TITLE: Quantifying risk of early relapse in high risk patients with first demyelinating events

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Abstract

Background: Clinical relapse after a first demyelinating event (clinically isolated syndrome, CIS) defines the conversion from CIS to clinically definite multiple sclerosis (MS). Not all patients with CIS convert to MS, even after long-term follow-up. Studies quantifying the time to MS conversion in patients with CIS have substantially informed the diagnostic criteria for MS. Baseline characteristics at the time of CIS examination also assist in identification of patient subsets who are at highest risk of early second attack, and could benefit the most from early disease-modifying drug (DMD) treatment. We prospectively examined independent determinants of risk of second attack in a cohort of 3296 CIS patients.

Methods: Patients with CIS were prospectively followed in the MSBase Incident Study (MSBASIS), a substudy of the MSBase global registry. Predictors of time to second attack were analysed using Cox proportional hazards regression and predictors of time to any post-CIS relapse event were studied using a conditional risk-set model.

Results: A total of 3296 patients from 50 clinics in 22 countries contributed a total of 5378.70 person-years of data. A total of 1953 (59.3%) patients recorded a second attack during follow-up at an incidence rate of 36.31 second attacks per 100 person-years (95% CI 34.73, 37.96). A higher EDSS at CIS, a brainstem or supratentorial neuroanatomical first symptom location relative to an optic pathways location, the presence of oligoclonal bands in CSF, at least 1 T1 gadolinium enhancing lesions, 3 or more periventricular lesions, at least 1 infratentorial and at least 1 juxtacortical lesion on baseline cerebral MRI were all independent predictors of shorter time to clinical relapse. Conversely, older age at CIS onset, any exposure to DMD during follow-up and an increasing proportion of post-CIS follow-up on treatment were all associated with a reduction in the rate of second attack. Positive oligoclonal banding in CSF and presence of at least one spinal cord lesion co-occurred so frequently that they could not be independently modelled, raising the possibility that

cord lesions and intrathecal antibody production are biologically linked. A prognostic nomogram based on this modelling permits individualised assessment of 12 month conversion risk at the time of clinically isolated syndrome.

Conclusions: This large multinational, prospective, observational study shows that age at CIS onset, DMD exposure, multiple baseline cerebral MRI criteria and the presence of oligoclonal bands on baseline CSF examination are all independently associated with shorter time to relapse after CIS.

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

Introduction:

The first relapse after clinically isolated syndrome (CIS) marks the conversion from CIS to clinically definite multiple sclerosis (CDMS). Conversion is common, with published estimates ranging from 20% in those with normal onset cerebral MRI to 75-88% in patients with a high number of MRI lesions combined with various lesion location criteria.¹⁻⁷ Establishing optimal timing for initiating disease-modifying drug (DMD) therapy following CIS is difficult.⁸ Early identification of patients at high risk of conversion can assist this treatment decision.⁹ as DMD therapy is often recommended for high risk CIS patients.^{8, 10,11} Baseline characteristics at the time of CIS including age,¹² lesion number and distribution characteristics on cerebral MRI^{1,4} and the baseline cerebrospinal fluid (CSF) examination assist in identification of patients at higher risk of early second attack and conversion, and thus those patients who may benefit from early treatment.¹³ The DMD's IFN β -1a, IFN β -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.¹⁴⁻¹⁷

MRI examination and CSF analysis are recommended investigations of CIS as they increase the specificity of diagnosis.^{12,18,19} Baseline cerebral MRI parameters are well established as predictors of conversion to CDMS.^{1,4,20} The presence of OCB on CSF examination supports the diagnosis of MS¹³ and has previously been demonstrated to increase the risk of a second attack in patients with CIS, independent of cerebral MRI parameters,²¹⁻²³ and assists the clinician in differentiating multiple sclerosis from alternate diagnoses, such as infection or vasculitis.^{24,25} 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.²⁶ In further confirmatory work, a recent prospective cohort study exploring a comparable suite of clinical and demographic factors at CIS to our study identified MRI lesion number and the presence of CSF oligoclonal bands as high- and medium-impact prognostic factors, respectively.²⁷

The objective of the current study was to utilise the prospectively documented CIS cohort of over 3000 patients (MSBasis substudy) 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 individualized risk of conversion to CDMS at 12 months.

