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Quantifying risk of early relapse in patients with first demyelinating events: Prediction in clinical practice

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Abstract

Background: Characteristics at clinically isolated syndrome (CIS) examination assist in identification of patient at highest risk of early second attack and could benefit the most from early disease-modifying drugs (DMDs).

Objective: To examine determinants of second attack and validate a prognostic nomogram for individualised risk assessment of clinical conversion.

Methods: Patients with CIS were prospectively followed up in the MSBase Incident Study. Predictors of clinical conversion were analysed using Cox proportional hazards regression. Prognostic nomograms were derived to calculate conversion probability and validated using concordance indices.

Results: A total of 3296 patients from 50 clinics in 22 countries were followed up for a median (interquartile range (IQR)) of 1.92 years (0.90, 3.71). In all, 1953 (59.3%) patients recorded a second attack. Higher Expanded Disability Status Scale (EDSS) at baseline, first symptom location, oligoclonal bands and various brain and spinal magnetic resonance imaging (MRI) metrics were all predictors of conversion. Conversely, older age and DMD exposure post-CIS were associated with reduced rates. Prognostic nomograms demonstrated high concordance between estimated and observed conversion probabilities.

Conclusion: This multinational study shows that age at CIS onset, DMD exposure, EDSS, multiple brain and spinal MRI criteria and oligoclonal bands are associated with shorter time to relapse. Nomogram assessment may be useful in clinical practice for estimating future clinical conversion.

Keywords: Nomogram, clinically isolated syndrome, clinically definite multiple sclerosis, second attack, disease-modifying drugs, MRI, CSF, MS, CIS

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Introduction

The first relapse after clinically isolated syndrome (CIS) marks the clinical conversion from CIS to clinically definite multiple sclerosis (CDMS). Conversion is common, with published estimates ranging from 20% in those with normal onset brain magnetic resonance imaging (MRI) to 75%–88% in patients with a high number of MRI lesions combined with various lesion location criteria.[1–6] Establishing optimal timing for initiating disease-modifying drug (DMD) therapy following CIS is difficult.[7] Early identification of patients with a higher probability of clinical conversion can assist this treatment decision,[8] as therapy is often recommended for high-risk CIS patients.[7,9] Characteristics at the time of CIS including age,[10] lesion number and distribution characteristics on brain MRI[1,3] and the cerebrospinal fluid (CSF) examination assist in identification of patients at higher risk

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of early second attack and thus those patients who may benefit from early treatment.[11] The DMD's IFNβ-1a, IFNβ-1b and glatiramer acetate have been trialled in high-risk CIS patients compared to placebo, and all have been shown to significantly reduce the proportion of patients converting to CDMS.[12–15]

MRI examination and CSF analysis are recommended investigations of CIS as they increase the specificity of diagnosis.[10,16] Baseline brain MRI parameters are well established as predictors of conversion to CDMS.[1,2,17] The presence of oligoclonal bands (OCBs) on CSF examination supports a diagnosis of MS[13] and has previously been demonstrated to increase the risk of conversion in patients with CIS, independent of brain MRI parameters,[18,19] and assists the clinician in differentiating multiple sclerosis (MS) from alternate diagnoses, such as infection or vasculitis.[20,21] A systematic review and meta-analysis of 48 studies concluded that the presence of OCB in CSF in CIS patients was a strong predictor of time to CDMS.[22] In further confirmatory work, a recent prospective cohort study exploring a comparable suite of demographic, clinical and examination factors at CIS to our study identified MRI lesion number and the presence of CSF OCBs as high- and medium-impact prognostic factors, respectively.[23]

The objective of this study was to utilise the prospectively documented CIS cohort from 50 MSBase centres to first examine demographic, clinical, diagnostic and treatment characteristics as predictors of time to second attack following CIS, and then, to use these data to create and internally validate a predictive nomogram to calculate individualised risk of clinical conversion to CDMS at 12 months.

Materials and methods

MSBase Registry

The MSBase Registry is an international online database accumulator that was established in 2004 which collects disease-related information from consenting patients attending MS clinics – www.msbase.org.[24] The MSBase Registry was approved by the Melbourne Health Human Research Ethics Committee and by the local ethics committees in all participating centres (or exemptions granted, according to applicable local laws and regulations). Informed consent from all patients according to local laws is required for participation in MSBase, and the project holds Human Research Ethics Committee approval or exemption at each contributing centre.

