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ORIGINAL COMMUNICATION

Predicting onset of secondary-progressive multiple sclerosis using genetic and non-genetic factors

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Abstract

Background Predicting the transition from relapsing–remitting (RR) to secondary-progressive (SP) multiple sclerosis (MS) from early in the disease course is challenging.

Objective To construct prediction models for SPMS using sociodemographic and self-reported clinical measures that would be available at/near MS onset, with specific considerations for MS genetic risk factors.

Methods We conducted a retrospective cross-sectional study based on 1295 white, non-Hispanic individuals. Cox proportional hazard prediction models were generated for three censored SPMS outcomes (ever transitioning, transitioning within 10 years, and transitioning within 20 years) using sociodemographic, comorbid health information, symptomatology, and other measures of early disease activity. *HLADRB1*15:01* and *HLA-A*02:01*, as well as a genetic risk score, were iteratively considered in each model. We also explored the relationships for all 200 MS risk variants located outside the major histocompatibility complex. Nomograms were generated for the final prediction models.

Results An older age of MS onset and being male predicted a short latency to SPMS, while a longer interval between the first two relapses predicted a much longer latency. Comorbid conditions and onset symptomatology variably predicted the risk for transitioning to SPMS for each censored outcome. The most notable observation was that *HLA-A*02:01*, which confers decreased risk for MS, also contributed to decreased hazards for SPMS.

Conclusions These results have the potential to advance prognostication for a person with MS using information available at or near onset, potentially improving care and quality of life for those who live with MS.

Keywords Secondary progressive · Risk prediction · Multiple sclerosis · Prognostics

Background

Multiple sclerosis (MS) is a neurodegenerative, autoimmune disease of the central nervous system affecting near 900,000 Americans [1, 2]. The MS disease course is highly variable, and most affected individuals will variably accrue neurological disability across multiple functional domains [3]. Approximately 85% of persons with MS (PwMS) present with relapsing–remitting (RR) MS, and experience cycles of symptom exacerbation and remission that can last for weeks or months for a time, with modest disability accrual upon relapse [4]. The majority of persons with RRMS will transition to secondary-progressive (SP) MS, a more debilitating form of the disease, where in lieu of relapses PwMS steadily accrue of neurological disability, as well as impairments across an increasing number of functional domains [5].

Anticipating the transition to SPMS, and therefore identifying factors conferring risk for transition, has substantive value as it would grant PwMS the opportunity to plan for possible changes in their independence and care, which would contribute to optimizing long-term quality of life. This is particularly salient considering most federally approved disease-modifying therapies modulate RR disease activity driven by inflammation and offer modest benefit to those with SPMS [6, 7]. To date, a few factors have

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been shown to consistently influence the transition from RR to SPMS across several studies, and they include being male and developing MS later in life [8–13]. Furthermore, prior studies have not investigated the potential impact of comorbid health conditions nor have they comprehensively explored the influence of MS genetic risk factors on the risk for transitioning to SPMS.

We conducted a retrospective cross-sectional study based on 1,295 non-Hispanic, white individuals who had RRMS at onset and whose data were available through an open-access repository from the United States. We constructed time-to-event prediction models for three censored SPMS outcomes (ever transitioning, transitioning within 10 years, and transitioning within 20 years) using sociodemographic and self-reported clinical measures that would be available at/near the onset of MS, with specific considerations for MS genetic risk factors, including a genetic risk score (GRS), *HLA-DRB1*15:01,* and *HLA-A*02:01*. These models are amongst the first to investigate the relationships between MS genetic risk factors and self-reported comorbid health and risk of SPMS.

Methods

Study population

The study population was derived from participants in the Accelerated Cure Project for MS (ACP), a repository of biological samples and epidemiological data for persons with demyelinating diseases, including MS. ACP recruited PwMS from the communities surrounding ten MS specialty clinics across the United States. All participants gave informed consent and completed an extensive survey administered by trained study staff or a neurologist. All non-genetic data used in this study were based on the participant-reported responses to this survey instrument. A diagnosis of MS was confirmed by a neurologist using the standard diagnostic criteria at the time of enrollment [14, 15]. Inclusion and exclusion criteria have been previously described [16]. For the current study, we restricted to ACP participants with an age of MS onset of ≥ 18 years, who had RRMS at onset, and were non-Hispanic white ($N = 1320$). There were multiple PwMS from several extended families, we randomly included one participant from each family to ensure independence amongst observations. The final sample consisted of 1295 PwMS.

Transition to SPMS

Time to SPMS was the difference between participant-reported age of onset of RRMS (defined as age of "first symptom or exacerbation") and age of onset of SPMS. 15.3% of study subjects had transitioned to SPMS at the time of the interview ($N = 197$; Table 1). This information was used to construct three censored outcomes for SPMS: ever transitioning, transitioning within 10 years, and transitioning within 20 years.

Predictors

Predictors of interests included sociodemographic and participant-reported clinical variables. Sociodemographic variables included age of MS onset, sex, years of education, a history of infectious mononucleosis prior MS onset, and whether the participant smoked tobacco products within 5 years prior to MS onset. Clinical variables included binary variables that captured several comorbid conditions existing prior to the onset of MS. We included individual variables for obesity, high cholesterol, high blood pressure, and type II diabetes, and variables for specific categories for other comorbid diseases, including cancer, neurological disease, physical disease, psychological disorders, and other autoimmune diseases (see Supplementary Methods). Clinical variables relevant to MS included 13 binary variables capturing impaired functional domains at onset (as previously described [17]), and categorical variables for time to second relapse (TT2R; ≤ 1, 2–5 and ≥ 6 years) and the number of relapses experienced in the first 2 years after MS onset (NR2Y; ≤ 1, 2–3, and ≥ 4 relapses). Predictors with ≤ 10% missingness were imputed using random forest imputation (package MissForest, R v3.5). NR2Y had > 10% missingness; therefore, it was recoded as an indicator variable with a category for missing values to retain observations.

Finally, genotypic information for MS risk variants was available for a subset of the study population. Genetic data for 1,036 study participants were available as a part of an international effort to identify susceptibility variants by the International MS Genetics Consortium (Supplementary Methods) [18]. These samples were genotyped using the Illumina iSelect platform consisting of approximately 200,000 variants from the Illumina Exome Core content and 90,000 custom-selected variants prioritized from earlier MS genetic studies [18]. Genetic data quality control, including the removal of genetic outliers and cryptically related samples for this sample has been outlined previously [17]. *HLA-A*02:01* and *HLA-DRB1*15:01* allele counts were determined by the tagging SNPs rs2975033T and rs3135388A, respectively. Also available were 200 autosomal, non-MHC, MS risk variants [18], whose risk alleles were summed to create a genetic risk score (GRS) that was normally distributed in this study population (Supplementary Fig. 1) [17]. Genotypic data for *HLA-A*02:01* and *HLA-DRB1*15:01* were available for an additional 130 participants who were genotyped on the Illumina MEGAEx BeadChip and met standard quality control criteria (Supplementary Methods).

