

# Defining high, medium and low impact prognostic factors for developing multiple sclerosis

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Natural history studies have identified factors that predict evolution to multiple sclerosis or risk of disability accumulation over time. Although these studies are based on large multicentre cohorts with long follow-ups, they have limitations such as lack of standardized protocols, a retrospective data collection or lack of a systematic magnetic resonance imaging acquisition and analysis protocol, often resulting in failure to take magnetic resonance and oligoclonal bands into account as joint covariates in the prediction models. To overcome some of these limitations, the aim of our study was to identify and stratify baseline demographic, clinical, radiological and biological characteristics that might predict multiple sclerosis development and disability accumulation using a multivariate approach based on a large prospective cohort of patients with clinically isolated syndromes. From 1995 to 2013, 1058 patients with clinically isolated syndromes were included. We evaluated the influence of baseline prognostic factors on the risk for developing clinically definite multiple sclerosis, McDonald multiple sclerosis, and disability accumulation (Expanded Disability Status Scale score of 3.0) based on univariate (hazard ratio with 95% confidence intervals) and multivariate (adjusted hazard ratio with 95% confidence intervals) Cox regression models. We ultimately included 1015 patients followed for a mean of 81 (standard deviation = 57) months. Female/male ratio was 2.1. Females exhibited a similar risk of conversion to multiple sclerosis and of disability accumulation compared to males. Each younger decade at onset was associated with a greater risk of conversion to multiple sclerosis and with a protective effect on disability. Patients with optic neuritis had a lower risk of clinically definite multiple sclerosis [hazard ratio 0.6 (0.5–0.8)] and disability progression [hazard ratio 0.5 (0.3–0.8)]; however, this protective effect remained marginal only for disability [adjusted hazard ratio 0.6 (0.4–1.0)] in adjusted models. The presence of oligoclonal bands increased the risk of clinically definite multiple sclerosis [adjusted hazard ratio 1.3 (1.0–1.8)] and of disability [adjusted hazard ratio 2.0 (1.2–3.6)] independently of other factors. The presence of 10 or more brain lesions on magnetic resonance increased the risk of clinically definite multiple sclerosis [adjusted hazard ratio 11.3 (6.7–19.3)] and disability [adjusted hazard ratio 2.9 (1.4–6.0)]. Disease-modifying treatment before the second attack reduced the risk of McDonald multiple sclerosis [adjusted hazard ratio 0.6 (0.4–0.9)] and disability accumulation [adjusted hazard ratio 0.5 (0.3–0.9)]. We conclude that the demographic and topographic characteristics are low-impact prognostic factors, the presence of oligoclonal bands is a medium-impact prognostic factor, and the number of lesions on brain magnetic resonance is a high-impact prognostic factor.

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Received September 26, 2014. Revised February 5, 2015. Accepted February 18, 2015.

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**Keywords:** clinically isolated syndromes; multiple sclerosis; epidemiology; imaging; demyelination

**Abbreviations:** CDMS = clinically definite multiple sclerosis; CIS = clinically isolated syndrome; DMT = disease-modifying treatment; EDSS = Expanded Disability Status Scale

## Introduction

A clinically isolated syndrome (CIS) is defined as an episode suggestive of CNS inflammatory demyelination (McDonald *et al.*, 2001). The majority of CIS cases ultimately progress to multiple sclerosis, a chronic disease that is characterized by further relapses and the accumulation of disability. Current evidence suggests that disease-modifying treatment (DMT) should be initiated at an early stage because it is likely to significantly impact the disease evolution (Jacobs *et al.*, 2000; Comi *et al.*, 2001, 2009; Kappos *et al.*, 2006). Thus, accurately identifying which patients will remain as CIS cases and which will develop multiple sclerosis and, above all, determining the degree of disability that they are likely to develop over the mid- to long-term is considered to be crucial for providing more individualized treatment. Natural history studies have shown that a younger age at disease onset is associated with a higher risk of conversion to clinically definite multiple sclerosis (CDMS) and that male gender is associated with a greater accumulation of disability according to the Kurtzke Expanded Disability Status Scale (EDSS) (Kurtzke, 1983; Weinshenker *et al.*, 1989*a, b*; Confavreux *et al.*, 2003; Confavreux and Vukusic, 2006*a, b*; Tremlett *et al.*, 2006; Leray *et al.*, 2010; Scalfari *et al.*, 2010). Regarding the clinical characteristics, patients with CIS presenting with optic neuritis exhibit a lower risk of developing both multiple sclerosis and disability accumulation compared with CIS patients displaying other topographic characteristics (Weinshenker *et al.*, 1989*a*; Runmarker and Andersen, 1993; Confavreux *et al.*, 2003). Regarding biological factors, a recent meta-analysis showed that the presence of IgG oligoclonal bands increases both the risk of experiencing a second attack and the risk of disability accumulation (Dobson *et al.*, 2013). To date, brain MRI remains the most reliable tool to predict future conversion to multiple sclerosis or the accumulation of disability. In this context, it has been demonstrated that a larger number of brain T<sup>2</sup> lesions or Barkhof criteria based on a baseline MRI correlates with an increased risk of developing multiple sclerosis and disability in the mid- to long-term (Tintore *et al.*, 2006; Fisniku *et al.*, 2008; Group, 2008; Young *et al.*, 2009).

However, although the aforementioned natural history studies are based on large multicentre cohorts with long follow-ups, these studies have several limitations (Weinshenker *et al.*, 1989*a, b*; Confavreux *et al.*, 2003; Confavreux and Vukusic, 2006*a, b*; Tremlett *et al.*, 2006;

Leray *et al.*, 2010; Scalfari *et al.*, 2010): they typically comprise data obtained both retrospectively and prospectively, which could lead to information bias; the baseline and follow-up visits do not follow a standardized protocol, which compromises the homogenization of the data acquired from the different centres; and a lack of MRI data is frequent, and when present, a systematic MRI protocol is lacking. These limitations often result in failing to take MRI and oligoclonal bands into account as joint covariates in the prediction models. Finally, the quantification of patients lost to follow-up and the corresponding causes were not registered, leading to survival bias. Alternatively, the longitudinal MRI cohort studies used a small sample size, did not execute a regular follow-up protocol, and optic neuritis was frequently over-represented, rendering subgroup analyses impossible (Tintore *et al.*, 2006; Fisniku *et al.*, 2008; Group, 2008; Young *et al.*, 2009). To overcome some of these limitations, the aim of our study was to identify and stratify which baseline demographic, clinical, radiological and biological characteristics predict multiple sclerosis development and disability accumulation using a unique multivariate approach based on a large prospective cohort.