MSBase Incident Study

The MSBase Incident Study (MSBASIS) is a substudy of the MSBase Registry. Commencing on the 18 November 2004, MSBASIS is an ongoing global, longitudinal, investigator-initiated and maintained observational cohort study designed to prospectively assess all registry MS patients with a CIS with symptom onset less than 12 months from the enrolment date.

Inclusions

MSBASIS requires a minimum entry data set at each clinic visit observation point consisting of the visit date, Neurostatus Expanded Disability Status Scale (EDSS) score, Kurtzke Functional Systems Score (KFSS), onset date of prospectively observed relapses, glucocorticoid therapy for relapses and, where applicable, initiation and discontinuation dates for MS disease-modifying therapy. EDSS scores recorded within 30 days of CIS onset were excluded. At least one EDSS otherwise recorded within 12 months of CIS onset was required. The first brain MRI scan classification for each patient, using Barkhof–Tintore criteria for lesion dissemination in space,[1,2,25,26] which had to be performed within 12 months of CIS onset, was required. Following the initial baseline visit, minimum annual follow-up was required. Patients with primary progressive multiple sclerosis (PPMS) were excluded. Baseline was defined as the recorded date of CIS onset. Of the 4313 patients enrolled in MSBASIS, a total of 3296 patients satisfied all inclusion criteria and were thus eligible for this study.

Outcome measure and definitions

The primary outcome of this analysis was time to first relapse following CIS. CDMS was defined as examination evidence of a symptomatic second neurological episode attributable to demyelination of more than 24 hours duration and more than 4 weeks from the initial attack, according to the Poser et al.[27] criteria. Follow-up time was defined as the time that lapsed between the date of CIS onset (baseline) and either the date of first post-CIS relapse or, where no subsequent post-CIS relapse was observed, the date of the last recorded clinic visit. First DMDs initiated during follow-up included in the analysis were IM-IFNβ-1a, SC-IFNβ-1a, IFNβ-1b, glatiramer acetate, natalizumab and fingolimod. Medication possession ratio (MPR) was defined as the number of follow-up days on DMD treatment divided by the total number of follow-up days contributed by a patient and was calculated at the level of the individual patient. Baseline CSF examination was included if a sample was collected and tested within 6 months of the baseline date.

Lesion number on baseline spinal MRI, if performed, was analysed as both a continuous variable (number of T1 gadolinium–enhancing and T2 hyperintense lesions) and a categorical variable (0 compared with 1+ lesions).

Statistical analyses

Sex, country, age at CIS onset, DMD exposure, MPR, identity of first DMD product initiated on follow-up, baseline MRI (both brain and spinal) and the presence of OCB in baseline CSF examination were analysed for association with time to first relapse following CIS. All models presented were adjusted for country to control for any residual inter-country heterogeneity. Categorical variables were summarised using frequency and percentage. Continuous variables were assessed for significant departure from normality using a Shapiro–Wilk test and summarised using mean and standard deviation (SD) or median and inter-quartile range (IQR), as appropriate. Kaplan–Meier survival curves were used to describe cumulative time without relapse over the observation period. Cox proportional hazards regression was used to investigate correlation between our a priori identified predictors and time to first post-CIS relapse. Interactions between predictor variables in the adjusted model were tested, and no significant interactions were observed for any of the presented models. Hazard proportionality was assessed through analysis of scaled Schoenfeld residuals. The linearity of association between candidate explanatory variables and the conversion end point were tested by incorporating quadratic transformations into the models. A subgroup analysis was performed disaggregating the models by DMD exposure status, with separate models run for the group of patients exposed to DMD during follow-up and those non-exposed. A subgroup analysis test for interaction was used to assess for subgroup-specific effects. In terms of deriving the multivariable models, two primary adjusted models were considered. The first included all baseline and time-varying factors assessed in the univariate analysis (and listed above), while the second was restricted to baseline factors only (i.e. excluding post-baseline DMD exposure). Both of these models exclude spinal MRI lesions secondary to significant co-linearity with OCB status. The adjusted DMD exposure sub-group analyses include the same suite of baseline predictors, while the sensitivity analysis summarised in Supplementary Table 1 again uses the same baseline predictor set, replacing OCB status for spinal MRI lesions. For the primary analysis, 0–2 T2 lesions were used as the reference group for this factor rather than 0 lesions secondary to the small number of patients with 0 T2 lesions at baseline. All modelling analysis was adjusted for country of clinic contributing the patient data. All reported *p*-values are two-tailed, and for each analysis, $p < 0.05$ was considered significant.