Table 1 Study population characteristics by disease state (quantitative variables are described by medians and interquartile ranges; categorical and binary variables are described by counts and percentages)

Characteristic	Variable	All ($N=1295$)	RRMS ($N=1098$)	SPMS ($N=197$)
Demographics	Age at MS onset	32 (25, 39)	32 (26, 39)	30 (25, 39)
	Age at SP onset	–	–	49 (42, 54)
	Male	283 (21.9%)	220 (20.0%)	63 (32.0%)
	Smoker within 5 years of onset	441 (34.1%)	364 (33.2%)	77 (39.1%)
	History of infectious mononucleosis	386 (29.8%)	333 (30.3%)	53 (26.9%)
	Years of education	16 (14, 18)	16 (14, 18)	16 (14, 18)
Disease-specific	Disease duration (years)	11 (5, 19)	9 (4, 16)	22 (14, 28)
	Time to second relapse			
	0–1 years	623 (48.1%)	553 (50.4%)	70 (35.5%)
	2–5 years	412 (31.8%)	338 (30.8%)	74 (37.6%)
	≥ 6 years	260 (20.1%)	207 (18.9%)	53 (26.9%)
	Number of early relapses			
	0–1	392 (30.3%)	339 (30.9%)	53 (26.9%)
	2–3	357 (27.6%)	315 (28.7%)	42 (21.3%)
	≥ 4	123 (9.5%)	105 (9.6%)	18 (9.1%)
	NA	423 (32.7%)	339 (30.9%)	84 (42.6%)
	Motor	603 (46.6%)	516 (47.0%)	87 (44.2%)
	Cerebellar	417 (32.2%)	355 (32.3%)	62 (31.5%)
	Spasticity	163 (12.6%)	145 (13.2%)	18 (9.1%)
	Optic nerve	361 (28.0%)	299 (27.2%)	62 (31.5%)
	Facial (motor)	134 (10.3%)	123 (11.2%)	11 (5.6%)
	Facial (sensory)	46 (3.6%)	41 (3.7%)	5 (2.5%)
	Brainstem/bulbar	398 (30.7%)	350 (31.9%)	48 (24.4%)
	Cognitive	145 (11.2%)	130 (11.8%)	15 (7.6%)
	Sexual	70 (5.4%)	62 (5.6%)	8 (4.1%)
	Bladder/bowel	150 (11.6%)	136 (12.4%)	14 (7.1%)
	Affect mood	133 (10.3%)	122 (11.1%)	11 (5.6%)
	Fatigue	349 (26.9%)	310 (28.2%)	39 (19.8%)
Comorbidities	Obesity	109 (8.4%)	102 (9.3%)	7 (3.6%)
	High cholesterol	102 (7.9%)	83 (7.6%)	19 (9.6%)
	High blood pressure	76 (5.9%)	67 (6.1%)	9 (4.6%)
	Type II diabetes	10 (0.8%)	7 (0.6%)	3 (1.5%)
	Neurological diseases	311 (24.0%)	285 (26.0%)	26 (13.2%)
	Other physical diseases	295 (22.8%)	260 (23.7%)	35 (17.8%)
	Mental disorders	219 (16.9%)	196 (17.9%)	23 (11.7%)
	Cancer	36 (2.8%)	31 (2.8%)	5 (2.5%)
	Autoimmune diseases	246 (19.0%)	220 (20.0%)	26 (13.2%)
Genetic variables	Median GRS (972)	203 (197, 209)	203 (197, 208)	204 (197, 209)
	*HLA-A*02:01* alleles			
	0	711 (54.9%)	589 (53.6%)	122 (61.9%)
	1	380 (29.3%)	331 (30.1%)	49 (24.9%)
	2	75 (5.8%)	69 (6.3%)	6 (3.0%)
	NA	129 (10.0%)	109 (9.9%)	20 (10.2%)
	*HLA-DRB1*15:01* alleles			
	0	644 (49.7%)	537 (48.9%)	107 (54.3%)
	1	487 (37.6%)	420 (38.3%)	67 (34.0%)
	2	74 (5.7%)	65 (5.9%)	9 (4.6%)
	NA	90 (6.9%)	76 (6.9%)	14 (7.1%)

Thus, genetic data for *HLA* variants were available in 90% ($N=1166$) of the study population, while the GRS was available in 75% of the study population ($N=972$).

Statistical analysis

Cox proportional hazards modeling was used to identify early predictors (measurable at or near MS onset) of risk for ever transitioning to SPMS irrespective of time, risk for transitioning within 10 years, and risk for transitioning within 20 years. Since the proportional hazards model assumes a continuous hazard function, we used the Breslow method to handle tied failures (*PHREG* procedure, SAS v15.1). We considered three censored outcomes due to the fact MS presentation varies with age of onset, and that increasing age of MS onset and disease duration confers increased SPMS risk [17, 19, 20]—thus, we hypothesized that the risk for transitioning to SPMS within specific timeframes would be influenced by similar and different combinations of predictors. Amongst the non-genetic variables there were uneven underlying correlations (Supplementary Fig. 2), therefore we employed a forward stepwise variable selection algorithm based on Akaike Information Criterion (AIC; unlike approaches based on a p value threshold for individual predictors). For each outcome, we selected the model consisting of a subset of the non-genetic predictors that minimized AIC. The primary genetic predictors of interest (*HLA-DRB1*15:01*, *HLA-A*02:01*, and the non-MHC GRS) were iteratively included in the final models, adjusting for variation in genetic ancestry. We also conducted exploratory analyses for 199 of the 200 non-MHC risk variants that had an allelic variation, similarly iteratively considering them in each of the three final non-genetic models.

The proportional hazard assumption for predictors within the final models was assessed by calculating the proportion of 1000 simulations that contain a maximum cumulative Martingale residual larger than the observed maximum cumulative residual (Supremum tests, SAS v15.1). The goodness-of-fit and variation explained were assessed for each of the final models using the Gronnesby and Borgan test (*stcoxgof* function, STATA v13.1) and a Royston's modification Nagelkerke's R^2 statistic (*str2ph* function, STATA v13.1), respectively [21]. Adjusted Kaplan–Meier curves were generated (*sts graph* function, STATAv13.1) and nomograms were constructed to visualize how the weights of the predictors in the final models could be used to predict transitioning to SPMS over the disease course, and within 10 and 20 years after MS onset (*nomocox* function, STATA v13.1) [22].

Ethics approval

This study was approved by the Case Western Reserve University Institutional Review Board (Protocol No. IRB-2016-1583).

Results

There were 1295 non-Hispanic white PwMS who contributed to these analyses (Table 1). At the time of data collection, 15.2% of subjects reported having SPMS. As expected, there was a female preponderance (78.1%) and the median age of MS onset was 32 years. Approximately 30% and 34% of subjects had a history of infectious mononucleosis or had smoked within 5 years of MS onset, respectively. The median years of education were 16.