MATERIALS & METHODS

MSBase Registry

The MSBase Registry is an international online database accumulator that was established in 2004 and collects disease related information from consenting patients attending Multiple Sclerosis (MS) clinics. The registry is a collaborative research group that prospectively collects a defined minimum dataset from MS patient treated at specialised MS centers, using an internet-based, physician owned and operated system www.msbase.org.²⁸ Each center enters patient data in either the offline iMed© local electronic database during routine clinic visits and intermittently uploads codified datasets to the MSBase server, or uses a codified MSBase online database. The minimum dataset consists of date of MS onset, Neurostatus Expanded Disability Status Score (EDSS) relapse characteristics, cerebral MRI lesion classification (and other investigations and diagnostic criteria used. Records are classified as complete and eligible for analyses if they meet a minimum required set of data. Quality of the EDSS assessment was assured by the requirement of online Neurostatus certification at each of the participating centres. 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.

MSBASIS

The MSBase Incident Study (MSBASIS) is a sub-study of the MSBase registry. Commencing on the 18th 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 clinically isolated syndrome (first demyelinating event) with symptom onset less than 12 months from the enrolment date. As of the 2nd April 2014, the date of data extract and compilation, the study had enrolled 4313 patients from 50 clinics across 22 countries contributing 37,569 clinic visit observation points.

Inclusions

MSBASIS requires a minimum entry dataset at each clinic visit observation point consisting of the visit date, Neurostatus EDSS, Kurtze functional systems score (KFS), onset date of prospectively observed relapses, glucocorticoid therapy for relapses and, where applicable, initiation and discontinuation dates for MS disease-modifying therapy. Patients were eligible for this analysis if the first complete visit at the participating centre occurred within 12 months of the CIS onset date. In addition, the first cerebral magnetic resonance imaging (MRI) scan classification for each patient, using Barkhof-Tintore criteria for lesion dissemination in space^{1,4,29,30}, which had to be performed within 12 months of CIS onset, was required. Following the initial visit, minimum annual follow-up was required, although details of all visits within any given year of follow-up were recorded and used in this analysis. Patients with primary progressive MS (PPMS) were excluded. 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 & definitions

The primary outcome of this analysis was time to first relapse following onset of clinically isolated syndrome (CIS). Clinically definite MS (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 criteria.³¹ Follow up time was defined as the time that lapsed between the date of CIS onset (baseline) as recorded by the participating clinician 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-IFN β -1a, SC-IFN β -1a, IFN β -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, were analysed as both a continuous variable (number of T1 gadolinium enhancing and T2 hyperintensive lesions) and a categorical variable (zero compared with 1+ lesions).

Statistical analyses

We analysed, as a priori predictors, sex, country, age at CIS onset, DMD exposure, medication possession ratio, identity of first DMD product initiated on follow-up, baseline MRI (both cerebral and spinal) and the presence of OCB in baseline CSF examination for association with time to first relapse following CIS. A baseline spinal MRI was reported for 1539 (46.7%) of the sample and test results for OCB in a baseline CSF examination were reported for 1657 (50.3%). Both baseline spinal MRI and OCB status were not required for inclusion. 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. First post-CIS relapse incidence rates were expressed as counts of relapse events per 100 person-years of follow-up. 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. Patients were either censored at the date of first post-CIS relapse or, where no relapse event was observed, the date of their last prospectively recorded study visit. All predictors were included in the adjusted model except where two or more related explanatory variables demonstrated significant co-linearity or overlap (e.g. binary exposure to DMD during following up and the identity of the first DMD product initiated during follow-up). In these instances, the included explanatory factor was selected based on both the predictor's performance on unadjusted modelling and clinical relevance and interpretability. Interactions between predictor variables in the adjusted model were tested. Hazard proportionality was assessed through analysis of scaled Schoenfeld residuals. A subgroup analysis was performed disaggregating these 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 sub-group specific effects. 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 predictive nomogram for conversion to CDMS using the method described by Katten et al.³²⁻³⁴ The nomogram was internally validated via derivation of the concordance index, supplemented with nomogram calibration. The concordance index captures the probability that a MS patient drawn randomly from our dataset who was known to convert to CDMS *before* another randomly drawn patient, 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) 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. Seven hundred and sixty one (23.1%) of patients were followed-up in Italian clinics, 410 (12.4%) Canadian, 380 (11.5%) Spanish, 319 (9.7%) Australian, 263 (8.0%) Turkish and 251 (7.6%) in Dutch clinics. 910 (27.6%) of patients initiated a first DMD during follow-up, of which 389 (42.7% of total initiates) commenced IM-IFN β -1a, 308 (33.8%) SC-IFN β -1a, 167 (18.4%) IFN β -1b and 125 (13.7%) glatiramer acetate. Mean (SD) medication possession ratio across the entire 3296 patients was 0.18 DMD days/follow up days (0.33).