Prognostic nomogram

Using the independent prognostic correlates of second attack observed in the baseline-adjusted modelling, we derived a prognostic nomogram for conversion to CDMS using the method described by Katten et al.[28] The nomogram was internally validated via derivation of the concordance index and nomogram calibration. The concordance index captures the probability that a MS patient drawn randomly from our data set who was known to convert to CDMS *before* another randomly drawn patient and actually records a higher conversion probability on the prognostic nomogram. The index was derived by taking 1500 bootstrapped random samples of the original 3296 patients used to derive the multivariable 'baseline only' Cox model described above. Another round of 1500 bootstrapped resamples was used to calibrate the nomogram. Patients were grouped according to their nomogram-predicted conversion probabilities and the means of these probability groups then compared against the empirically observed Kaplan–Meier conversion estimates on a calibration curve. These calibration curves represent the agreement between observed and predicted values across a range of predicted conversion probabilities. All analyses were conducted in Stata version 13 (StataCorp, College Station, TX, USA) and R (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

A total of 3296 patients from 50 clinics across 22 countries were eligible for this analysis (for patient characteristics, see Table 1), contributing a total of 5378.70 person-years of data. In all, 389 (42.7% of total initiates) commenced IM-IFNβ-1a, 308 (33.8%) SC-IFNβ-1a, 167 (18.4%) IFNβ-1b and 125 (13.7%) glatiramer acetate. Of the eligible patients, 1953 (59.3%) recorded a first post-CIS relapse event during follow-up. Incidence of first post-CIS relapse varied markedly by whether a patient was exposed to DMD therapy during observation or not, with the exposed subset recording an incidence of 17.1 relapses per 100 person-years (95% confidence interval (CI) 15.6, 18.8) compared with 53.8 per 100 person-years in the non-exposed group. A total of 571 (17.3%) patients recorded ⩾1 T1 gadolinium–enhancing lesions, while

Table 1. Demography, disease, treatment and examination characteristics.

Characteristic	Level	All ($n=3296$)
Second events – *n* (%)	–	1953 (59.3)
Cumulative follow-up[a] – person-years	–	5378.7
Time to second event (years)	Mean (SD)	1.09 (1.42)
	Median (IQR)	0.50 (0.23, 1.27)
Gender – *n* (%)	Female	2324 (70.5)
	Male	972 (29.5)
Age at MS onset – median (IQR)	–	31.61 (25.26, 39.33)
EDSS at CIS – median (IQR)		2 (1, 2.5)
Medication possession ratio (MPR)[a] – mean (SD)		0.18 (0.33)
DMD exposed		910 (27.6)
Neuroanatomical location of first symptoms	Optic pathways	713 (21.6)
	Supratentorial	675 (20.5)
	Brainstem	710 (21.5)
	Spinal cord	847 (25.7)
Baseline cerebral MRI	1+ T1 gadolinium–enhancing lesion	571 (17.3)
	9+ T2 hyperintense lesions[b]	909 (27.6)
	1+ infratentorial lesion	1246 (37.8)
	1+ juxtacortical lesion	1479 (44.9)
	2+ periventricular lesions	1547 (46.9)
Baseline spinal MRI[c]	1+ T1 gadolinium–enhancing lesion	49 (1.5)
	1+ T2 hyperintense lesion	535 (16.2)
Baseline CSF[d]	Oligoclonal bands positive	1059 (32.1)

EDSS: Expanded Disability Status Scale; CIS: clinically isolated syndrome; DMD: Disease-modifying drug; MRI: magnetic resonance imaging; CSF: cerebrospinal fluid; IQR: inter-quartile range; SD: standard deviation.
[a]The medication possession ratio is the proportion of follow-up time spent treated with a disease-modifying drug.
[b]$n=142$ patients recorded 0 T2 lesions, $n=195$ recorded 1–2 and $n=1613$ recorded 3–8 T2 lesions.
[c]Baseline spinal MRI was available for $n=1539$ patients.
[d]Baseline CSF examination was available for $n=3104$ patients. Of these, $n=1265$ recorded an oligoclonal band (OCB) status of absent or detected.

909 (27.6%) recorded ⩾9 T2 hyperintense lesions. Normal T1 and T2 scans were recorded in 1749 and 142 patients, respectively.