## Patients and methods

This was an observational study based on a prospective, open cohort initiated in 1995 (Fig. 1). We included patients aged < 50 years who exhibited a CIS that was suggestive of CNS demyelination and was not attributable to other diseases, with symptom onset within 3 months of the first clinical evaluation. At baseline, the demographic data, previous history of neurological abnormalities, the CIS topography, steroid use, and disability according to the EDSS score were recorded. The patients were evaluated on a regular basis (every 3 to 6 months or annually depending on each patient's characteristics) to assess both the EDSS score and the occurrence of relapses. For the purpose of this analysis, the database was locked on 15 March 2013. The patients who did not attend two consecutive follow-up visits were defined as 'lost to follow-up'. The baseline characteristics of the patients with complete and incomplete follow-up were compared.

The IgG oligoclonal bands were examined within the first 3 months of disease onset. The remaining serum and CSF samples were stored at -80°C. The IgG oligoclonal bands were examined via agarose isoelectric focusing combined

with immunoblotting and avidin-biotin-amplified double-antibody peroxidase staining (Andersson *et al.*, 1994).

A diagnostic brain/spinal cord MRI at the time of the first event was often but not always performed at our hospital, but a baseline brain MRI was systematically performed 3 to 5 months after the CIS at our centre and repeated after 12 months and every 5 years. A baseline spinal cord MRI was systematically performed beginning in 2007 (Fig. 1), but these results were not considered in this study. The T<sub>2</sub> lesion volume and the brain parenchymal fraction were also determined since 2001. A brain MRI analysis was routinely performed by two neuroradiologists with expertise in inflammatory demyelinating diseases. Brain MRI was performed using a 1.5 or 3.0 T magnet and included the following sequences: transverse proton density and T<sub>2</sub>-weighted conventional or fast spin-echo, transverse and sagittal T<sub>2</sub>-FLAIR, and unenhanced and contrast-enhanced (0.1–2.0 mmol/kg; scan delay, 5–10 min) T<sub>1</sub>-weighted spin-echo. All sequences were obtained using a contiguous 3–5 mm slice thickness covering the entire brain.

The demographic and clinical variables included in the analysis were age, gender, date of the CIS, CIS topography, steroid treatment, date of the second demyelinating attack, EDSS (at each time point), the administration of DMT (considered a time-dependent variable), date of DMT initiation and date of the most recent follow-up.

The biological variable was the presence of IgG oligoclonal bands in CSF.

The brain MRI variables included the number and location of T<sub>2</sub> lesions, the presence of gadolinium-enhancing lesions, and the number of new T<sub>2</sub> lesions (on follow-up). A normal brain MRI was defined as a brain MRI displaying 0 lesions. Four different categories for the number of lesions were considered: 0, 1–3, 4–9 and 10 or more T<sub>2</sub> lesions. We also determined the fulfilment of the Barkhof criteria (Barkhof *et al.*, 1997; Tintore *et al.*, 2000). Patients with one or two Barkhof criteria and patients with three or four Barkhof criteria were grouped based on their similar behaviour; thus, three different Barkhof criteria categories were specified: 0 Barkhof criteria, 1–2 Barkhof criteria, and 3–4 Barkhof criteria.

## Outcomes

### Clinically definite multiple sclerosis

Conversion to CDMS was ascertained when new symptoms suggestive of relapse occurred after an interval of at least

1 month and only when other diagnoses had been excluded. CDMS was diagnosed when there was a second attack displaying a new neurological abnormality that was confirmed via examination (Poser *et al.*, 1983).

### McDonald 2005 multiple sclerosis criteria

According to the MRI component of the 2005 McDonald criteria, evidence of dissemination in space (DIS) was attained based on one of two criteria: (DIS1) the fulfilment of at least three of four Barkhof criteria based on MRI; or (DIS2) the presence of at least two T<sub>2</sub> lesions and oligoclonal bands. The dissemination in time (DIT) was defined as at least one new T<sub>2</sub> lesion appearing on the follow-up brain MRI scan. The MRI criteria were satisfied when the patients exhibited the MRI-based definitions of DIS and DIT. Additionally, the patients experiencing a second clinical attack also satisfied the 2005 McDonald criteria (Polman *et al.*, 2005).

### Expanded Disability Status Scale 3.0

Disability was evaluated according to the EDSS scale at each visit, and only those EDSS evaluations performed during stable periods were considered (Kurtzke, 1983). The threshold for establishing the presence of disability was an EDSS score  $\geq 3.0$  in two evaluations.

The follow-up duration was calculated as the difference between the date of the most recent visit and the date of the CIS event.

## Disease-modifying treatment

The initiation of DMT was advised to all patients who complied with the current indications established by the health authorities. After 1996, according to the Catalan Regulatory Recommendation, only active patients presenting at least two attacks in the previous 3 years were candidates for DMT. When such level of clinical activity was documented, DMT was offered. After 2001, patients presenting with a high risk CIS (defined as three to four Barkhof criteria) were also candidates for treatment.

## Database

The patients' clinical and radiological data were prospectively entered and updated into an online platform. Access to this

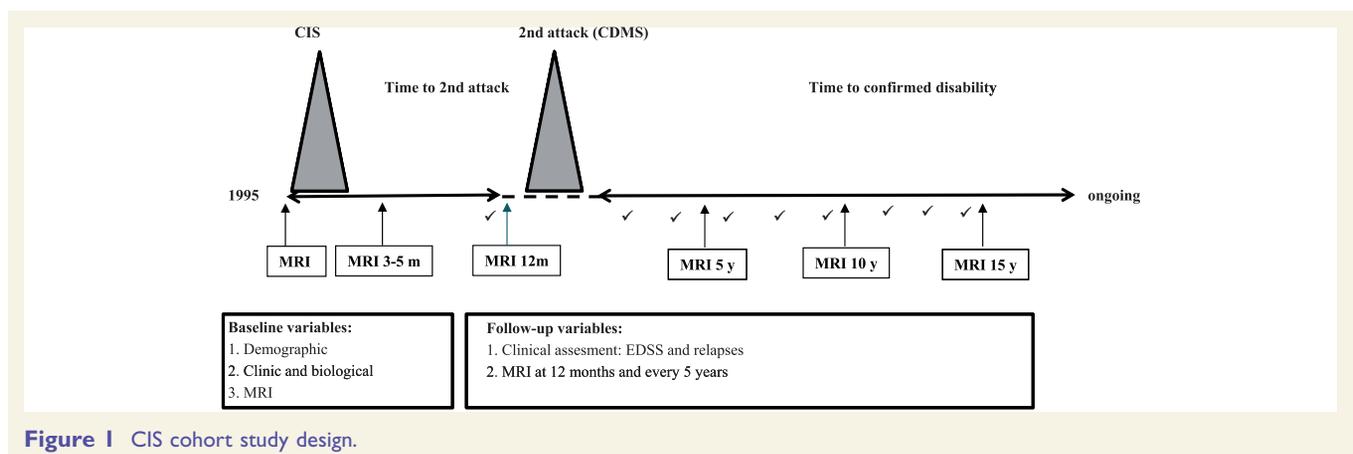


Figure 1 CIS cohort study design.

platform was monitored and was restricted to authorised users. Quality controls were performed, including a review of the data using the primary sources of 10 randomly selected patients every month.