Of the 3296 eligible patients, 1953 (59.3%) recorded a first post-CIS relapse event during follow-up at an incidence rate of 36.31 first post-CIS relapses per 100 person-years of follow-up (95% CI 34.73, 37.96). 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% CI 15.6, 18.8) compared with 53.8 per 100 person-years in the non-exposed group.

Predictors of conversion to CDMS

Older age at CIS onset was associated with a 10% reduction in the risk of conversion (5-year units, HR 0.90, 95% CI 0.88, 0.92; *Table 2*). Sex had no effect in the adjusted model including both baseline and time-varying factors. 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*) whilst 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). As a sensitivity analysis, we further modelled MPR as a dichotomous predictor variable cut at a range of percentage points (for example MPR $\geq$ 50% compared with $<$ 50%). Increasing the percentage of follow-up time on DMD treatment from $\geq$ 25% (uHR 0.37, 95% CI 0.33, 0.41, $p < 0.001$) to $\geq$ 90% (uHR 0.28, 95% CI 0.22, 0.36, $p < 0.001$) was associated with a less than 10% difference in the relapse rate reduction. In separate modelling, all individual DMD products first initiated during follow-up were associated with relapse reduction in comparison to untreated patients, with IM-IFN β -1a, glatiramer acetate, SC-IFN β -1a & IFN β -1b demonstrating 65%, 63%, 60% and 58% rate reductions in time to first relapse, respectively.

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 cerebral 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) whilst 3 or more periventricular lesions were associated with 1.68 times the rate of relapse compared with zero lesions. At least 1 infratentorial and at least 1 juxtacortical lesion on cerebral 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 zero lesions. A greater number of T2 hyperintensive lesions, although associated on unadjusted modelling, did not remain predictive on adjusted modelling. Spinal T2 lesions were excluded from the adjusted modelling secondary to collinearity with the presence of OCB – meaning that both predictors explained a significantly similar amount of variation in the time to second attack and were too highly correlated to be included as independent predictors in the final, adjusted model. As an additional sensitivity analysis we re-analysed the adjusted model substituting spinal T2 lesions for the presence of OCB predictor (*Supplementary table 1*). The resultant adjusted model was comparable to the model including oligoclonal bands with no change in the pattern of significant predictors and only marginal shifts in the reported hazards, further confirming that both the presence of T2 lesions on spinal MRI and the presence of OCB in CSF perform similarly and interchangeably as predictors of time to second attack.

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 2*). Unlike the primary model, T1 Gd+ lesions were no longer associated with conversion whilst female sex now correlated with an increased rate of conversion (aHR 1.12, 95% CI 1.01, 1.23). Using the significant independent baseline correlates of conversion identified in this adjusted Cox model, we derived a series of predictive nomograms to predict 12 month conversion (*Figures 2*). The degree of contribution of each independent explanatory variable to the 12-month conversion nomogram points were, in descending order: EDSS at CIS, age, first symptom neuroanatomical location, periventricular lesions, the presence of oligoclonal bands in CSF, 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

Sensitivity analysis

As a sensitivity analysis, we re-derived the model incorporating both baseline and time-varying factors to investigate how these predictor variables performed within the first 12 months following CIS only (*Table 2*). For most predictors, the magnitude of both the hazard ratio point estimates and associated confidence intervals remained largely consistent with that observed in the primary analysis model. The notable exception to this was medication possession ratio, with every 1 unit increase in MPR associating with an 86% reduction in the rate of 12 month conversion (HR 0.14, 95% CI 0.08, 0.25) compared with the smaller 65% reduction observed in the primary model. To further investigate whether these associations varied by particular time intervals within follow-up, we repeated the analysis censoring the adjusted models at 6, 18 and 24 months respectively (*Supplementary Table 2*). Older age at CIS onset remained consistently predictive regardless of the censor points employed with progressively larger effect sizes (i.e. greater relapse rate reductions) observed as the models progressed in time from the first 6 months only model through the 12, 18 and 24 month models. A similar effect was observed with MPR, with the reduction in relapse rate associated with a 1 unit increase in MPR increasing from 64% in the 6-month censored model (HR 0.36, 95% CI 0.06, 0.068) up to an 81% reduction in the 24-month censored model (HR 0.19, 95% CI 0.12, 0.30). Conversely the opposite trend - progressively *smaller* effects over time - was observed in the association between the first relapse outcome and the proportion of patients who reported exposure to DMD during the follow-up period under consideration. The reduction in the rate of first post-CIS relapse decreased from 83% in the 6-month censored model (HR 0.17, 95% CI 0.09, 0.33) through to 32% in the 24-month censored model (HR 0.68, 95% CI 0.52, 0.90). Cerebral MRI lesion count and distribution metrics remained stable across the four alternate time-censored models