Predictors of conversion to CDMS

Older age at CIS was associated with a 10% reduction in the risk of clinical conversion (5-year units, adjusted hazard ratio (aHR: 0.90), 95% CI: 0.88, 0.92; Table 3). Every point increase in baseline EDSS at CIS was associated with 1.16 times the rate of subsequent conversion (aHR: 1.16, 95% CI: 1.12, 1.20). Neuroanatomical location of first symptoms was also associated with rate of conversion, with a brainstem and supratentorial location associated with 1.17 (aHR: 1.17, 95% CI: 1.02, 1.36) and 1.29 (aHR: 1.29, 95% CI: 1.12, 1.48) times the rate of second attack, respectively, relative to an optic pathway location. Any exposure to DMD during follow-up was associated with a 42% rate reduction in time to first relapse compared with DMD-naïve patients (aHR: 0.58, 95% CI: 0.46, 0.73) (Figure 1), while a 1-unit increase in MPR was associated with a 65% reduction in the rate of relapse (aHR: 0.35, 95% CI: 0.25, 0.49).

The presence of CSF-restricted OCB was associated with 1.52 times the rate of relapse compared with OCB absence (aHR: 1.52, 95% CI: 1.22, 1.88). Baseline brain and spinal MRI lesion number and distribution were also associated with first post-CIS relapse. At least 1 T1 gadolinium–enhancing lesion was associated with 1.24 times the rate of relapse (aHR: 1.24, 95% CI: 1.09, 1.41), while 3 or more periventricular lesions were associated with 1.68 times the rate of relapse compared with 0 lesions. At least 1 infratentorial and at least 1 juxtacortical lesion on brain MRI were associated with 1.21 times (aHR: 1.21, 95% CI: 1.08, 1.36) and 1.21 times (aHR: 1.21, 95% CI: 1.06, 1.37) the rate of first post-CIS relapse, respectively, when compared with

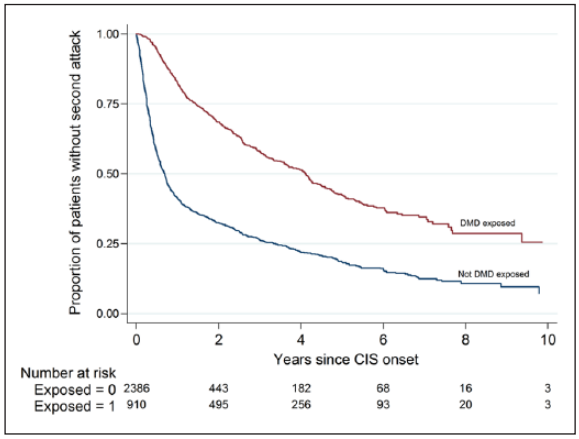

Figure 1. Kaplan–Meier survival curve – time to second attack by DMD exposure status.

0 lesions. A greater number of T2 hyperintense lesions, although associated with unadjusted modelling, were not predictive on adjusted modelling. Spinal T2 lesions were excluded from the adjusted modelling secondary to co-linearity with the presence of OCB. As an additional sensitivity analysis, we re-analysed the adjusted model substituting spinal T2 lesions for the presence of OCB predictor (Supplementary Table 1).

Prognostic nomogram

When the primary model was limited to baseline characteristics only (i.e. only factors recorded at CIS, excluding post-CIS DMD exposure metrics), age, female sex, EDSS, neuroanatomical location of first symptoms, T1 Gd+ infratentorial and periventricular lesions and the presence of OCB in baseline CSF again correlated with subsequent conversion (Table 1). Using the significant baseline correlates of clinical conversion identified in this adjusted Cox model, we derived a nomogram to predict 12-month conversion (Figure 2). The degree of contribution of each independent explanatory variable to the 12-month conversion nomogram points was in descending order: higher EDSS at CIS, younger age, supratentorial or brainstem onset locations, periventricular lesions, the presence of CSF OCBs, infratentorial lesions and female sex. The concordance index for the 12-month conversion model was 0.81. Additional nomograms for 6-month, 2-, 3-, 4- and 5-year conversion are presented as supplementary figures (Supplementary Figures 1–5). The concordance indices for the 6-month, 2-, 3-, 4-and 5-year conversion models were 0.76, 0.81, 0.82, 0.83 and 0.83, respectively. Supplementary Figure 6 provides a worked example of how to interpret the nomogram using a hypothetical patient. The calibration curve (Figure 3) illustrates how well the nomogram predictions compared with the actual observed cohort outcomes.