The time-to-event models of non-genetic predictors that minimized AIC for each of the three outcomes are presented in Table 2. Increases in an age of MS onset increased the hazards for transitioning to SP irrespective of when observations were censored (HR_{Ever} 1.07, 95% confidence interval [CI] 1.06–1.09, $p<0.001$; HR_{year10} 1.06, 95% CI 1.03–1.09, $p<0.001$; HR_{year20} 1.07, 95% CI 1.05–1.09, $p<0.001$). Males also had increased hazards of transitioning to SP compared to females; the hazard was near threefold greater for converting by year 10 compared to twofold at year 20 or at any time point on average (HR_{Ever} 1.97, 95% CI 1.46–2.66, $p<0.001$; HR_{year10} 2.96, 95% CI 1.77–4.97, $p<0.001$; HR_{year20} 1.87, 95% CI 1.27–2.57, $p<0.001$; Supplementary Fig. 3). There was also a consistently decreased hazard for transitioning to SP irrespective of when observations were censored for those whose TT2R was ≥ 6 years compared to 0–1 year (HR_{Ever} 0.65, 95% CI 0.45–0.94, $p=0.021$; HR_{year10} 0.32, 95% CI 0.14–0.74, $p=0.008$; HR_{year20} 0.56, 95% CI 0.36–0.86, $p=0.010$).

Specific comorbid conditions and impaired functional domains at onset variably contributed to predicting SP risk across the models. Risk for ever transitioning to SPMS was lower amongst those reporting a neurological disorder (HR_{Ever} 0.58, 95% CI 0.38–0.88, $p=0.009$) or spasticity symptoms (HR_{Ever} 0.57, 95% CI 0.35–0.93, $p=0.024$) at MS onset. The risk for transitioning to SPMS within 10 years was threefold higher for the 2.8% of PwMS reporting a history of cancer by MS onset (HR_{year10} 3.11, 95% CI 1.20–8.10, $p=0.02$); while the hazard was decreased for those reporting brainstem/bulbar symptoms. The hazards for transitioning to SPMS within 20 years were also decreased for PwMS who reported histories of obesity and other neurological disorders. Across the time-to-event models, having a comorbid cardiovascular, physical, psychological, or other autoimmune diseases at MS onset did not contribute to predicting the transition to SPMS.

Table 2 Multivariable Cox proportional hazard effect estimates for retained non-genetic predictors per outcome

Predictor	Ever transition			Transition within 10 years			Transition within 20 years		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Age of MS onset	1.07	1.06, 1.09	< 0.001	1.06	1.03, 1.09	< 0.001	1.07	1.05, 1.09	< 0.001
Sex (M)	1.97	1.46, 2.66	< 0.001	2.96	1.77, 4.97	< 0.001	1.87	1.27, 2.57	< 0.001
Time to second relapse									
0–1 years	Ref	–	–	Ref	–	–	Ref	–	–
2–5 years	1.12	0.80, 1.55	0.518	0.71	0.40, 1.25	0.233	0.91	0.68, 1.41	0.642
≥ 6 years	0.65	0.45, 0.94	0.021	0.32	0.14, 0.74	0.008	0.56	0.36, 0.86	0.010
Obesity	NA	–	–	NA	–	–	0.36	0.11, 0.85	0.047
Neurological disorders	0.58	0.38, 0.88	0.009	NA	–	–	0.44	0.27, 0.77	0.003
Cancer	NA	–	–	3.11	1.20, 8.10	0.020	NA	–	–
Spasticity	0.57	0.35, 0.93	0.024	NA	–	–	NA	–	–
Brainstem/bulbar	NA	–	–	0.45	0.23, 0.90	0.024	NA	–	–
GRS[a]	1.01	0.99, 1.03	0.290	0.99	0.95, 1.02	0.426	1.02	0.99, 1.04	0.190
*HLA-A*02:01*[b]	0.73	0.56, 0.97	0.030	0.60	0.35, 1.04	0.067	0.56	0.39, 0.80	0.001
*HLA-DRB1*15:01*[c]	1.05	0.80, 1.38	0.736	0.84	0.51, 1.38	0.487	0.94	0.68, 1.30	0.698

Effect estimates for genetic variables are based on models including the retained non-genetic predictors for each outcome

CI confidence interval, *GRS* genetic risk score, *HR* hazard ratio

[a]GRS effect estimates and *p* values are reported for the models adjusted for all predictors in the non-genetic models ($N = 956$)

[b]*HLA-A*02:01* effect estimates and *p* values are reported for the models adjusted for all predictors in the non-genetic models ($N = 1166$)

[c]*HLA-DRB1*15:01* effect estimates and *p* values are reported for the models adjusted for all predictors in the non-genetic models ($N = 1166$)

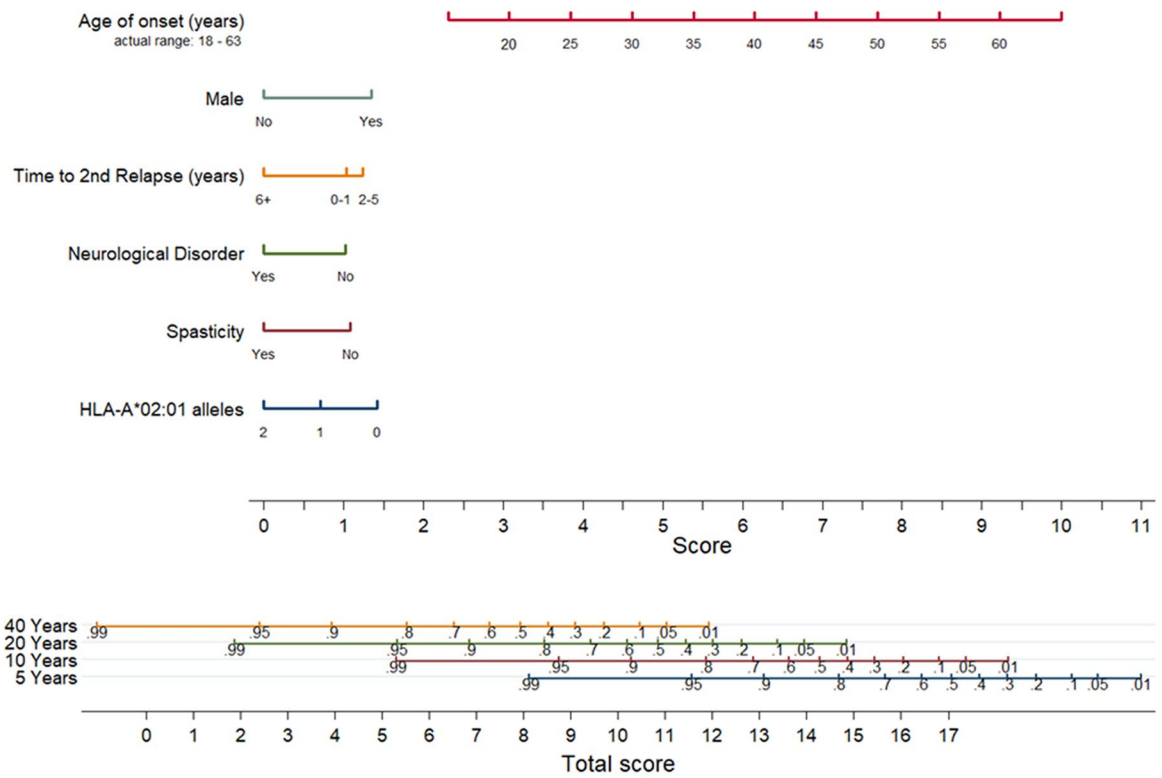
The genetic variables were iteratively considered in each of the prediction models. Interestingly, *HLA-DRB1*15:01* and the non-MHC GRS were not associated with SPMS risk; however, *HLA-A*02:01* significantly reduced the hazard of SPMS which is similar to its effect on MS susceptibility (HR_{Ever} 0.73, 95% CI 0.56–0.97, $p = 0.030$; HR_{year10} 0.60, 95% CI 0.35–1.04, $p = 0.067$; HR_{year20} 0.56, 95% CI 0.39–0.80, $p = 0.001$). Of the 199 autosomal, non-MHC risk variants explored, only one risk variant (rs6072343; 1.3 Kb upstream of *LPIN3*) was associated with increased hazards of SPMS across the three models (HR range 1.5–2.0; Supplementary Table 1); however, results were not significant after adjusting for multiple testing.

