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Introduction

Antibodies directed against myelin oligodendrocyte glycoprotein (MOG-Ab) have been reported in the serum of pediatric patients with non-multiple sclerosis (MS) acquired demyelinating syndromes (ADS), and in adult patients with neuromyelitis optica spectrum disorders (NMOSD).¹⁻³ Previous data about disability outcome associated to MOG-Ab are limited and contradictory.¹⁻⁵ Our goal was to investigate disability outcome associated to MOG-Ab in adults with NMO related disorder compared to aquaporin-4 antibody (AQP4-Ab) positive patients.

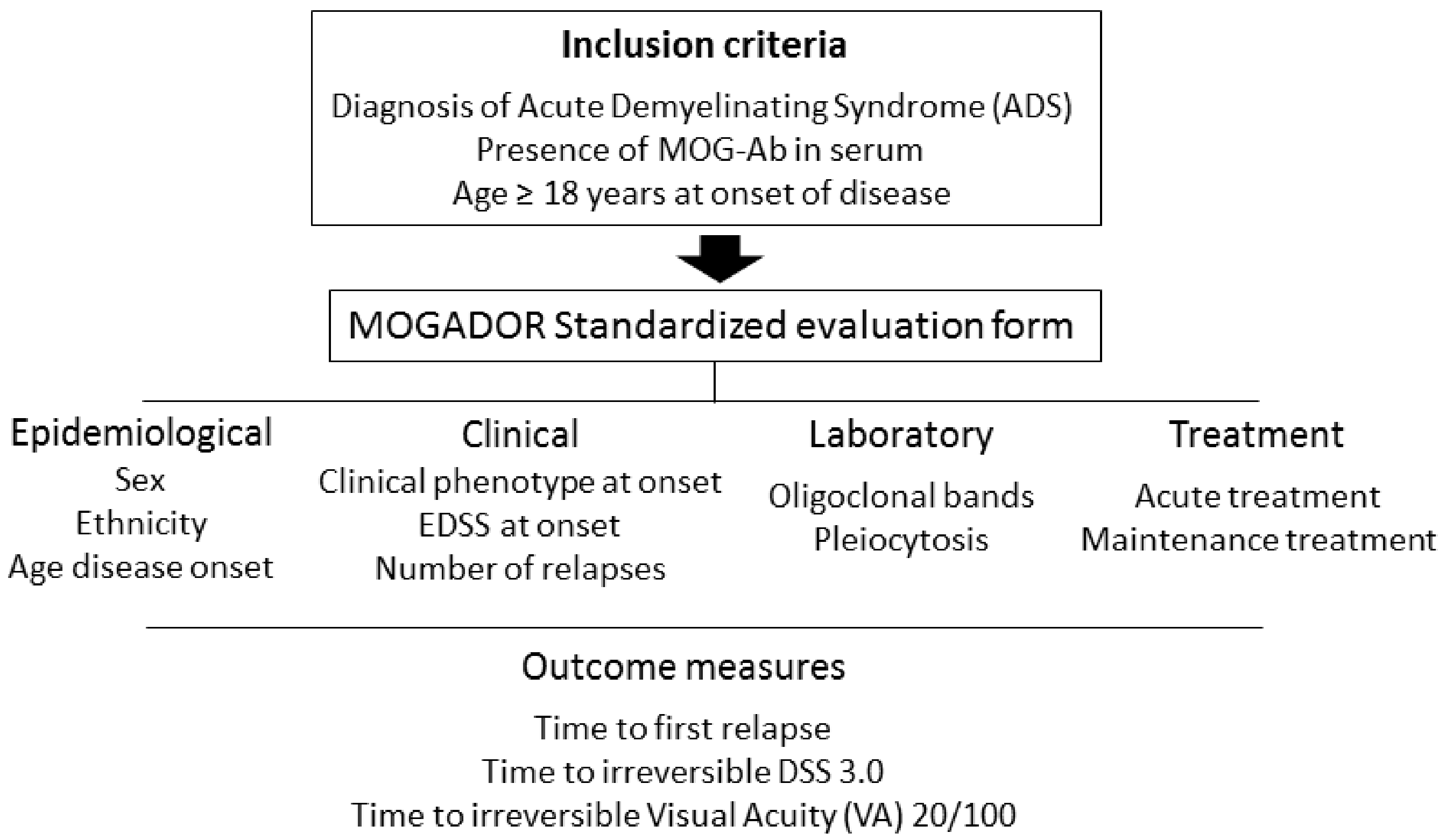
Methods and subjects

Inclusion criteria and recruitment

This is a multicentric retrospective study from all the French referral centers within the scope of *observatoire français de la sclérose en plaques* (OFSEP) performed between January 2014- January 2017. Patients were included when fulfilling the following inclusion criteria: 1) diagnosis of ADS, 2) presence of MOG-Ab in serum detected either at onset of disease or during follow-up 3) age ≥ 18 years at onset of disease.

Epidemiological and clinical data were prospectively collected in standardized evaluation forms dedicated to the MOGADOR study (**Figure 1**).

Figure 1. Inclusion criteria, variables and outcome measures



Same information from AQP4-Ab-positive patients were extracted from the files included in the NOMADMUS database during the study period.

Autoantibody detection

Within the period of the study, 16.181 serum samples were tested for AQP4-Ab and MOG-Ab by cell-based assay with live HEK293.

Prognosis analysis

For motor disability, we included all patients who presented with non-optic neuritis (ON) phenotypes, and for visual disability we only included those who presented with ON, at first ADS.

Results

General MOG and AQP4-Ab-positive features