Subgroup analysis – DMD exposure

A subgroup analysis of patients who reported (1) DMD exposure during follow-up or (2) remained untreated during follow-up showed differences in both the pattern of the predictors and the magnitude of their associations (Table 2). Many of the associations observed at the level of the entire sample decreased in magnitude and/or level of significance when limited to the DMD-exposed subgroup only. By contrast, these associations were generally larger and more significant in the non-DMD-exposed subgroup. Among those patients who experienced a second event, there was no difference in EDSS at the time of second relapse between the DMD-naïve and exposed subgroups (mean: 2.13, SD: 1.38 vs mean: 2.04, SD: 1.17; p (signed-rank) = 0.3788.

Discussion

This multinational, prospective study represents the largest post-CIS cohort reported to date, examining predictors of time to first relapse in 3296 CIS patients. We confirmed that, in a multivariable model, younger age at CIS onset and higher baseline EDSS scores were clinical predictors of shorter time to relapse, whereas sex had no independent effect. Each of the Barkhof–Tintore criteria retained independent predictive power. Total brain T2 lesion number was not predictive of time to relapse attack, whereas the presence of 1+ brain Gd–enhancing lesion was predictive. Importantly, presence of OCBs was an independent predictor of shorter time to relapse, but this was highly collinear with the presence of 1+ spinal cord lesions. DMD exposure was strongly protective against relapse, consistent with results of several phase 3 trials. These results corroborate and extend prior, albeit smaller, studies observing similar sets of predictors of clinical conversion probability.[10,19,29] The recent Tintore study, based on follow-up in a single centre on 1015 patients, reports younger age at onset, presence of OCB and more than 10 brain MRI lesions as prognostic factors for developing MS.[25] We report similar results on demographic characteristics and biological results and extend these to observe a sex effect in the ‘baseline factors only’ model. Our larger multicentre study provides greater power to assess the predictive value of individual brain MRI criteria, with each of the Barkhof–Tintore criteria confirmed as independent factors shortening time to second attack.

Table 2. Predictors of first post-CIS relapse.

Predictor	Level	uHR (95% CI) *p*-value	Baseline and time-varying covariates	Baseline covariates only
			aHR (95% CI) *p*-value[a,b]	aHR (95% CI) *p*-value[a,c]
Gender	Female	1.10 (1.00, 1.22) 0.053	1.05 (0.95, 1.16) 0.338	1.12 (1.01, 1.23) 0.031
	Male	1.00	1.00	1.00
Age at MS onset (5 years)	–	0.93 (0.91, 0.95) <0.001	0.90 (0.88, 0.92) <0.001	0.92 (0.90, 0.94) <0.001
EDSS (continuous)	–	1.13 (1.10, 1.17) <0.001	1.16 (1.12, 1.20) <0.001	1.15 (1.11, 1.19) <0.001
Exposed to DMD during follow-up	–	0.37 (0.33, 0.42) <0.001	0.58 (0.46, 0.73) <0.001	
Medication possession ratio (MPR)	–	0.24 (0.20, 0.28) <0.001	0.35 (0.25, 0.49) <0.001	
First symptoms location	Optic pathways	1.00	1.00	1.00
	Supratentorial	1.40 (1.22, 1.61) <0.001	1.29 (1.12, 1.48) 0.001	1.36 (1.18, 1.56) <0.001
	Brainstem	1.30 (1.14, 1.50) <0.001	1.17 (1.02, 1.36) 0.030	1.20 (1.04, 1.38) 0.015
	Spinal cord	1.20 (1.05, 1.37) 0.009	1.10 (0.96, 1.27) 0.179	1.15 (1.00, 1.31) 0.054
T1 gadolinium lesions	0	1.00	1.00	1.00
	1+	1.18 (1.04, 1.33) 0.008	1.24 (1.09, 1.41) 0.001	1.09 (0.96, 1.24) 0.189
T2 hyperintense lesions	0–2	1.00	1.00	1.00
	3–8	1.22 (1.04, 1.44) 0.018	0.98 (0.81, 1.20) 0.873	1.03 (0.85, 1.25) 0.760
	9+	1.36 (1.14, 1.62) <0.001	0.96 (0.77, 1.20) 0.714	0.99 (0.79, 1.23) 0.909
Infratentorial lesions	0	1.00	1.00	1.00
	1+	1.36 (1.23, 1.51) <0.001	1.21 (1.08, 1.36) 0.001	1.15 (1.03, 1.29) 0.013
Juxtacortical lesions	0	1.00	1.00	1.00
	1+	1.21 (1.09, 1.34) 0.001	1.21 (1.06, 1.37) 0.004	1.03 (0.91, 1.17) 0.654
Periventricular lesions	0	1.00	1.00	1.00
	1–2	1.09 (0.91, 131) 0.326	1.15 (0.95, 1.40) 0.157	1.04 (0.86, 1.25) 0.689
	3+	1.48 (1.28, 1.72) <0.001	1.68 (1.38, 2.04) <0.001	1.36 (1.16, 1.59) <0.001
Number of spinal T1 gadolinium lesions (1+ vs 0)	–	1.11 (0.94, 1.31) 0.215	Co-linear with oligoclonal bands	Co-linear with oligoclonal bands
Number of spinal T2 lesions (1+ vs 0)	–	1.11 (1.05, 1.17) <0.001		
Oligoclonal bands in CSF	Absent	1.00	1.00	1.00
	Present	1.24 (1.01, 1.54) 0.044	1.52 (1.22, 1.88) <0.001	1.25 (1.01, 1.55) 0.042