## Standard protocol approvals, registrations and patient consent

This study received approval from the local ethical committee, and all patients signed a written informed consent form.

## Statistical analysis

Descriptive statistics were performed on the demographic and clinical variables. Kaplan-Meier analyses were used to estimate the cumulative risk of developing CDMS, McDonald multiple sclerosis and disability progression. We analysed the time from CIS onset to the second attack, to the time of diagnosis of McDonald multiple sclerosis and to the time of exhibiting an EDSS score of 3.0. Univariate and multivariate Cox proportional hazards regression analyses were performed using the conversion to CDMS or McDonald multiple sclerosis and progression to an EDSS score of 3.0 as the outcome variables; these results were expressed as the hazard ratios (HRs) with 95% confidence intervals (CIs). Covariates including age, gender, clinical topography, oligoclonal bands, MRI criteria (Barkhof criteria and the number of lesions) and DMT onset prior to the diagnosis of CDMS or McDonald 2005 multiple sclerosis criteria, depending on the outcome, were considered. Possible interactions between age, gender, topographic characteristics, the presence of oligoclonal bands, the number of lesions and DMT were also evaluated. DMT was used in these models as a time-dependent variable to take into account the date of treatment onset. To better understand the impact of patients lost to follow-up, a sensitivity analysis was undertaken.

The statistical tests were performed at the 0.05 level of significance using the Statistical Package for the Social Sciences software version 20.0 (SPSS).

## Results

### Study population

From January 1995 to February 2013, 1058 patients were enrolled in the prospective cohort study; 43 (4%) were ultimately excluded for various reasons: previous attack ( $n = 7$ ), age over 50 ( $n = 4$ ), exceeded entry window ( $n = 12$ ), and alternative diagnosis ( $n = 20$ ). These alternative diagnoses included acute disseminated encephalomyelitis ( $n = 1$ ), neuromyelitis optica ( $n = 5$ ), neuromyelitis optica spectrum disorder ( $n = 1$ ), brain tumour ( $n = 4$ ), ischaemic stroke ( $n = 2$ ), CADASIL (cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy,  $n = 1$ ), anterior ischaemic optic neuropathy ( $n = 1$ ), Leber's hereditary optic neuropathy ( $n = 1$ ), atypical brainstem lesions ( $n = 2$ ), alcoholic polyneuropathy with vitamin B deficiency ( $n = 1$ ), and unspecified ophthalmological condition ( $n = 1$ ).

Ultimately, 1015 patients were included in this analysis. Of these, seven (0.7%) died during follow-up: car accident ( $n = 1$ ), myocardial infarction ( $n = 1$ ), pancreatic cancer ( $n = 1$ ), meningitis as a complication of septoplasty ( $n = 1$ ), septic shock in a patient with severe disability ( $n = 1$ ), cardiogenic shock of unknown origin ( $n = 1$ ) and acute leukaemia in a patient who received mitoxantrone ( $n = 1$ ).

## Demographic and clinical characteristics

Of the 1015 patients, 686 (67.6%) were female and 329 (32.4%) were male. The mean age at CIS onset was 31.1 (SD 8.2) years. Three hundred and seventy-three (36.7%) patients presented with optic neuritis; 271 (26.7%) presented with brainstem symptoms; 261 (25.7%) presented with a spinal cord syndrome, and 110 (10.8%) presented with other clinical characteristics (hemispheric, multiregional or undetermined topography) (Table 1).

The mean clinical follow-up duration was 81 (SD = 57) months (range: 0.3–220 months). The baseline characteristics of the patients according to complete or incomplete follow-up are presented in Supplementary Table 1. The percentage of patients lost to follow-up ranged from 21% to 27% depending on the particular outcome. Patients exhibiting zero Barkhof criteria were over-represented among the patients lost to follow-up, indicating that the patients suffering from milder disease were more likely to discontinue follow-up.

## Oligoclonal band determination

Of the total cohort, 792 (78.6%) underwent a CSF tap, among whom 453 (57.2%) exhibited positive oligoclonal bands. When the percentage of patients exhibiting positive oligoclonal bands was examined according to the MRI criteria, oligoclonal bands were positive for 19.1% of the patients exhibiting a normal brain MRI and for 82.2% of the patients exhibiting three to four Barkhof criteria (Table 1).

## Baseline brain MRI

The brain MRI was analysed in 951 (94%) of the patients. The baseline brain MRI was normal in 31.4% of the patients; 28.8% displayed between one and nine T<sub>2</sub> lesions, and 39.7% displayed  $\geq 10$  T<sub>2</sub> lesions. A similar distribution was observed when the MRI results were examined according to the number of Barkhof criteria (0, 1–2 and 3–4) (Table 1).

## Disease-modifying treatment

Out of the entire cohort, 388 (38.3%) patients were on DMT at least once during follow-up, primarily one of the three available beta-interferons or glatiramer acetate; 174 (45%) had initiated treatment prior to their second attack and 376 (97%) prior to reaching an EDSS score of 3.0. Considering the subgroup of patients with three to four

**Table 1** Baseline clinical and demographic characteristics

<b>Demographic characteristics</b>	
Females: <i>n</i> (%)	686 (67.6)
Age at onset (mean, SD)	31.1 (8.2)
<b>CIS topography</b>	
ON <i>n</i> (%)	373 (36.7)
BS	271 (26.7)
SC	261 (25.7)
Other	110 (10.8)
<b>Oligoclonal bands</b>	
Positive OB <i>n</i> (%)	453 (57.2)
<b>Positive OB according to MRI</b>	
Normal MRI <i>n</i> (%)	41 (19.1)
Pathological MRI	402 (73.5)
0 BC	75 (26.4)
1–2 BC	117 (67.6)
3–4 BC	250 (82.2)
<b>MRI</b>	
<b>Number of lesions on T<sub>2</sub>-weighted images</b>	
0 <i>n</i> (%)	299 (31.4)
1–3	137 (14.4)
4–9	137 (14.4)
≥10	378 (39.7)
<b>Number of Barkhof criteria</b>	
0 <i>n</i> (%)	375 (39.6)
1–2	198 (20.9)
3–4	375 (36.9)
<b>Baseline MRI</b>	
Normal <i>n</i> (%)	299 (31.4)
Pathological	652 (68.6)
<b>Follow-up</b>	
Follow-up (mean, SD)	81 (57)
<b>Disease-modifying treatment</b>	
Entire cohort <i>n</i> (%)	388 (38.3)
Patients with pathological MRI	372 (57.1)
Patients with 3–4 Barkhof criteria	281 (75.3)

ON = optic neuritis; BS = brainstem; SC = spinal cord; OB = oligoclonal bands; BC = Barkhof criteria. Follow-up is expressed in months.