We identified 197 MOG and 169 AQP4-Ab-positive patients.

Among MOG-Ab- positives, 77 patients presented with non-ON phenotypes and 136 patients with ON, at first ADS.

Among AQP4-Ab- positives, 105 patients presented with non-ON phenotypes and 66 patients with ON, at first ADS.

Baseline differences between MOG and AQP4-Ab-positive patients are depicted in **table 1**.

Table 1. Baseline features in MOG and AQP4-Ab-positive patients

VARIABLES	MOG-Ab-positive patients N=197	AQP4-Ab-positive patients N=169	p-value
Females, n (%)	97 (49.24)	154 (91.12)	< 0.001
Age at onset, y median (range)	36.46 (18.97-76.75)	39.29 (18.23-84.97)	0.040
Caucasian, n (%)	183 (92.89)	132 (78.11)	< 0.001
Follow-up, m median (range)	15.77 (1-556.64)	69.36 (1-437.16)	< 0.001
EDSS at onset, median (range)	3 (0-9.5)	4 (0-9)	0.013
Relapsing disease, n (%)	83/197 (42.13)	126/169 (74.56)	< 0.001
ARR, mean (SD)	0.37 (0.79)	0.53 (0.77)	0.050
Acute therapy (MTP/PLEX/ IgIV)	183 (92.89)	156 (92.31)	0.831
Maintenance therapy following presentation (%)	34/197 (17.26)	45/169 (26.63)	0.030
Maintenance therapy at final follow-up, n (%)	115 (58.38)	158 (93.49)	< 0.001
^a CSF features			
OCB, n (%)	10/175 (5.71)	33/127 (25.98)	< 0.001
Pleiocytosis (>5 cells/mm ³)	61/138 (44.20)	21/56 (37.5)	0.392

^aOnly lumbar puncture performed within one month from onset of symptoms were considered

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Outcome in MOG-Ab associated diseases

MOG-Ab-positive patients were at lower risk to reach a first relapse (Hazard Ratio [HR], 0.45; 95% Confidence interval [95%CI] 0.26-0.79; p=0.005) in comparison with AQP4-Ab-positive patients. A higher EDSS at onset (HR, 0.86; 95%CI 0.78-0.96; p=0.005) and the presence of maintenance therapy (HR, 0.43; 95%CI 0.24-0.75; p=0.003) were also related to a lower risk for clinical relapse (**table 2**).