EDSS: Expanded Disability Status Scale; CIS: clinically isolated syndrome; DMD: disease-modifying drug; CSF: cerebrospinal fluid; uHR: unadjusted hazard ratio; aHR: adjusted hazard ratio; MS: multiple sclerosis; CI: confidence interval.
[a]Additionally adjusted for country.
[b]Hazard proportionality test: $p = 0.8225$.
[c]Hazard proportionality test: $p = 0.7928$.

Table 3. Predictors of first post-CIS relapse – by DMD exposure status.

Predictor	Level	Exposed to DMD during follow-up ($n=910$)[a,b,d]	Not exposed to DMD during follow-up ($n=2386$)[a,c,d]
		Second event – $n=438$	Second event – $n=1515$
		aHR (95% CI) p-value[b]	aHR (95% CI) p-value[c]
Gender	Female	1.11 (0.90, 1.38) 0.318	1.04 (0.93, 1.17) 0.489
	Male	1.00	1.00
Age at MS onset	–	0.92 (0.87, 0.97) 0.002	0.91 (0.89, 0.93) <0.001
EDSS (continuous)	–	1.22 (1.10, 1.34) <0.001	1.16 (1.12, 1.21) <0.001
First symptoms location	Optic pathways	1.00	1.00
	Supratentorial	1.24 (0.84, 1.83) 0.272	1.28 (1.08, 1.52) 0.005
	Brainstem	0.89 (0.59, 1.34) 0.575	1.30 (1.10, 1.55) 0.003
	Spinal cord	0.74 (0.49, 1.11) 0.145	1.18 (1.00, 1.40) 0.054
T1 gadolinium lesions	0	1.00	1.00
	1+	1.44 (1.08, 1.91) 0.012	1.29 (1.11, 1.50) 0.001
T2 hyperintense lesions	0–2	1.00	1.00
	3–8	1.24 (0.65, 2.35) 0.514	1.19 (0.61, 2.10) 0.489
	9+	1.18 (0.60, 2.32) 0.628	1.15 (0.58, 2.18) 0.397
Infratentorial lesions	0	1.00	1.00
	1+	1.23 (0.95, 1.58) 0.116	1.29 (1.14, 1.47) <0.001
Juxtacortical lesions	0	1.00	1.00
	1+	1.15 (0.86, 1.54) 0.354	1.17 (1.01, 1.34) 0.032
Periventricular lesions	0	1.00	1.00
	1–2	0.93 (0.49, 1.75) 0.818	0.96 (0.63, 1.51) 0.703
	3+	1.00 (0.53, 1.90) 0.991	1.70 (1.39, 2.08) <0.001
Oligoclonal bands in CSF	Absent	1.00	1.00
	Present	1.27 (0.68, 2.37) 0.454	1.40 (1.11, 1.77) 0.004

EDSS: Expanded Disability Status Scale; CIS: clinically isolated syndrome; DMD: disease-modifying drug; CSF: cerebrospinal fluid; aHR: adjusted hazard ratio; MS: multiple sclerosis; CI: confidence interval.
[a]Additionally adjusted for country.
[b]Hazard proportionality test: $p=0.3688$.
[c]Hazard proportionality test: $p=0.4555$.
[d]Test of interaction: $p=0.002$.