Barkhof criteria at baseline, 281/375 (75.3%) were receiving DMT, 51% of those prior to their second attack and 97% again prior to EDSS score of 3.0. (Table 1)

The mean time from CIS onset to drug prescription was 23.4 months (SD 30). The mean time to DMT was significantly shorter in the patients with CIS from 2002–07 compared with those from 1995–2001 (15.2 months SD = 21 versus 41.5 months, SD = 38,  $P < 0.001$ ).

## Survival analysis: time to CDMS, time to McDonald multiple sclerosis criteria and time to confirmed EDSS score of 3.0

Of the 299 patients exhibiting a normal baseline brain MRI, 21 (7%) patients experienced a second attack within a mean clinical follow-up time of 81 (SD = 57)

months, and 27 (9%) developed multiple sclerosis according to the 2005 McDonald criteria. A total of 652 patients (68.6%) displayed at least one lesion on the baseline brain MRI. Of these, 367 (56.3%) developed CDMS and 468 (72%) developed multiple sclerosis according to the McDonald 2005 criteria. These percentages increased to 64% and 81% among the patients displaying ≥10 T<sub>2</sub> brain lesions. The conversion to CDMS or to McDonald multiple sclerosis during the study period according to the number of baseline lesions and the number of fulfilled Barkhof criteria is shown in Table 2. The conversion to CDMS or McDonald multiple sclerosis was 13% and 16%, respectively for zero Barkhof criteria; this increased to 66% and 84% for three to four Barkhof criteria.

Survival curves corresponding to the cumulative probability of developing CDMS during follow-up according to the baseline brain MRI features are shown in Fig. 2. The mean time to a diagnosis of CDMS according to each category is shown in Table 2. Notably, the time to the diagnosis of CDMS was shorter for those displaying a greater number of lesions and/or fulfilled Barkhof criteria.

Of the 299 patients displaying a normal baseline brain MRI, 12 (4%) had an EDSS score of 3.0. This percentage increased to 22% for the patients displaying ≥10 T<sub>2</sub> lesions on the baseline MRI (HR 4.4; 95% CI 2.4–8.0) or three to four Barkhof criteria (HR 3.4; 95% CI 2.4–8.0). The Kaplan-Meier curves also showed that during the first 5 years after the CIS, the proportion of patients attaining an EDSS score of 3.0 was very small. In summary, only 11% of the patients displaying ≥10 T<sub>2</sub> lesions on the baseline MRI attained an EDSS score ≥3.0 by year 5, but 30% and 41% attained this outcome by 10 years and 15 years, respectively, according to the Kaplan-Meier curves. Only 3% of the patients who remained as CIS during follow-up had an EDSS score ≥3.0 at year 5 compared with 11% of those who progressed to CDMS (4% versus 26% at 10 years and 7% versus 39% at 15 years).

## Univariate and multivariate regression models of progression to CDMS or McDonald multiple sclerosis criteria

### Univariate CDMS model

As shown in Fig. 3, no effect of gender on the conversion to CDMS was detected. However, younger patients displayed a higher risk of developing a second attack compared with patients aged 40–49. The HR was 1.5 (95% CI 1.1–2.1) for patients aged 30–39 years and 1.6 (95% CI 1.0–2.5) for patients <20 years of age. Patients with optic neuritis displayed a lower risk of developing CDMS compared with the patients presenting with other topographies, (HR 0.6; 95% CI 0.5–0.8). The presence of oligoclonal bands (HR 2.8; 95% CI 2.2–3.7) and, especially, the presence of 10 or more T<sub>2</sub> lesions (HR 12.7; 95% CI 8.1–19.8)

**Table 2** Patients converting to CDMS or to McDonald multiple sclerosis and patients attaining an EDSS score of 3.0 according to the baseline MRI

	CDMS					McDonald multiple sclerosis					EDSS 3.0				
	NI/N2	%	HR	95% CI	Mean survival time (SD)	NI/N2	%	HR	95% CI	Mean survival time (SD)	NI/N2	%	HR	95% CI	Mean survival time (SD)
<b>Number of Barkhof criteria</b>															
0	48/375	13	1*		170 (4.9)	60/375	16	1*		163 (5.1)	20/375	5	1*		211 (3.7)
1-2	96/198	49	4.4	3.1-6.3	91 (6.7)	119/198	60	5.0	3.7-6.9	67 (6.4)	16/198	8	1.2	0.6-2.4	184 (4.7)
3-4	246/375	66	7.3	5.4-10	66.5 (4.7)	315/375	84	12.0	9.1-16.0	27 (2.9)	82/375	22	3.4	2.1-5.6	157 (4.4)
<b>Number of T<sub>2</sub> lesions</b>															
0	21/299	7	1*		186 (4.5)	27/299	9	1*		180 (4.9)	12/299	4	1*		194 (2.8)
1-3	56/137	41	5.7	3.5-9.4	113 (8.0)	66/137	48	5.9	3.8-9.2	97 (8.4)	10/137	7	1.2	0.5-2.9	209 (5.7)
4-9	71/137	52	8.7	5.4-14.2	83 (7.3)	93/137	68	11.4	7.4-17.5	46 (5.3)	13/137	10	1.7	0.8-3.8	171 (5.1)
≥10	240/378	64	12.7	8.1-19.8	69 (4.8)	306/378	81	19.7	13.3-29.4	31 (3.3)	83/378	22	4.4	2.4-8.0	155 (4.5)

NI = number of patients fulfilling the outcome; N2 = total number of patients. The mean survival time is expressed in months.

strongly correlated with a higher risk of conversion to CDMS. The patients who received DMT prior to the second attack displayed a higher risk of conversion to CDMS (HR 1.7; 95% CI 1.4-2.1).

#### Univariate McDonald multiple sclerosis model

When analysing McDonald multiple sclerosis criteria as the dependent variable, similar results to those reported for CDMS were obtained (Supplementary Fig. 2).