Regarding motor outcome, MOG-Ab-serostatus appeared to display a protective effect to reach DSS 3.0 (HR, 0.46; 95%CI, 0.22-0.94; p=0.033). Moreover, a higher EDSS at onset was related to a worse motor outcome (HR, 1.32; 95%CI, 1.16-1.50); p<0.001 (**table 2**).

We found that MOG-Ab-serostatus was related to a lower risk to reach VA 20/100 (HR, 0.23; 95%CI, 0.07-0.72; p=0.012). Higher severity at onset of symptoms (HR, 1.52; 95%CI, 1.12-2.05; p=0.007) was also associated with worse visual outcome (**table 2**).

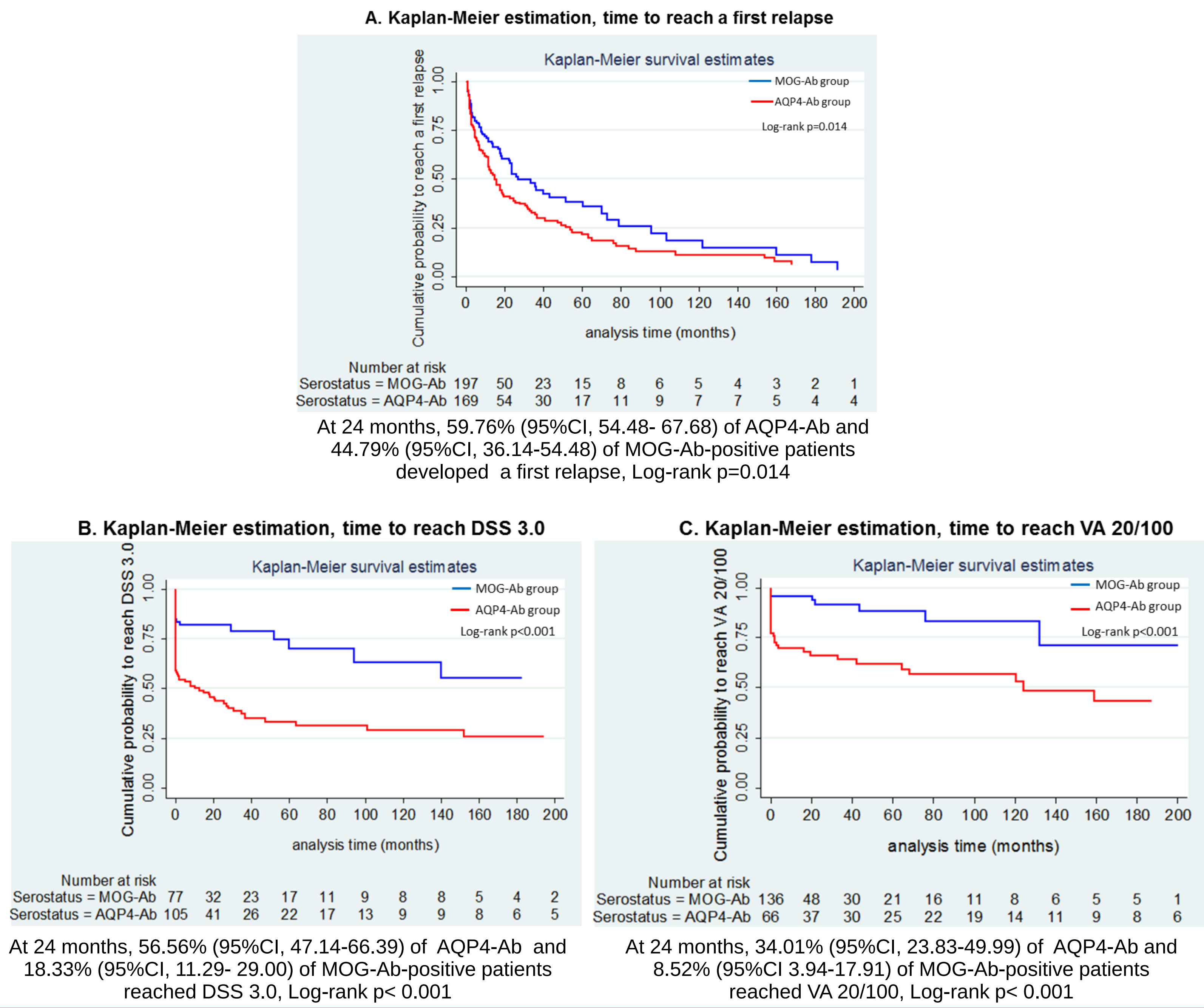
Table 2. Effects of baseline features on time to reach a first relapse, time to reach DSS 3.0, and time to reach VA 20/100.