Identification of patient, disease and examination factors associated with higher probability of second attack in clinical practice may enable clinicians to flag patients that could benefit from more intensive follow-up and consideration of early DMD treatment intervention, facilitating more favourable patient outcomes. The observation that, across both full and 'baseline factors only' models, the lesion location covariates out-perform lesion count metrics confirms the finding that brain lesion location is preferable to

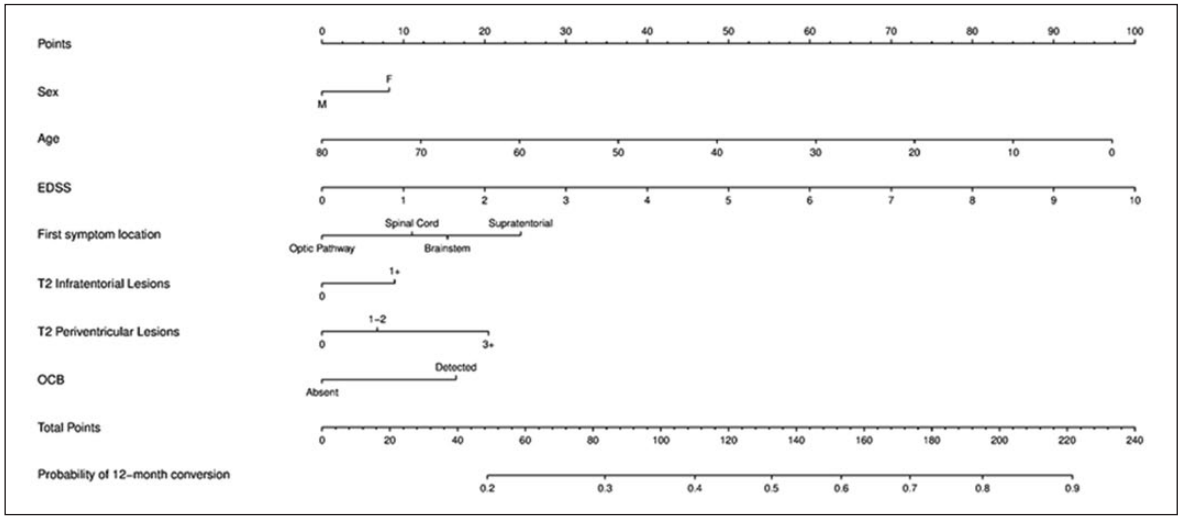

Figure 2. Nomogram for 12-month conversion. To calculate total points for a patient, match response for a predictor to the top points scale, repeat for all prognostic factors and sum to derive total points. Match position on the total points scale to the conversion probability scale to identify the individualised probability of 12-month conversion.

lesion number in calculating risk rate of second attack, as demonstrated by Swanton et al.[29] and incorporated into the 2010 revisions of the McDonald criteria for diagnosis of MS.[16]

Across both the primary and subgroup analyses, *any* exposure to DMD appears to be a more important and consistent predictor of first post-CIS outcome than the precise amount of exposure. These results support early initiation of DMD, particularly for those subsets that demonstrate overall higher probability of first post-CIS relapse (younger age at CIS, higher number of brain MRI lesions in specific locations and lesion presence on spinal MRI or OCB presence in CSF). Furthermore, the precise identity of the DMD product initiated did not change the effect greatly. This result is consistent with observations from the recent phase 3 REFLEX Trial comparing two dosing frequencies of subcutaneous IFNβ-1a in first clinical demyelinating event patients which observed that either treatment delayed subsequent clinical relapse post-CIS, regardless of the dosing regimen used.[30]

The high correlation between the T2 hyperintense lesions on spinal MRI with presence of OCB on baseline CSF examination could suggest a role for possible rationalisation of the battery of investigations around the time of onset. While greater lesion loads on brain MRI in patients with CIS has been correlated with a higher probability of finding OCB in concurrently sampled CSF,[18,20] our results are novel in that the concurrence of spinal lesions and OCB presence is so strong that a multivariable statistical model cannot be performed with both predictors present due to collinearity. It is reasonable to hypothesise that there is a biological explanation that either OCBs (i.e. oligoclonal antibodies) could be produced preferentially in or near spinal lesions or OCBs could be causally involved in the generation of spinal lesions.

The nomogram permits calculation of the cumulative effect of multiple prognostic factors of individualised conversion probability. By weighting the influence of each factor, the nomogram provides an appreciation of the *relative* magnitude of influence of each prognostic factor on conversion probability. Younger age, higher EDSS at CIS and brain lesions in periventricular and infratentorial locations dominated the nomogram in terms of relative contribution to total points and subsequent conversion probability, consistent with prior literature detailing risk factors for conversion. The advantage of a nomogram over an adjusted regression model is that, while the latter returns estimates of the average effects across a population, the nomogram permits individualised predictions to be made, which may be useful for both patient management and potentially inform future revisions of diagnostic criteria, which are typically based on predictors of time to clinical relapse. While our own internal validation suggested good performance, both an additional training-validation approach and an external validation through the application of the nomogram to a separate MS data set or population are required to confirm the generalisability of the nomogram. Furthermore, a larger sample of patients, including a greater number with 0 T2 lesions on baseline brain MRI, would permit better characterisation of the influence of separate T2 lesions (including 0) on subsequent conversion risk.