#### Multivariate clinically definite multiple sclerosis model

When all of the examined prognostic factors were included in the model, gender did not impact the risk of experiencing a second attack, and the effect of age was reinforced. Considering the older decade (40-49 years) as a reference, we obtained an adjusted HR of 1.4 (95% CI 1.0-2.0) for 30-39 years, 1.8 (95% CI 1.3-2.5) for 20-29 years and 1.9 (95% CI 1.2-3.2) for 19 years or younger. Interestingly, the protective effect of optic neuritis was lost when the other variables were included (adjusted HR 0.9; 95% CI 0.7-1.2). The presence of oligoclonal bands and a greater number of brain T<sub>2</sub> lesions were confirmed as prognostic risk factors for conversion to CDMS: the adjusted HR was 1.3 (95% CI 1.0-1.8) for oligoclonal bands, 5.1 (95% CI 2.9-8.9) for one to three lesions, 7.5 (95% CI 4.3-13.1) for four to nine lesions and 11.3 (95% CI 6.7-19.3) for ≥10 lesions. When controlling for all of the examined variables, a trend toward a protective effect of receiving DMT prior to the second relapse was detected; however, this trend did not reach statistical significance (adjusted HR 0.9; 95% CI 0.6-1.2).

#### Multivariate McDonald multiple sclerosis model

Again, when analysing McDonald multiple sclerosis criteria as the dependent variable, similar results were detected (Supplementary Fig. 2). Notably, a protective effect of receiving DMT prior to multiple sclerosis diagnosis based

on the McDonald 2005 criteria was detected (adjusted HR 0.6; 95% CI 0.4-0.9).

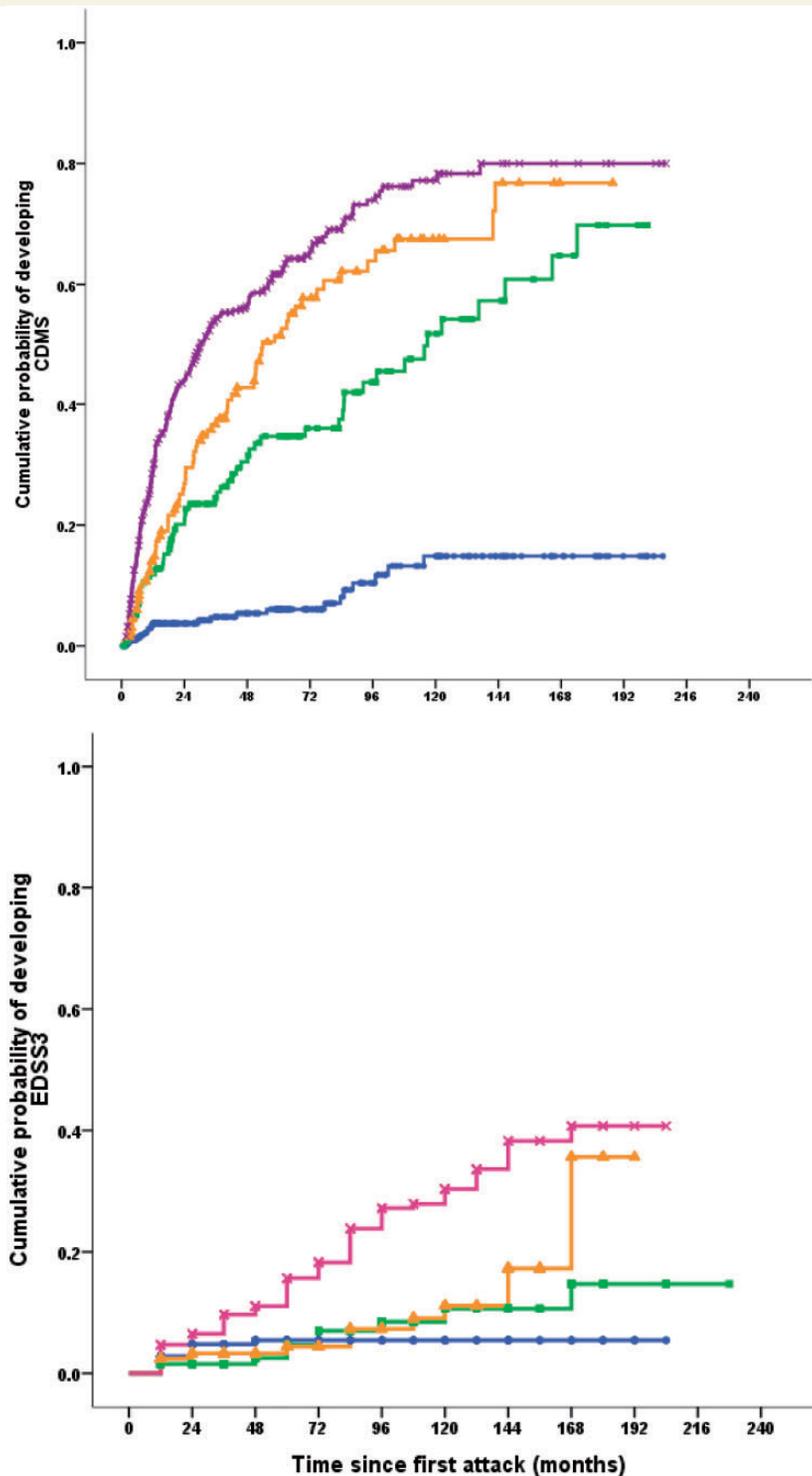
## Univariate and multivariate regression models of attaining an EDSS score of 3.0

#### Univariate EDSS score of 3.0 model

As shown in Fig. 4, females (HR 0.7; 95% CI 0.5-1.1) and younger patients appeared to display a lower risk of reaching an EDSS score of 3.0: the HR was 0.7 (95% CI 0.4-1.2) for 30-39 years, 0.6 (95% CI 0.4-1.0) for 20-29 years and 0.7 (95% CI 0.3-1.5) for 19 years or younger. Patients with optic neuritis were also associated with a better prognosis in terms of the accumulation of disability (HR 0.5; 95% CI 0.3-0.8). In contrast, the patients exhibiting positive oligoclonal bands (HR 2.6; 95% CI 1.6-4.2) and displaying ≥10 or more brain T<sub>2</sub> lesions (HR 4.3; 95% CI 2.4-8.0) were associated with a worse outcome. Receiving DMT treatment prior to the second attack did not alter the risk of attaining an EDSS score of 3.0 (HR 1.1; 95% CI 0.7-1.9).

#### Multivariate EDSS score of 3.0 model

Based on the multivariate analysis, the protective effect of younger age was only marginally maintained for the patients between 20 and 29 years (adjusted HR 0.6; 0.3-1.0). The patients suffering from optic neuritis displayed a lower risk of disability (adjusted HR 0.6; 95% CI 0.4-1.0). The presence of oligoclonal bands and ≥10 brain T<sub>2</sub> lesions on the baseline MRI was associated with a higher risk of the accumulation of disability with adjusted HR scores of 2.0 (95% CI 1.2-3.6) and 2.9 (95% CI 1.4-6.0), respectively. Receiving DMT prior to the second attack was associated with a lower risk of attaining an EDSS score of 3.0 (adjusted HR 0.5; 95% CI 0.3-0.9).