whilst OCB on baseline CSF, although initially not associated in the 6-month censored model, became significant associated as follow-up time accumulated in the 18-month and 24-month censored models. Although limited to the unadjusted modelling due to co-linearity with OCB, increasing T2 lesions on spinal MRI was consistently associated with increased risk of second attack regardless of the censor points used.

A subgroup analysis of patients who reported 1) DMD exposure during follow-up or 2) remained untreated during follow-up showed differences in the both the pattern of the predictors and the magnitude of their associations (*Table 3*). 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 speaking, larger and more significant in the non-DMD exposed subgroup. By extending the model to test formally for an interaction between DMD exposure and MRI metric we observed a significant difference in the association between MRI metrics and second attack rate by DMD exposure group (all $p < 0.001$), with the exception of T2 hyperintensive lesions ($p = 0.438$). Neuroanatomical location of first symptoms and the presence of oligoclonal bands both remained predictive within the untreated group but fell out of significance in the DMD exposed group.

DISCUSSION

This multinational, prospective observational 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 increased baseline EDSS scores were clinical predictors of shorter time to relapse, whereas sex had no independent effect. Each of the Barkhof-Tintore criteria (3+ periventricular lesions, 1+ infratentorial lesions, 1+ juxtacortical lesions) retained

independent predictive power. Total cerebral T2 lesion number was not predictive of time to relapse attack, whereas the presence of 1+ cerebral Gd-enhancing lesion was predictive. Importantly, presence of oligoclonal bands was an independent predictor of shorter time to relapse, but this was highly collinear with the presence of 1+ spinal cord lesions. During follow-up, DMD exposure was strongly protective against relapse, consistent with results of several phase three trials. These results corroborate and extend prior, albeit smaller, studies observing similar sets of predictors of conversion probability.^{12,23,35-37} The recent study of Tintore, based on longitudinal follow-up in a single centre on 1015 patients, reports younger age at onset, presence of oligoclonal band and more than 10 brain MRI lesions as prognostic factors for developing MS.²⁷ 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.

Identification of patient, disease and examination characteristics associated with higher probability of second attack in clinical practice enables the clinician to flag subsets of patients that could benefit from closer, 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 cerebral lesion location is preferable to lesion number in calculating risk rate of second attack, as demonstrated by Swanton et al, (2007), and incorporated into the 2010 revisions of the McDonald criteria for diagnosis of MS.^{30,36}

Across both the primary analysis and the various companion subgroup and sensitivity 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, with only modest reductions in relapse rate observed when

the medication possession ratio was increased from a minimum of 25% of a patient's follow-up to a minimum of 90%. This effect is time dependent, with greatest effect during the first 6 months after CIS onset. Taken together, 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 cerebral 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 IFN β -1a in first clinical demyelinating event patients which observed that either treatment delayed subsequent clinical relapse post-CIS, regardless of the dosing regimen used.³⁸

The associations demonstrated by this study were generally stronger, both in terms of magnitude and level of significance, in the subgroup who recorded no exposure to DMD during the follow-up period. Baseline MRI parameters and CSF examination, which in themselves may have in part at least informed the original decision by the clinician to commence treatment prior to observation of a first post-CIS relapse, were markedly less associated when modelling was limited to the DMD exposed sub-group only, particularly when compared to the equivalent associations in the non-exposed subgroup. This further supports consideration of early DMD initiation post-CIS in the clinical setting as a means of reducing the risk of post-CIS relapse events imparted by the other risk factors described by our analysis. It is worth noting, however, that the exposure group (438 relapse events from 910 patients) was smaller than the non-exposure group (1515 relapse events from 2386 patients) thus the exposure subgroup modelling, although based on a large total of 438 observed second attack events, is comparatively under-powered, at least relative to the non-exposure subgroup.