The three final models of non-genetic predictors with and without *HLA-A*02:01* and genetic ancestry had good fit (data not shown), and all predictors in their respective models met proportional hazard assumptions (Supplementary Table 2). The variation explained by these final models was high, with the models for ever transition explaining 28–32%, transitioning within 10 years explaining 50–56%, and transitioning within 20 years explaining 34–40% (Supplementary Table 2). We, therefore, used these models to generate nomograms that could be used to predict the probability of transitioning to SPMS at various points in time (Fig. 1; approximate nomogram points assigned to each predictor per model is presented in Supplementary Table 3). Adjusted Kaplan–Meier survival curves for *HLA-A*02:01* allele counts based on the ever transitioning to SPMS model are presented in Fig. 2.

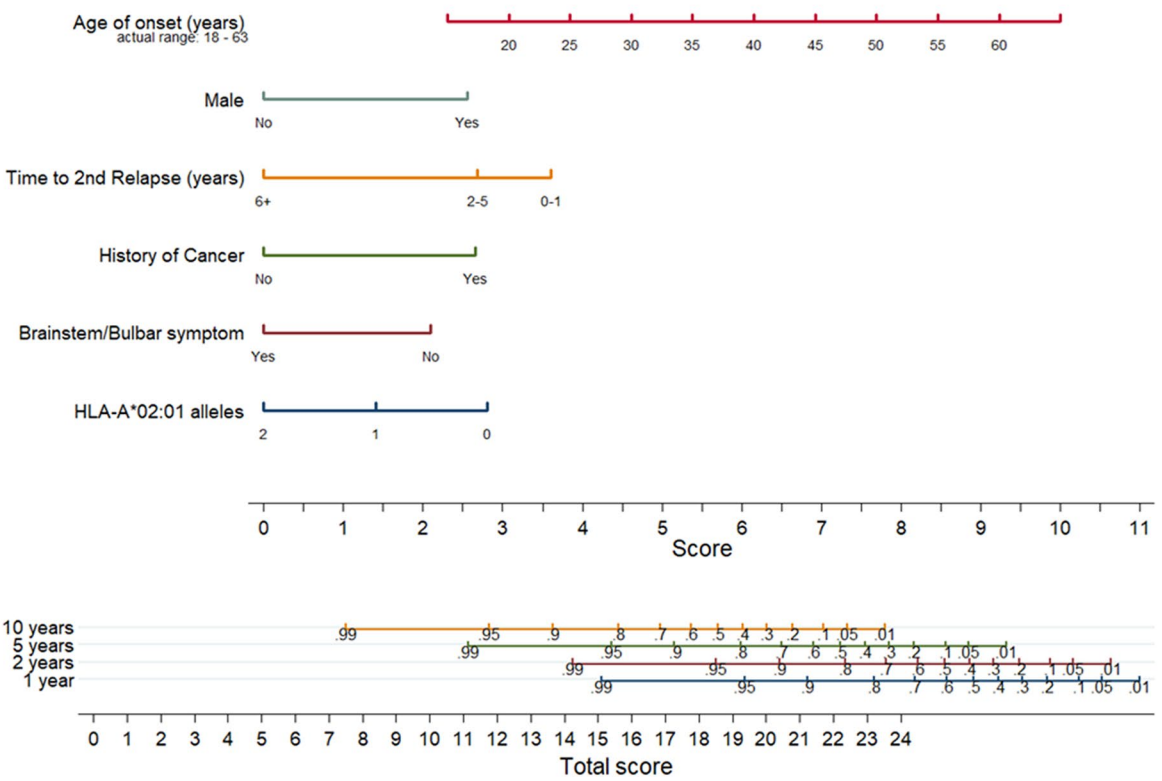
Discussion

We investigated three censored SPMS outcomes (ever transitioning, transitioning within 10 years, and transitioning within 20 years) and constructed time-to-event prediction models using non-genetic variables measurable at/near the onset of MS, with specific considerations for MS genetic risk factors, including a non-MHC GRS, *HLA-DRB1*15:01,* and *HLA-A*02:01*. We also conducted exploratory analyses investigating 199 of 200 non-MHC risk variants. Collectively, these models are amongst the first to comprehensively investigate the relationships between MS genetic risk factors and the risk of SPMS. We observed a consistently increased hazard for SPMS for an older age of MS onset and male sex, and decreased hazard for a longer interval between first and second relapse (TT2R), while comorbid conditions and onset symptomatology variably contributed to the prediction models. As for genetic factors, *HLA-A*02:01* which confers

A Model predicting ever transitioning



B Model predicting transition within 10 years



◀ **Fig. 1** Nomograms illustrating the probability of surviving the transition to SPMS based on baseline predictors for the three outcome models presented in Table 2 that also included *HLA-A*02:01*. The points assigned to each predictor is determined by their value in relation to the scoreline. Points are then added across predictors to generate the total score which is compared to the probability of surviving the transitioning to SPMS (thus, the probability of not transitioning). For example, in Panel B, the total points for a PwMS with an onset age of 45 years (7 points), who is male (2.5 points), who experienced his second relapse within 1 year (~2.6 points), who did not have a history of cancer (0 points), who presented with brainstem/bulbar symptoms at onset (0 points), and who had no copies of *HLA-A*02:01* (~2.8 points) would be 14.9 points; therefore, the probability of not transitioning to SPMS in year 1 is 99%, year 2 is ~98%, in year 5 is ~96%, and in year 10 is ~83%

a decreased risk for MS also contributed to a decreased hazard for SPMS.

Sociodemographic factors

Age of RRMS onset was a significant predictor of the transition to SPMS, with a younger age of onset associated with a longer latency to SPMS—consistent with multiple survival analyses of at least 150 SPMS cases conducted in the last 2 decades [8, 9, 12, 19, 23]. Age of onset is also a strong predictor of other aspects of the MS phenotype, including increased relapse activity, TT2R, and reaching disability milestones at a younger age [17, 23–27]. Only a few studies have sought to characterize factors that contribute to variation in the age of onset of MS, which includes older onset for males and those who report a history of obesity [17, 28]. There is also strong evidence that the genetic risk component for MS, specifically *HLA-DRB1*15:01* and the non-MHC GRS, is associated with an earlier onset age [17]. This latter observation is interesting, considering that these genetic factors were not associated with SPMS risk in the current analyses.