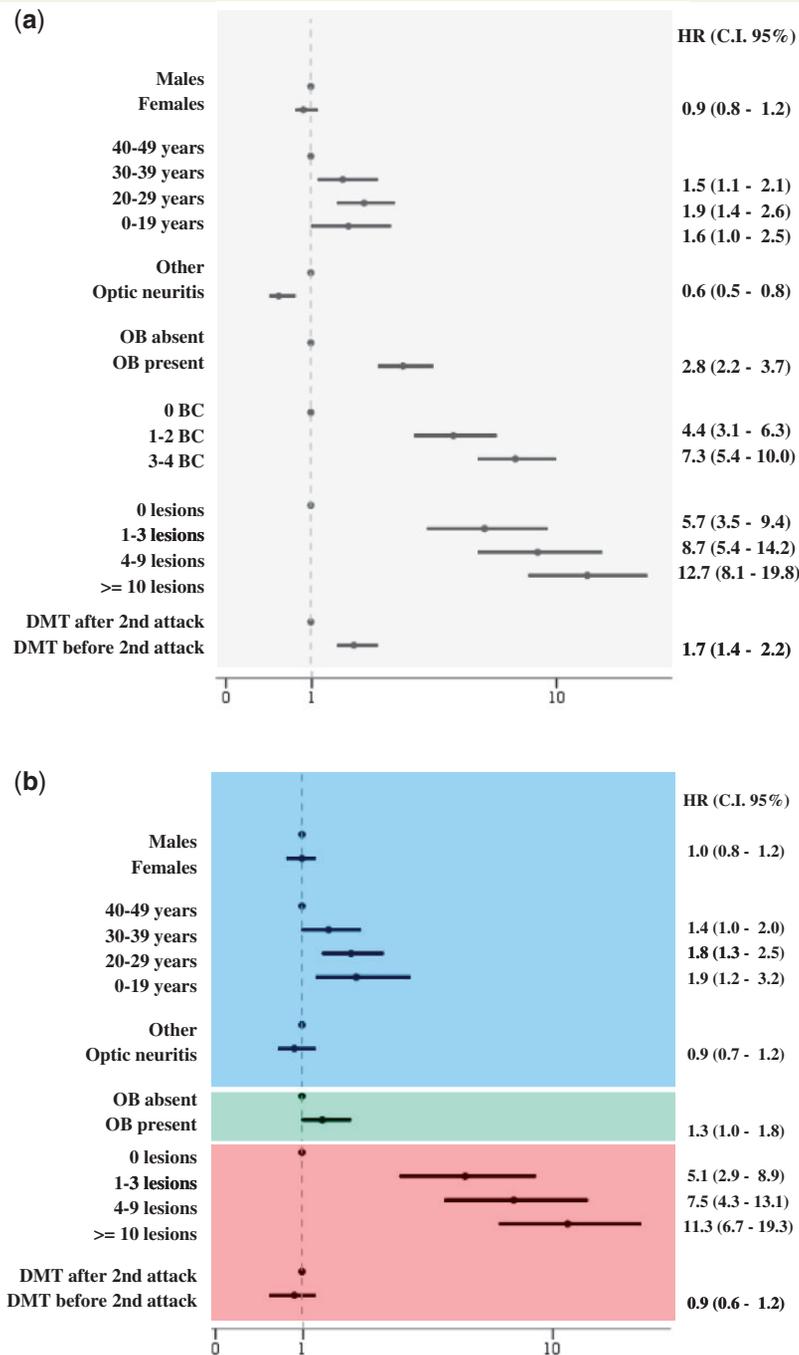


**Figure 2** Development of CDMS and an EDSS score of 3.0 according to the number of lesions on the baseline MRI. Crosses:  $\geq 10$  lesions; triangles: 4–9 lesions; squares: 1–3 lesions; circles: 0 lesions.

## Discussion

Our study represents the first attempt to perform a multivariate analysis incorporating demographic, clinical, radiological and biological data available at baseline.

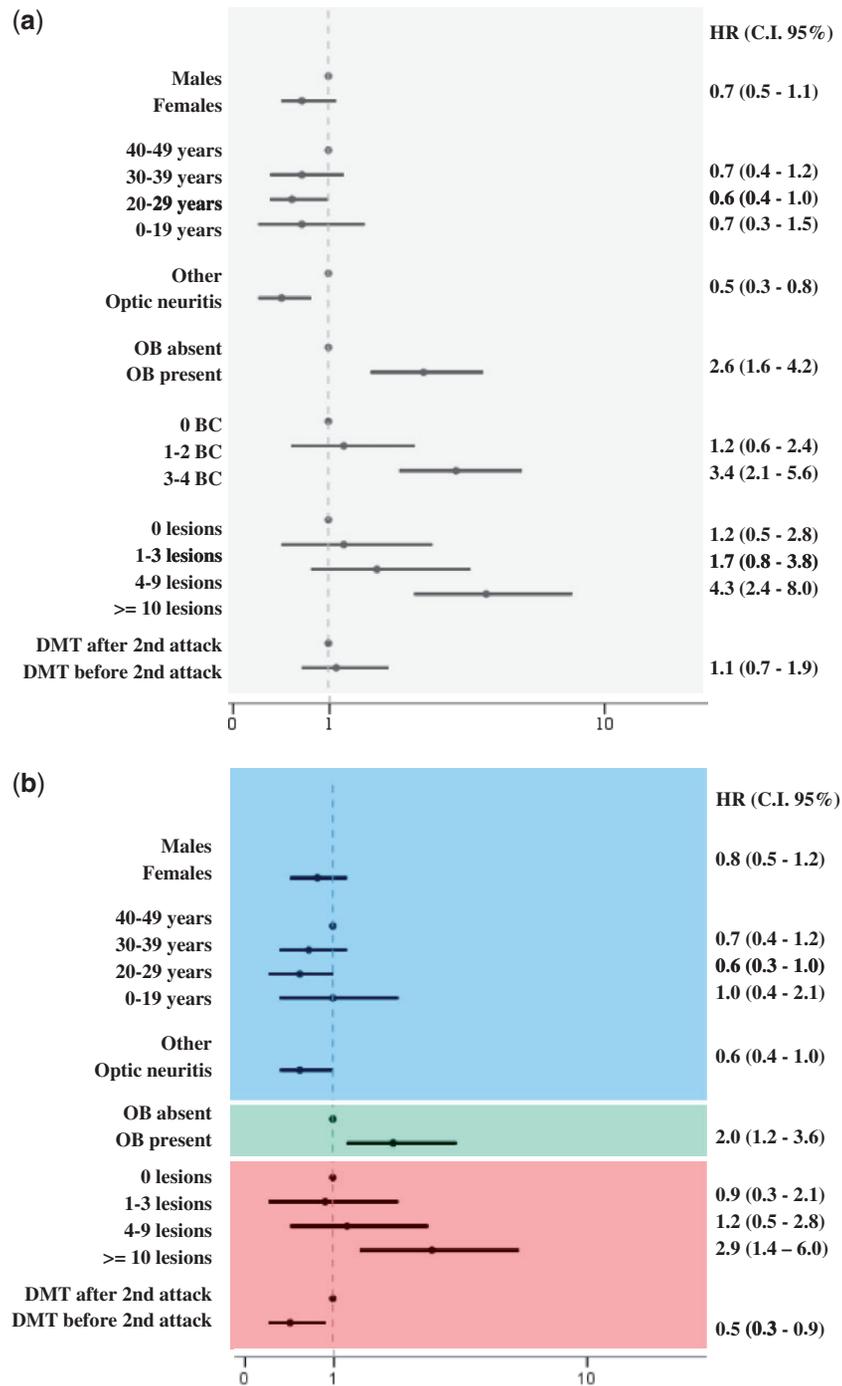
This multivariate approach is critical to confirm the effect of these baseline characteristics but also to weigh their impact on the outcomes. Until now, none of the previous studies has been able to classify such prognostic factors.