Trialling our model over a series of successively longer censor points suggests the relationship between some of our explanatory variables and the second attack outcome are not necessarily constant over time. In fact, the association between the proportion of the modelled sample exposed to DMD and a subsequent reduction in relapse risk was greatest within the first 6 months of follow-up, decreasing in magnitude with increasing time from baseline, suggesting the greatest impact of therapy, in terms of minimising the risk of second attack, occurs in the first 6 months following CIS onset. Stratifying the patient population by age, MRI and CSF examination could further permit better identification of cohorts with maximal benefit from early treatment intervention.

The high correlation between the presence of a T2 hyperintense lesion 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 cerebral MRI in patients with CIS has been correlated with a higher probability of finding OCB in concurrently sampled CSF,^{21,24} 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 hypothesize that there is a biological explanation- either OCB's (i.e. oligoclonal antibodies) could be produced preferentially in or near spinal lesions, or OCB's could be causally involved in the generation of spinal lesions.

Graphically representing the results of the adjusted model as a 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 and higher EDSS at CIS dominated the nomogram in terms relative contribution to total points and subsequent conversion probability, consistent with prior literature detailing risk factors for conversion, across all conversion risk time periods considered. Exerting a comparatively moderate influence on

conversion probability was neuroanatomical location of first symptoms whilst baseline MRI lesions, OCB and female sex demonstrated smaller influences. The advantage of a nomogram approach over an adjusted regression model is that, whilst the latter returns estimates of the average effects across a population, the nomogram permits individualised predictions to be made, which may be useful in the context of MS patient management, but could also inform future revisions of diagnostic criteria, which are typically based on predictors of time to clinical relapse. Whilst our own internal validation suggested good performance (concordance index ranging from 0.76 to 0.85), external validation through the application of the nomogram to a separate MS dataset or population is required to confirm the generalisability of the nomogram.

Conclusions

This large post-CIS follow-up study comprehensively describes the independent predictive effect of demographic, clinical, radiological and CSF predictors of time to clinically definite MS. Our results confirm and extend those of many prior studies and validates 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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Table titles and legends

Table 1 – Demography, disease, treatment and examination characteristics

EDSS = Expanded Disability Status Scale, CIS = clinically isolated syndrome, DMD = Disease-modifying drug, MRI = magnetic resonance imaging, CSF = cerebrospinal fluid

a. The medication possession ratio is the proportion of follow-up time spent treated with a disease-modifying drug

b. 1539 (46.7%) of the sample recorded a spinal MRI at baseline

Table 2 – Predictors of first post-CIS relapse

Legend for table 2

EDSS = Expanded Disability Status Scale, CIS = clinically isolated syndrome, DMD = Disease-modifying drug, MRI = magnetic resonance imaging, CSF = cerebrospinal fluid, uHR = unadjusted Hazard Ratio, aHR = adjusted Hazard ratio

a. Adjusted for country

b. Hazard proportionality test: $p=0.8225$

c. Hazard proportionality test: $p=0.7928$

d. Hazard proportionality test: $p=0.6952$

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

EDSS = Expanded Disability Status Scale, CIS = clinically isolated syndrome, DMD = Disease-modifying drug, MRI = magnetic resonance imaging, CSF = cerebrospinal fluid, aHR = adjusted Hazard ratio

a. Adjusted for country

b. Hazard proportionality test: $p=0.3688$

c. Hazard proportionality test: $p=0.4555$

d. Test of interaction: $p=0.002$

Supplementary Table 1 – Predictors of first post-CIS relapse – alternate model substituting T2 lesions on spinal MRI for oligoclonal bands on CSF examination

EDSS = Expanded Disability Status Scale, CIS = clinically isolated syndrome, DMD = Disease-modifying drug, MRI = magnetic resonance imaging, CSF = cerebrospinal fluid, aHR = adjusted Hazard ratio

a. Adjusted for country

b. Hazard proportionality test: $p=0.7819$

Supplementary Table 2 - Predictors of first post-CIS relapse –for a range of censor points

EDSS = Expanded Disability Status Scale, CIS = clinically isolated syndrome, DMD = Disease-modifying drug, MRI = magnetic resonance imaging, CSF = cerebrospinal fluid, aHR = adjusted Hazard ratio

a. Adjusted for country

b. Hazard proportionality test: $p=0.2496$

c. Hazard proportionality test: $p=0.3155$

d. Hazard proportionality test: $p=0.4901$

Figure title and legend

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

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.

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 gray diagonal line.

Supplementary Figures 1-5 – Nomograms for 6-month, 2-, 3-, 4- and 5-year conversion

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