We observed that males with MS had a shorter latency to SPMS, which is consistent with several prior studies [8, 9, 12, 29, 30]; however, there have also been null findings [19]. Prior studies have reported a 25–50% increased hazard for SPMS amongst males compared to females from adjusted survival regression models [12, 30, 31]. Our HR for risk of SPMS across the time period was twofold greater for males, which is greater than the prior effect estimates generated for Canadian, European and international (< 4% were from the US) study populations; interestingly, there is some evidence that disability may vary across continental populations which may explain a portion of this difference [32]. We also observed that the hazards for transitioning to SPMS within 10 years were threefold greater for males—this finding emphasizes the importance of modeling distinct censored outcomes, which prior study has not done. Thus, even though the proportional hazard assumptions were not violated for any model, the risk for SPMS in males is elevated for the earlier transition.

Other demographic variables were not retained in the final models, including being a smoker within 5 years of onset, a history of infectious mononucleosis, and years of education. Smoking, measured as 'ever versus never' or 'current, former, or never', has been shown to contribute to disability accrual in PwMS [33–35]; however, the relationship with risk for SPMS is not definitive. A meta-analysis of four studies suggest that there may be an association for 'ever versus never' and SPMS risk (risk ratio = 1.88, 95% CI: 0.98, 3.61), but there was significant heterogeneity between studies [36]. Being a smoker confers increased risk for MS, but risk diminishes after 5–10 years after quitting [37], and we, therefore, considered an analogous variable, which has been shown to also influence MS presentation near onset [17]. No other study of MS progression has considered this operational definition of smoking.

Variation in MS presentation near onset

Several studies (including at least 150 SPMS cases conducted within the last 2 decades) have investigated the predictive potential of various measures of the presentation of MS near onset and subsequent transition to SPMS, including early relapse activity, symptom burden, impaired functional domains, disability measures, radiological observations, and TT2R [8, 9, 12, 19, 30, 31, 38, 39]. Amongst the studies that focused on evaluating multivariable models for ever transitioning to SPMS, many of the promising results await independent replication (i.e., rapid worsening measured by annualized disability trajectory [19]). The only predictor with consistent associations in two prior studies, and now our own, was TT2R, where a longer interval between the first two relapses was predictive of a longer SPMS latency [30, 38]. We also showed that TT2R was even more predictive (smaller HR) of transitioning to SP within 10 years. Considering TT2R strong effect on SPMS, it has the potential to be an informative prognostication measure, since it can be readily obtained early in the disease course.

MS symptomatology at/near onset has also been investigated across several studies; however, no specific impairment pattern has demonstrated consistent predictive associations—however, this may be due to the fact that different symptom definitions have been investigated [8, 9, 12, 19, 30]. We found that spasticity and brainstem/bulbar symptoms at MS onset were associated with longer latency to SPMS over the disease course and within 10 years, respectively. Spasticity has not been investigated in other studies, while brainstem alone or brainstem/cerebellar impairments have not been associated with ever transitioning to SPMS [8, 12, 30]. This latter observation is consistent with our

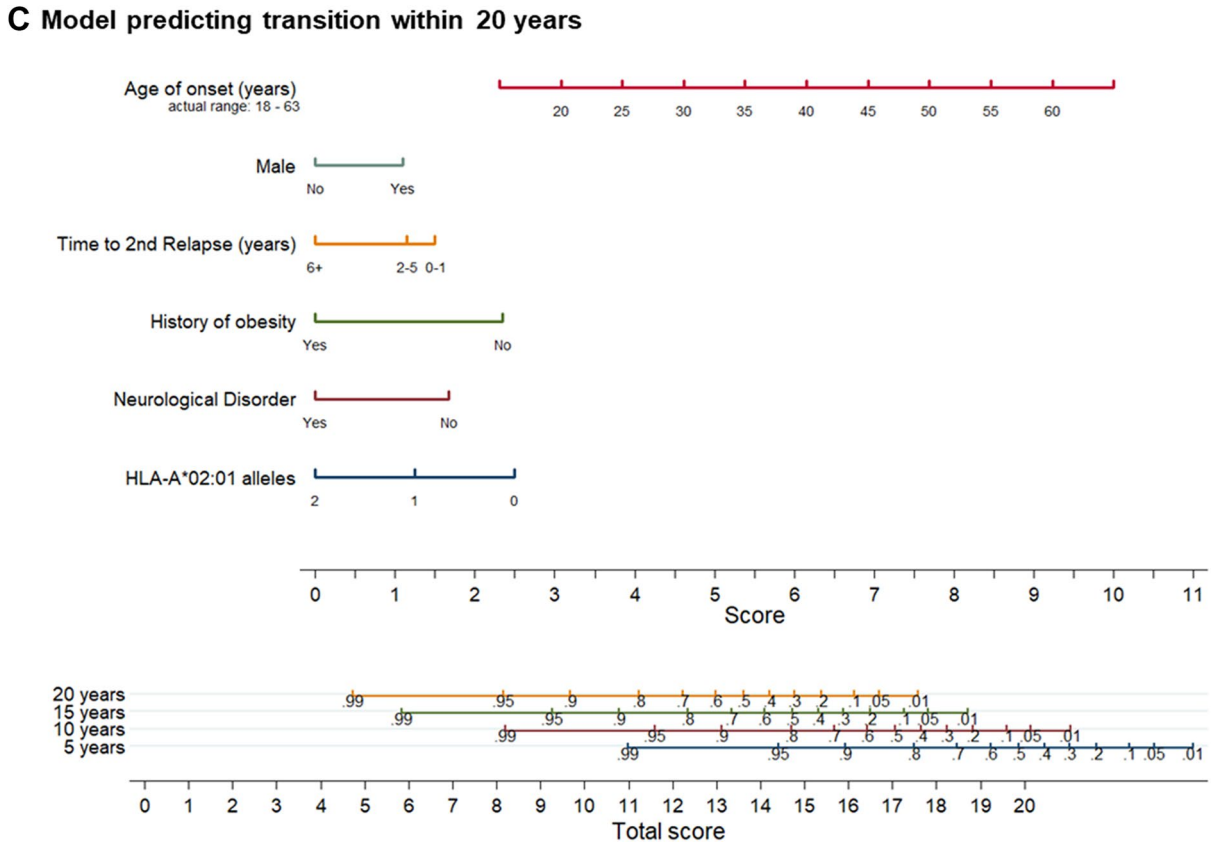


Fig. 1 (continued)

