cutoff and observed a clear risk reduction over time to the here evaluated EDSS steps, supporting an improvement in the management of NMOSD and MOGAD over the past years. Other research underlines this in showing also a clear reduction of the rare but possibly fatal risk of respiratory failure as complication of attacks in AQP4-IgG<sup>+</sup> and MOGAD patients between the years 1999 and 2021.<sup>43</sup> In addition to improvements in treatment, higher awareness for these diseases may have also contributed to these findings. Still, medications have only been approved for AQP4-IgG<sup>+</sup> NMOSD patients so far, with inconclusive data for AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD and MOGAD patients. Considering the clear difference between MOGAD and NMOSD in our cohort with regard to time to disability milestones and the distinct pathogenesis, distinct treatment approaches may be necessary. Considering the increasing number of MOGAD patients, further efforts for approved therapies should be made especially in this group. The

presumably more benign disease course with on average less devastating attacks in MOGAD can be seen as an encouragement for physicians to include these patients in placebo controlled randomized clinical trials. Moreover, disease subgroups might benefit from specific treatment regimes. For example, our findings on mortality might suggest that older age at onset is a risk factor. Studies on optimum treatment strategies in the elderly population are an unmet need. Comorbidities, comediations, and increased adverse effects under immunosuppressive treatment have to be carefully managed, nonetheless the poor attack outcome of elderly patients warrants consequent acute and special attention to long-term treatment as well.<sup>36,44</sup> Moreover, future studies should address the question when (if it all) to stop an immunotherapy,<sup>45</sup> especially for MOGAD patients with controlled disease, who show a lower relapse risk in extended disease stages than AQP4-IgG<sup>+</sup> patients.<sup>46</sup> Taken together, our results underline the importance of investigator-initiated and collaborative clinical recommendations in rare diseases.

### **Limitations**

Our study has several limitations. The registry contains few patients with documented high EDSS scores, likely due to loss to follow-up due to severe disability or even death. Moreover, the EDSS has inherent limitations such as the fact that visual impairment and even complete blindness can only lead to a maximum EDSS of 4 per definition, while higher scores on the EDSS scale (EDSS  $\geq 5.5$ ) are essentially caused by severe restrictions of mobility. The association of higher EDSS scores after incipient myelitis (rather than optic neuritis) may well be a result of this skewed representation of impairments. In addition, disabilities in other functional systems that are often also burdensome for patients may therefore not be adequately represented by the EDSS. Additionally, for a comprehensive view of the overall disease burden, yet other factors such as pain, changes in cognitive abilities and mood should be taken into account, but contribute very little to the EDSS.<sup>47</sup> Still, a more comprehensive, disease-specific measure of disability or disease burden in patients with NMOSD or MOGAD is lacking so far. Although our data point at interesting demographic differences between AQP4-IgG<sup>+</sup> and AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD patients, the observed cohort of AQP4-IgG<sup>-</sup>/MOG-IgG<sup>-</sup> NMOSD patients (n = 54) is still small and larger studies are needed to gather more information on this subgroup of NMOSD patients. At the same time, the rather recent differentiation of patients with MOG-IgG-associated syndromes outside the NMOSD spectrum has only very recently led to a first international consensus on diagnostic criteria for MOGAD in 2023.<sup>48</sup> Although, first

recommendations based on cell-based assay testing and clinical/radiological findings have been published before.<sup>7</sup> Furthermore, as most NEMOS centers are not providing pediatric care, our cohort does not fully represent the age spectrum of MOGAD and underrepresents patients in their childhood especially manifesting with acute disseminated encephalomyelitis in their childhood.

### Conclusion

Seropositive NMOSD, MOGAD, and double-seronegative patients show distinctive long-term disability progression profiles, with MOGAD having overall a more benign disease course. Improved disease outcomes for all three diseases over the past years are evident and likely reflect the improvements in diagnosis, more adequate (acute and long-term) treatment, the publication of investigator-initiated treatment studies as well as of off-label treatment recommendations and guidelines by the neurological research community. This underlines the importance of investigator-driven collaborative research in rare diseases.

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### Author Contributions

Ankelien Duchow, Judith Bellmann-Strobl, Tim Friede, Jan-Patrick Stellmann and Vivien Häußler contributed to the conception and design of the study; Ankelien Duchow, Judith Bellmann-Strobl, Tim Friede, Ilya Aizenberg, Achim Berthele, Eva Dawin, Daniel Engels, Katinka Fischer, Martina Flaskamp, Katrin Gighuber, Matthias Grothe, Joachim Havla, Martin W. Hümmert, Sven Jarius, Matthias Kaste, Peter Kern, Ingo Kleiter, Luisa Klotz, Mirjam Korporal-Kuhnke, Markus Kraemer, Markus Krumbholz, Tania Kümpfel, Lisa Lohmann, Marius Ringelstein, Paulus Rommer, Patrick Schindler,

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### Potential Conflicts of Interest

None of the authors have any disclosure related to the submitted work.

### Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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