**Figure 3** Effect of baseline clinical, biological and MRI characteristics on the conversion to CDMS. **(A)** CDMS univariate analysis; **(B)** CDMS multivariate analysis. BC = Barkhof criteria. Blue colour indicates low-impact prognostic factor; green indicates medium-impact prognostic factor; and red indicates high-impact prognostic factor.

According to our study, although the risk of occurrence of a CIS is higher in females, gender seems not to be a risk factor for further relapse or the development of disability. Epidemiological studies from the past six decades have shown that females are more likely to develop multiple sclerosis than males. Currently, the female:male ratio for multiple sclerosis incidence ranges from 2:1 to 3:1 and varies by region (Koch-Henriksen and Sorensen, 2010).

A recent meta-analysis examining the effect of gender on CIS found that the overall relative risk of CIS in females to that in males was 2.12 (95% CI 1.94–2.32) (Dobson *et al.*, 2012). Our cohort also displayed a 2.1:1 female:male ratio. The female:male ratio has increased in the past six decades in most studied locations (Koch-Henriksen and Sorensen, 2010). The reason for this increased incidence of multiple sclerosis in females has been implicated as an



**Figure 4** Effect of baseline clinical, biological and MRI characteristics on the risk of attaining an EDSS score of 3.0. (A) EDSS 3.0 univariate analysis; (B) EDSS 3.0 multivariate analysis. BC = Barkhof criteria. Blue colour indicates low-impact prognostic factor; green indicates medium-impact prognostic factor; and red indicates high-impact prognostic factor.

environmental or genetic–environmental interaction (Sellner *et al.*, 2011). Despite the relatively short observation period of our study (1995–2012), this ratio has remained stable since 1995 (data not shown). The previously mentioned meta-analysis also found a 20% greater risk of developing multiple sclerosis for females experiencing a CIS compared

with males (Dobson *et al.*, 2012). However, our study did not detect any differences between gender regarding the risk of experiencing a second attack or of a diagnosis of McDonald multiple sclerosis. Large natural history studies, such as those of the Lyon and British Columbia cohorts, have shown that the time from disease onset to a given

disability level is shorter for males (Confavreux *et al.*, 2003; Koch *et al.*, 2010). In our study, no beneficial effect was associated with female gender based on the multivariate analyses. However, we cannot exclude the possibility that a longer follow-up period or other disability endpoints, such as reaching an EDSS score of 6.0, may reveal a difference in prognosis between genders. Gender appears to be a low-impact prognostic factor for relapsing forms of multiple sclerosis. Younger age at CIS onset has been associated with a higher risk of further relapse (Mowry *et al.*, 2009). Our cohort also demonstrated that compared with patients aged 40 to 49 years at disease onset, each younger decade was associated with a greater risk of relapse. Regarding the accumulation of disability, we found a tendency towards a better outcome in younger patients; however, the statistical significance of this result was marginal. This finding is in accordance with that of a previous study on child-onset multiple sclerosis in which patients younger than 18 years of age took 10 years longer than adult-onset patients with multiple sclerosis to reach secondary-progressive multiple sclerosis (Renoux *et al.*, 2007).

Another important clinical factor related to multiple sclerosis prognosis is CIS topography. Optic neuritis presentations have been repeatedly associated with a better outcome (Weinshenker *et al.*, 1989a, b; Runmarker and Andersen, 1993; Confavreux *et al.*, 2003). However, regarding the conversion to CDMS, clinical trials performed on CIS patients have not shown differences in outcomes between different topographies (Jacobs *et al.*, 2000; Comi *et al.*, 2001, 2009; Polman *et al.*, 2008; Kappos *et al.*, 2010). Our group showed that patients with optic neuritis may display a lower risk of conversion to multiple sclerosis, but this result is due to the different prevalence of abnormal baseline MRI scans in CIS patients according to topography (Tintore *et al.*, 2005). Our current study confirms these previous results. Regarding the conversion to CDMS, optic neuritis patients displayed a lower risk of experiencing a second attack compared with those presenting with other topographies, but this difference was not maintained when the brain MRI characteristics and other possible confounding factors were included in the multivariate analysis. Alternatively, concerning the accumulation of disability, patients with optic neuritis displayed a lower risk of attaining an EDSS score of 3.0 based on both univariate and multivariate analyses. Ethnicity has been associated with a more aggressive clinical course, but this variable was not addressed in our study because of the low number of non-white (non-Caucasian) patients in our population (Mowry *et al.*, 2009).

According to a recent meta-analysis, 68% of the patients who experience a CIS are oligoclonal band-positive (Dobson *et al.*, 2013). A meta-analysis also concluded that the presence of oligoclonal bands is associated with a marked increase in the risk of conversion to CDMS regardless of the anatomical location of the CIS or of reaching a specified disability outcome at follow-up compared

with patients who were oligoclonal band-negative (Dobson *et al.*, 2013). An important limitation of this meta-analysis was that the presence of oligoclonal bands was always considered to be a unique prognostic factor. In our CIS cohort, oligoclonal bands were present in 57.2% of the patients, ranging from 19% for the patients displaying a normal brain MRI, to 73.5% for the patients displaying an abnormal brain MRI. Our study confirms the important role of oligoclonal bands in predicting both the conversion to multiple sclerosis and disability accumulation based on univariate analysis and, most importantly, confirms that the presence of oligoclonal bands remains predictive after controlling for other demographic, clinical, DMT and magnetic resonance variables.