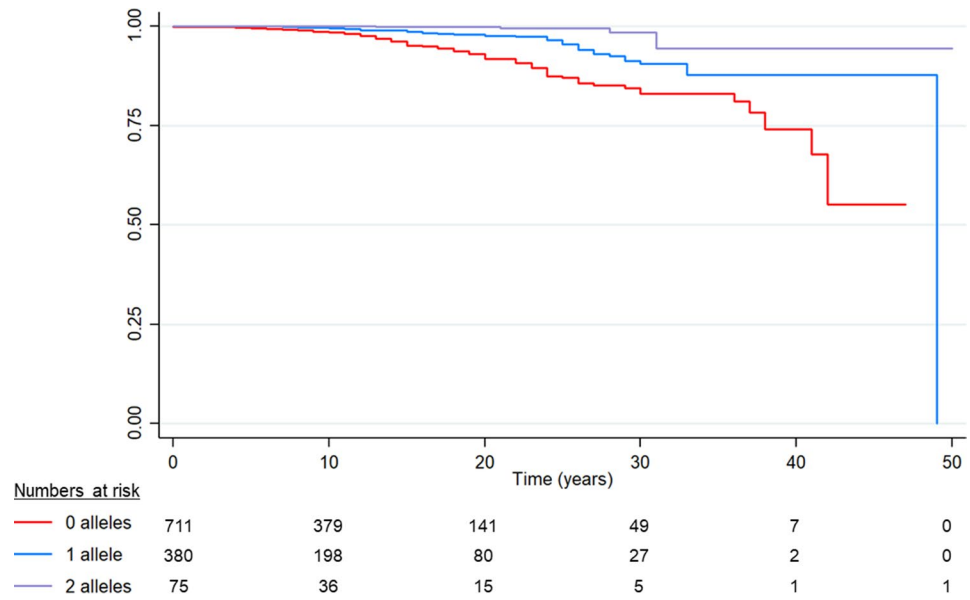


Fig. 2 Kaplan–Meier curve for *HLA-A*02:01* genotypes in the multivariable adjusted model for ever transitioning to SPMS

findings, as we only observed an association for transitioning within 10 years. However, further investigations are warranted to confirm these associations.

We do note that the number of relapses in the first 2 years was not retained in any of our models after variable selection. A post hoc χ^2 assessment of the non-missing distribution of our categorical variable between RRMS who did

and did not transition to SPMS (Table 1) was not significant (data not shown). Prior studies have reported mixed findings, with a trend toward increased SPMS risk for those with increased relapses [12, 38].

Comorbid health conditions

Comorbidity is common in PwMS; they also contribute to adverse outcomes, including the accrual of physical and psychological impairments [34, 40]. To the best of our knowledge, no prior study of SPMS has considered the potential impact of comorbidities, much less comorbidities existing at the onset of MS. We observed unexpected associations. First, cardiovascular conditions, such as hypertension, were not informative in our models. There is an increasing evidence that these traits, specifically hypertension, contribute to adverse MS outcomes [34, 41, 42]. Possible reasons for the lack of associations in the current study are that we assessed the predictive nature of comorbid conditions occurring at MS onset, and not across the life-span; thus, it is possible future studies of these traits occurring at any point in time may be associated with SPMS risk. Similarly, not informative were a history of autoimmune diseases, psychological disorders, and other physical disorders.

We did observe that those reporting having other neurological diseases had a ~ 50% decreased hazards for ever transitioning to SPMS and transitioning within 20 years. For our analyses, the comorbid neurological disease was a binary variable of having at least one of a list of neurological diseases (Supplementary Methods). Interestingly, 91.3% (284 of 311) of the PwMS with a comorbid neurological disease was due to reporting a history of migraines. Post hoc analyses demonstrated that the decreased hazards were driven by a history of migraines and not other neurological conditions (data not shown). Migraines were originally considered an uncommon symptom of MS [43]; however, the relationship with MS is currently unclear. There is evidence which suggests that migraines may be associated with increased MS risk, a greater number of impaired domains, and that it might in fact be a common comorbidity [44–47]. However, there is also a growing number of studies, showing that migraineurs may be misdiagnosed with MS, and thus we can speculate that some of our study population might have also been misdiagnosed, which would contribute to the decreased SPMS hazards [48–50]. We also observed that a history of obesity by MS onset was associated with a longer latency for SPMS. This finding may be due, in part, to sampling variability, since only 8.4% ($N = 109$) of our study population had a history of obesity and only 6.4% ($N = 7$) of these had transitioned to SPMS. Our last unexpected finding was that having had cancer by MS onset was the strongest predictor of transitioning to SPMS within 10 years (HR = 3.11). Only 2.8% ($N = 36$) PwMS had had cancer and 13.9% ($N = 5$) of these individuals had transitioned to SPMS, and thus, it is possible that sampling variation may be a factor; however, it is worth noting that both cancer and MS have substantial immune system components [51], and that PwMS may have an increased cancer risk [52].

MS genetic risk component

There have been several genetic studies of various aspects of MS phenotype, yet no robust associations have been identified, which may be largely due to variation in how the outcomes were measured. Currently, we do know that MS risk variants, specifically *HLA-DRB1*15:01* and the non-MHC GRS, are associated with earlier age of onset of MS, but not with the other measures of MS presentation (i.e., TT2R), relapse activity, or disease severity (i.e. MS Severity Scale) [53–56]. A few studies have investigated the relationships between *HLA-A*02:01* and MS outcomes, and have reported mixed findings of either null or protective effects for *HLA-A*02* on disease severity (i.e., Expanded Disease Status Scale) and radiographic outcomes [56–58]. No prior study has investigated the contribution of genetic factors on the risk for transitioning to SPMS. In our study, we observed *HLA-A*02:01* conferred a ~ 30–45% decreased risk for transitioning to SPMS, analogous to its relationship with MS risk [18]. While this novel finding warrants replication, it adds to the limited literature, suggesting that this protective genetic factor contributes to both MS risk and progression.

Study strengths and limitations

The current study has several strengths, including the fact that this study was the first to incorporate genetic and comorbidity information in evaluating risk for transitioning to SPMS. It is also one of the first studies limited to a modestly sized study population of PwMS from U.S. We also had detailed information on impaired functional domains at onset. In addition, we applied a robust variable selection approach to identify key predictors of SPMS transition, for three censored time points. This is unlike prior studies which assumed that a single model would be effective in predicting outcomes at various time points, even though there were no violations to the proportional hazards assumptions. Furthermore, we present nomograms that can be readily used to inform prognostication efforts based on information measured at/near onset.

There are several limitations to acknowledge. The first is that this study utilized a cross-sectional study design and may be vulnerable to length-sampling bias which refers to the possibility that those with a longer disease duration were more likely to have been sampled. This is a concern considering disability accrues with time, and thus, it is possible that participants with a longer disease duration may have a

less severe manifestation than their counterpart non-participants. Another limitation is that all the non-genetic variables were based on self-reported responses and, therefore, subject to recall and measurement error biases. We would assume that these biases would result in non-differential misclassification of the exposures and outcome, and bias the associations toward the null for binary measures. Considering the strong magnitude of associations observed, it is unlikely that residual confounding could explain the observed associations. Furthermore, a validation study of self-reported comorbidity in PwMS has reported moderate or better levels of agreement with medical records [59]. The last limitation relates to the generalizability of the study population beyond those of other ethnicities and racial populations.

Conclusions

We constructed time-to-event prediction models using non-genetic variables measurable at/near the onset of MS, with specific considerations for MS genetic risk factors. Our results show established effects of age of disease onset and biological sex, as well as indicators of early relapse activity, which were predictive of SPMS across time points. We notably demonstrated for the first time that key protective genetic variants for MS risk may also be protective against the transition to SPMS. Collectively, these findings and the included nomograms have the potential to advance prognostication for PwMS using information that would be available at/near onset, with the hope of improving care and quality of life for those living with MS.