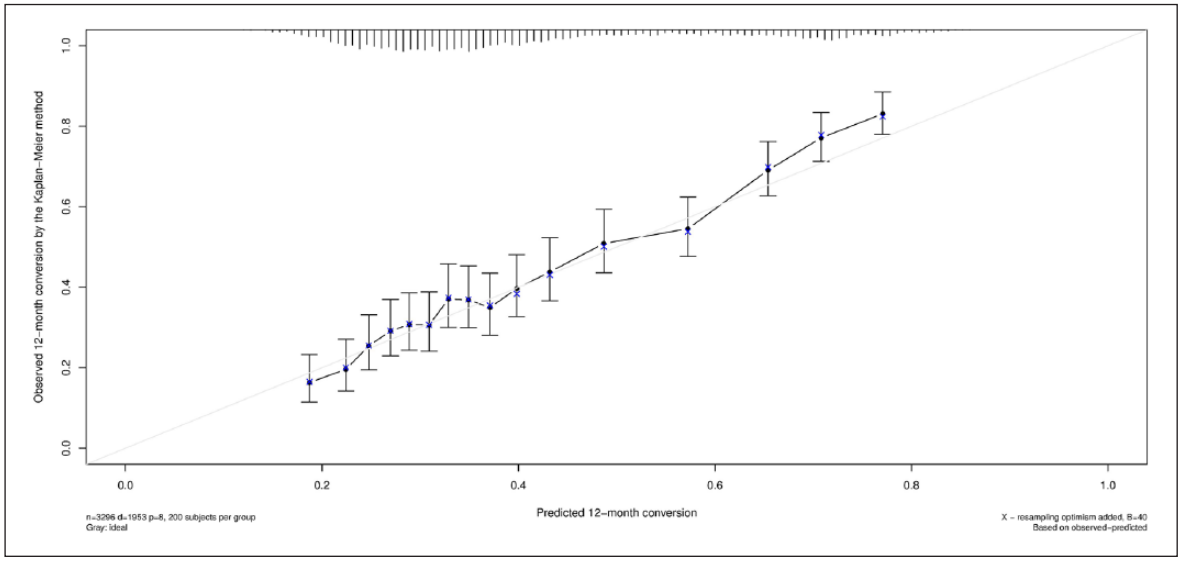

Figure 3. Calibration curve for 12-month conversion. Nomogram-predicted conversion probability is represented on the *x*-axis, while the *y*-axis gives the actual 12-month conversion probability by the Kaplan–Meier method. Perfect agreement between actual and predicted conversion probability is represented by the blue-grey diagonal line.

This large post-CIS prospective study describes the independent predictive effect of demographic, clinical, radiological and CSF predictors of time to CDMS. Our results confirm and extend those of many prior studies and validate the use of predictors in clinical practice. The characterisation of independent predictors allows more accurate prognosis for CIS patients and could inform future revisions of the diagnostic criteria of relapsing-remitting MS.

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Author contribution

Tim Spelman conceptualised and designed the study, conducted and interpreted the analysis and drafted, revised and approved the manuscript. Claire Meyniel conceptualised and designed the study, interpreted the analysis and drafted, revised and approved the manuscript. Helmut Butzkueven conceptualised the study, interpreted the analysis and revised and approved the manuscript. Juan Ignacio Rojas, Tomas Kalincik and Vilija Jokubaitis interpreted the analysis, revised and approved the manuscript. Alessandra Lugaresi, Guillermo Izquierdo, Francois Grand'Maison, Cavit Boz, Raed Alroughani, Eva Havrdova, Dana Horakova, Gerardo Iuliano, Pierre Duquette, Murat Terzi, Pierre Grammond, Jose Antonio Cabrera-Gomez, Raymond Hupperts, Jeannette Lechner-Scott, Celia Oreja-Guevara, Ricardo Fernández Bolaños, Eugenio Pucci, Freek Verheul, Marcela Fiol, Vincent Van Pesch, Edgardo Cristiano, Thor Petersen, Tatjana Petkovska-Boskova, Fraser Moore, Ilya Kister and Maria Trojano contributed substantially to data acquisition, interpretation of the analysis and have revised and approved the manuscript.

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