Approximately two-thirds of CIS patients exhibit multiple asymptomatic brain white matter lesions that are suggestive of demyelination at presentation (Tintore *et al.*, 2006). Studies in the 1990s revealed that the presence of brain T<sub>2</sub> lesions was associated with a higher risk of future clinical events. Three long-term studies consisting of a follow-up period of 7, 15 and 20 years on 156, 107 and 389 patients, respectively, reported rates of conversion to CDMS of 65%, 72% and 80%, respectively, in patients displaying an abnormal brain MRI and 8%, 25% and 20%, respectively in those displaying a normal brain MRI (Tintore *et al.*, 2006; Fisniku *et al.*, 2008; Group, 2008). We found similar rates of conversion in this larger cohort (Table 2). When including the McDonald criteria of multiple sclerosis, this percentage ranged from 81 to 84% for the patients displaying baseline MRI containing  $\geq 10$  lesions or exhibiting three to four Barkhof criteria, and to 9% for those displaying a normal brain MRI. As demonstrated by the Kaplan-Meier curves, the number of lesions at baseline correlated with the time to reach multiple sclerosis. Therefore, patients displaying fewer brain lesions at baseline require a longer follow-up period to reach conversion rates that are similar to the patients displaying a larger number of baseline lesions. In a subgroup univariate analysis of patients with spinal cord MRI (data not shown), the presence of one or more spinal cord lesions was significantly associated with conversion to multiple sclerosis as well as disability progression. These results will need to be confirmed in future analyses of this cohort with a larger number of patients with spinal cord MRI data and longer follow-up.

Our cohort shows that brain MRI at baseline is the most robust predictive factor for both conversion to multiple sclerosis and disability accumulation after controlling for all of the other variables examined. Other longitudinal measures, that were not available for analysis in the present study, such as brain atrophy or T<sub>2</sub> lesion load change occurring during the first year after a CIS, might also help in predicting clinical status during follow-up (Di Filippo *et al.*, 2010).

Although the aim of our study was not to evaluate the effect of treatment, it is important to consider its impact on other prognostic factors. DMT was specifically prescribed

to patients exhibiting a more aggressive disease course, which most likely explains the finding that patients receiving treatment prior to the second attack displayed a higher risk of conversion to multiple sclerosis based on the univariate analyses. However, upon controlling for the variables that could be irregularly distributed between the treated and non-treated patients, DMT displayed a protective effect on the conversion to McDonald multiple sclerosis and a non-significant protective effect on conversion to CDMS. When considering disability accumulation, treating patients prior to the second attack was also associated with a decreased risk of reaching moderate disability.

Our study has some methodological limitations. First, our cohort was collected at a single and highly specialized centre; however, our hospital has a wide primary catchment area (415 000 inhabitants), and health services are universal in our country, allowing all types of patients to enter our centre. Alternatively, this limitation also supports quality and accuracy of the data. Second, several patients were lost to follow-up, and the more benign cases were more prone to discontinue follow-up. To better understand the impact of these losses in our results, we have undertaken a sensitivity analysis. The results were very similar (data not shown), with slightly higher hazard ratios, showing that the risk conferred by the predictive variables in our results could be minimally underestimated. Finally, the updated 2010 McDonald criteria were not applied, as the required information regarding the MRI DIS criteria was not available for many patients (spinal cord MRI was only obtained from a minority of our patients) (Polman *et al.*, 2011).

In conclusion, according to our results, the risk factors for developing further attacks and disability accumulation in CIS patients are categorized as follows: demographic and topographic characteristics are low-impact prognostic factors; the presence of oligoclonal bands is a medium-impact prognostic factor; and brain MRI is a high-impact prognostic factor.

## Funding

M. Tintoré has received compensation for consulting services and speaking honoraria from Bayer-Schering, Merck-Serono, Biogen-Idec, Teva, Sanofi, Genzyme, Almirall and Novartis. M. Tintore is editor of Multiple Sclerosis Journal Experimental Translational and Clinical. A. Rovira serves on scientific advisory boards for NeuroTEC and on the editorial board of the American Journal of Neuroradiology and Neuroradiology, has received speaker honoraria from Bayer Schering Pharma, Sanofi, Bracco, Merck Serono, Teva Pharmaceutical Industries Ltd. and Biogen Idec, receives research support from Bayer Schering Pharma, and serves as a consultant for Novartis. J. Río has received speaking honoraria and personal compensation for participating on Advisory Boards from: Almirall; Bayer-Schering Healthcare; Biogen-Idec;

Genzyme; Merck-Serono; Novartis; Teva and Sanofi. G. Arrambide has received travel expenses for scientific meetings from Merck-Serono and Sanofi. M. Comabella has received compensation for consulting services and speaking honoraria from Bayer Schering Pharma, Merck Serono, Biogen-Idec, Teva Pharmaceuticals, Sanofi, and Novartis. J. Sastre-Garriga has received compensation for consulting services and speaking honoraria from Merck-Serono, Biogen-Idec, Teva, and Novartis. X. Montalban has received speaking honoraria and travel expenses for scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past with Bayer Schering Pharma, Biogen Idec, EMD Merck Serono, Genentech, Genzyme, Novartis, Sanofi, Teva Pharmaceuticals, and Almirall. L. Negrotto is supported by a McDonald Fellowship grant from the MSIF. This work has been financed with grants of the Spanish Ministry of Economy and Competitiveness by the Fondo de Investigación Sanitaria (FIS), the Instituto de Salud Carlos III (PI12/01313 granted to M.T. and PI14/01439 granted to X.M.). It has also received support from the “Red Española de Esclerosis Múltiple (REEM)”, which is sponsored by FIS, the Instituto de Salud Carlos III, the Ministry of Economy and Competitiveness in Spain, and the “Ajuts per donar Suport als Grups de Recerca de Catalunya, which is sponsored by the “Agència de Gestió d’Ajuts Universitaris i de Recerca” (AGAUR) of the Generalitat de Catalunya in Spain. S.O. and G.A. are supported by a personal unrestricted grant from the pharmaceutical company Novartis®. This work is independent of all the funding bodies, which have played no part in any of its stages (design, data analysis or manuscript writing).

## Acknowledgement

We thank the Statistics and Bioinformatic Unit (UEB) of the Vall d’Hebron Hospital for their input in data analysis.

## Supplementary material

Supplementary material is available at *Brain* online.

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