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Compliance with ethical standards

Conflicts of interest The authors do not have any conflicts of interest to disclose.

References

1. Wallin MT, Culpepper WJ, Campbell JD, Nelson LM, Langer-Gould A, Marrie RA, Cutter GR, Kaye WE, Wagner L, Tremlett H, Buka SL, Dilokthornsakul P, Topol B, Chen LH, LaRocca NG, Workgroup USMSP (2019) The prevalence of MS in the United States: a population-based estimate using health claims data. Neurology 92(10):e1029–e1040. https://doi.org/10.1212/WNL.0000000000007035
2. Briggs FB, Hill E (2019) Estimating the prevalence of multiple sclerosis using 56.6 million electronic health records from the United States. Mult Scler. https://doi.org/10.1177/1352458519864681
3. Karabudak R, Dahdaleh M, Aljumah M, Alroughani R, Alsharoqi IA, AlTahan AM, Bohlega SA, Daif A, Deleu D, Amous A, Inshasi JS, Rieckmann P, Sahraian MA, Yamout BI (2015) Functional clinical outcomes in multiple sclerosis: current status and future prospects. Mult Scler Relat Disord 4(3):192–201. https://doi.org/10.1016/j.msard.2015.03.004
4. Confavreux C, Vukusic S (2014) The clinical course of multiple sclerosis. Handb Clin Neurol 122:343–369. https://doi.org/10.1016/B978-0-444-52001-2.00014-5
5. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sorensen PS, Thompson AJ, Wolinsky JS, Balcer LJ, Banwell B, Barkhof F, Bebo B Jr, Calabresi PA, Clanet M, Comi G, Fox RJ, Freedman MS, Goodman AD, Inglese M, Kappos L, Kieseier BC, Lincoln JA, Lubetzki C, Miller AE, Montalban X, O'Connor PW, Petkau J, Pozzilli C, Rudick RA, Sormani MP, Stuve O, Waubant E, Polman CH (2014) Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 83(3):278–286. https://doi.org/10.1212/WNL.0000000000000560
6. Coret F, Perez-Miralles FC, Gascon F, Alcala C, Navarre A, Bernad A, Bosca I, Escutia M, Gil-Perotin S, Casanova B (2018) Onset of secondary progressive multiple sclerosis is not influenced by current relapsing multiple sclerosis therapies. Mult Scler J Exp Transl Clin 4(2):2055217318783347. https://doi.org/10.1177/2055217318783347
7. University of California SFMSET, Cree BA, Gourraud PA, Oksenberg JR, Bevan C, Crabtree-Hartman E, Gelfand JM, Goodin DS, Graves J, Green AJ, Mowry E, Okuda DT, Pelletier D, von Budingen HC, Zamvil SS, Agrawal A, Caillier S, Ciocca C, Gomez R, Kanner R, Lincoln R, Lizee A, Qualley P, Santaniello A, Suleiman L, Bucci M, Panara V, Papinutto N, Stern WA, Zhu AH, Cutter GR, Baranzini S, Henry RG, Hauser SL (2016) Long-term evolution of multiple sclerosis disability in the treatment era. Ann Neurol 80(4):499–510. https://doi.org/10.1002/ana.24747
8. Koch M, Kingwell E, Rieckmann P, Tremlett H, Neurologists UMC (2010) The natural history of secondary progressive multiple sclerosis. J Neurol Neurosurg Psychiatry 81(9):1039–1043. https://doi.org/10.1136/jnnp.2010.208173
9. Manouchehrinia A, Zhu F, Piani-Meier D, Lange M, Silva DG, Carruthers R, Glaser A, Kingwell E, Tremlett H, Hillert J (2018) Predicting risk of secondary progression in multiple sclerosis: a nomogram. Mult Scler. https://doi.org/10.1177/1352458518783667
10. Voskuhl RR, Gold SM (2012) Sex-related factors in multiple sclerosis susceptibility and progression. Nat Rev Neurol 8(5):255–263. https://doi.org/10.1038/nrneurol.2012.43
11. Tremlett H, Yousefi M, Devonshire V, Rieckmann P, Zhao Y, Neurologists UBC (2009) Impact of multiple sclerosis relapses on progression diminishes with time. Neurology 73(20):1616–1623. https://doi.org/10.1212/WNL.0b013e3181c1e44f
12. Scalfari A, Neuhaus A, Daumer M, Muraro PA, Ebers GC (2014) Onset of secondary progressive phase and long-term evolution of multiple sclerosis. J Neurol Neurosurg Psychiatry 85(1):67–75. https://doi.org/10.1136/jnnp-2012-304333
13. Koch-Henriksen N, Sorensen PS (2010) The changing demographic pattern of multiple sclerosis epidemiology. Lancet Neurol 9(5):520–532. https://doi.org/10.1016/S1474-4422(10)70064-8
14. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Montalban X, O'Connor P, Sandberg-Wollheim M, Thompson AJ, Waubant E, Weinshenker B, Wolinsky JS (2011) Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 69(2):292–302. https://doi.org/10.1002/ana.22366
15. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, Lublin FD, Metz LM, McFarland HF, O'Connor PW,