Basal variables	Time to reach a first relapse		Time to reach DSS 3.0		Time to reach VA 20/100	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
MOG-Ab serostatus	0.70 (0.53-0.93), 0.013	0.45 (0.26-0.79), 0.005	0.36 (0.2-0.59), <0.001	0.46 (0.22-0.94), 0.033	0.23 (0.11-0.46), <0.001	0.23 (0.07- 0.72), 0.012
Female	1.32 (0.97-1.82), 0.075	1.09 (0.59-2.01), 0.774	1.91 (1.11-3.80), 0.020	2.00 (0.80-5.00), 0.138	2.32 (1.02-5.25), 0.044	2.45 (0.49-12-24), 0.276
≥60 y (ref)	--	--	--	--	--	--
40-59.9 y	1.33 (0.73-2.42), 0.348		0.61 (0.34-1.10), 0.103	0.81 (0.38-1.73), 0.586	0.49 (0.13-1.78), 0.276	
18-39.9 y	1.28 (0.72-2.27), 0.400		0.32 (0.17-0.58), <0.001	0.73 (0.33-1.61), 0.433	0.56 (0.17-1.88), 0.349	
Caucasian ethnicity	0.74 (0.50-1.09), 0.124		0.68 (0.40-1.18), 0.169		0.47 (0.22-0.99), 0.048	1.12 (0.28-4.42), 0.876
EDSS at onset	0.88 (0.80-0.96), 0.006	0.86 (0.78-0.96), 0.005	1.33 (1.17-1.50), <0.001	1.32 (1.16-1.50), <0.001	1.41 (1.07- 1.87), 0.014	1.52 (1.12-2.05), 0.007
CSF OCB	1.40 (0.96-2.05), 0.081	1.12 (0.62-2.02), 0.705	1.07 (0.61-1.86), 0.822		1.21 (0.36-4.04), 0.916	
CSF pleiocytosis (>5 cells/mm ³)	0.93 (0.67-1.28), 0.647		0.86 (0.54-1.37), 0.524		1.05 (0.45-2.41), 0.916	
Maintenance therapy	0.55 (0.36-0.82), 0.003	0.43 (0.24-0.75), 0.003	0.91 (0.46-1.80), 0.779		2.82 (1.21-6.58), 0.016	0.29 (0.03-2.74), 0.267

In univariate and multivariate analysis, data are given as follows: Hazard ratio (95% Confidence interval), p- value

Kaplan-Meier estimation of time to first relapse, time to DSS 3.0 and time to VA 20/100 are depicted in **figure 2**.

Figure 2. Kaplan-Meier curves



Discussion

MOG-Ab-positive patients were initially associated with a monophasic and less severe disease course, in comparison to AQP4-Ab-positive ones.¹⁻³ Recently, a longer follow-up time revealed a higher frequency of relapses than initially described with potential more important disability.⁴ However, these studies were based on small-sized cohort of patients, mixed features from adults and pediatrics, and did not consider time when performing outcome analysis. In the present study, we showed that MOG-Ab are associated with a better motor and visual outcome when compared to AQP4-Ab after a first ADS. This distinction is supported by pathological findings showing an oligodendrocytopathy in MOG-Ab and astrocytopathy in AQP4-Ab-positive patients, and experimental studies demonstrating that MOG-Ab induce a transient myelin alteration with complete recovery in mice.^{6,7}

Conclusion

In our study, MOG-Ab is associated to a better outcome than AQP4-Ab in patients presenting with NMO or associated disorders. This should be considered for future clinical trials.

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