Sandberg-Wollheim M, Thompson AJ, Weinshenker BG, Wolinsky JS (2005) Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol 58(6):840–846. https://doi.org/10.1002/ana.20703
16. Saroufim P, Zweig SA, Conway DS, Briggs FBS (2018) Cardiovascular conditions in persons with multiple sclerosis, neuromyelitis optica and transverse myelitis. Mult Scler Relat Disord 25:21–25. https://doi.org/10.1016/j.msard.2018.07.011
17. Briggs FBS, Yu JC, Davis MF, Jiangyang J, Fu S, Parrotta E, Gunzler DD, Ontaneda D (2019) Multiple sclerosis risk factors contribute to onset heterogeneity. Mult Scler Relat Disord 28:11–16. https://doi.org/10.1016/j.msard.2018.12.007
18. Patsopoulos N, Baranzini SE, Santaniello A, Shoostari P, Cotsapas C, Wong G, James T, Replogle J, Vlachos IS (2019) Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility. Science. https://doi.org/10.1126/science.aav7188
19. Fambiatos A, Jokubaitis V, Horakova D, Kubala Havrdova E, Trojano M, Prat A, Girard M, Duquette P, Lugaresi A, Izquierdo G, Grand'Maison F, Grammond P, Sola P, Ferraro D, Alroughani R, Terzi M, Hupperts R, Boz C, Lechner-Scott J, Pucci E, Bergamaschi R, Van Pesch V, Ozakbas S, Granella F, Turkoglu R, Iuliano G, Spitaleri D, McCombe P, Solaro C, Slee M, Ampapa R, Soysal A, Petersen T, Sanchez-Menoyo JL, Verheul F, Prevost J, Sidhom Y, Van Wijmeersch B, Vucic S, Cristiano E, Saladino ML, Deri N, Barnett M, Olascoaga J, Moore F, Skibina O, Gray O, Fragoso Y, Yamout B, Shaw C, Singhal B, Shuey N, Hodgkinson S, Altintas A, Al-Harbi T, Csepany T, Taylor B, Hughes J, Jun JK, van der Walt A, Spelman T, Butzkueven H, Kalincik T (2019) Risk of secondary progressive multiple sclerosis: a longitudinal study. Mult Scler. https://doi.org/10.1177/1352458519868990
20. Cossburn M, Ingram G, Hirst C, Ben-Shlomo Y, Pickersgill TP, Robertson NP (2012) Age at onset as a determinant of presenting phenotype and initial relapse recovery in multiple sclerosis. Mult Scler 18(1):45–54. https://doi.org/10.1177/1352458511417479
21. Royston P (2006) Explained variation for survival models. Stata J 6(1):83–96. https://doi.org/10.1177/1536867x0600600105
22. Zlotnik A, Abraira V (2015) A general-purpose nomogram generator for predictive logistic regression models. Stata J 15(2):537–546. https://doi.org/10.1177/1536867x1501500212
23. Scalfari A, Lederer C, Daumer M, Nicholas R, Ebers GC, Muraro PA (2016) The relationship of age with the clinical phenotype in multiple sclerosis. Mult Scler 22(13):1750–1758. https://doi.org/10.1177/1352458516630396
24. Leray E, Yaouanq J, Le Page E, Coustans M, Laplaud D, Oger J, Edan G (2010) Evidence for a two-stage disability progression in multiple sclerosis. Brain 133(Pt 7):1900–1913. https://doi.org/10.1093/brain/awq076
25. Mowry EM, Pesic M, Grimes B, Deen SR, Bacchetti P, Waubant E (2009) Clinical predictors of early second event in patients with clinically isolated syndrome. J Neurol 256(7):1061–1066. https://doi.org/10.1007/s00415-009-5063-0
26. D'Alessandro R, Vignatelli L, Lugaresi A, Baldin E, Granella F, Tola MR, Malagu S, Motti L, Neri W, Galeotti M, Santangelo M, Fiorani L, Montanari E, Scandellari C, Benedetti MD, Leone M (2013) Risk of multiple sclerosis following clinically isolated syndrome: a 4-year prospective study. J Neurol 260(6):1583–1593. https://doi.org/10.1007/s00415-013-6838-x
27. Spelman T, Meyniel C, Rojas JI, Lugaresi A, Izquierdo G, Grand'Maison F, Boz C, Alroughani R, Havrdova E, Horakova D, Iuliano G, Duquette P, Terzi M, Grammond P, Hupperts R, Lechner-Scott J, Oreja-Guevara C, Pucci E, Verheul F, Fiol M, Van Pesch V, Cristiano E, Petersen T, Moore F, Kalincik T, Jokubaitis V, Trojano M, Butzkueven H, Investigators MS (2016) Quantifying risk of early relapse in patients with first demyelinating events: Prediction in clinical practice. Mult Scler. https://doi.org/10.1177/1352458516679893
28. Marrie RA, Horwitz RI, Cutter G, Tyry T, Vollmer T (2011) Association between comorbidity and clinical characteristics of MS. Acta Neurol Scand 124(2):135–141. https://doi.org/10.1111/j.1600-0404.2010.01436.x
29. Koch M, Uyttenboogaart M, van Harten A, De Keyser J (2008) Factors associated with the risk of secondary progression in multiple sclerosis. Mult Scler 14(6):799–803. https://doi.org/10.1177/1352458508089361
30. Vukusic S, Confavreux C (2003) Prognostic factors for progression of disability in the secondary progressive phase of multiple sclerosis. J Neurol Sci 206(2):135–137. https://doi.org/10.1016/s0022-510x(02)00426-4
31. Confavreux C, Vukusic S, Moreau T, Adeleine P (2000) Relapses and progression of disability in multiple sclerosis. N Engl J Med 343(20):1430–1438. https://doi.org/10.1056/NEJM200011163432001
32. Reilly GD, Mahkawnghta AS, Jelinek PL, De Livera AM, Weiland TJ, Brown CR, Taylor KL, Neate SL, Jelinek GA, Marck CH (2017) International differences in multiple sclerosis health outcomes and associated factors in a cross-sectional survey. Front Neurol 8:229. https://doi.org/10.3389/fneur.2017.00229
33. Briggs FB, Gunzler DD, Ontaneda D, Marrie RA (2017) Smokers with MS have greater decrements in quality of life and disability than non-smokers. Mult Scler 23(13):1772–1781. https://doi.org/10.1177/1352458516685169
34. Briggs FBS, Thompson NR, Conway DS (2019) Prognostic factors of disability in relapsing remitting multiple sclerosis. Mult Scler Relat Disord 30:9–16. https://doi.org/10.1016/j.msard.2019.01.045
35. Hempel S, Graham GD, Fu N, Estrada E, Chen AY, Miake-Lye I, Miles JN, Shanman R, Shekelle PG, Beroes JM, Wallin MT (2017) A systematic review of modifiable risk factors in the progression of multiple sclerosis. Mult Scler 23(4):525–533. https://doi.org/10.1177/1352458517690270
36. Handel AE, Williamson AJ, Disanto G, Dobson R, Giovannoni G, Ramagopalan SV (2011) Smoking and multiple sclerosis: an updated meta-analysis. PLoS ONE 6(1):e16149. https://doi.org/10.1371/journal.pone.0016149
37. Hedstrom AK, Hillert J, Olsson T, Alfredsson L (2013) Smoking and multiple sclerosis susceptibility. Eur J Epidemiol 28(11):867–874. https://doi.org/10.1007/s10654-013-9853-4
38. Scalfari A, Neuhaus A, Degenhardt A, Rice GP, Muraro PA, Daumer M, Ebers GC (2010) The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. Brain 133(Pt 7):1914–1929. https://doi.org/10.1093/brain/awq118
39. Scalfari A, Neuhaus A, Daumer M, Deluca GC, Muraro PA, Ebers GC (2013) Early relapses, onset of progression, and late outcome in multiple sclerosis. JAMA Neurol 70(2):214–222. https://doi.org/10.1001/jamaneurol.2013.599
40. Marrie RA (2017) Comorbidity in multiple sclerosis: implications for patient care. Nat Rev Neurol 13(6):375–382. https://doi.org/10.1038/nrneurol.2017.33
41. Marrie RA, Rudick R, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer T (2010) Vascular comorbidity is associated with more rapid disability progression in multiple sclerosis. Neurology 74(13):1041–1047. https://doi.org/10.1212/WNL.0b013e3181d6b125
42. Jakimovski D, Gandhi S, Paunkoski I, Bergsland N, Hagemeier J, Ramasamy DP, Hojnacki D, Kolb C, Benedict RHB, Weinstock-Guttman B, Zivadinov R (2019) Hypertension and heart disease are associated with development of brain atrophy in multiple sclerosis: a 5-year longitudinal study. Eur J Neurol 26(1):87–e88. https://doi.org/10.1111/ene.13769

43. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG (2000) Multiple sclerosis. N Engl J Med 343(13):938–952. https://doi.org/10.1056/NEJM200009283431307
44. Kister I, Munger KL, Herbert J, Ascherio A (2012) Increased risk of multiple sclerosis among women with migraine in the Nurses' Health Study II. Mult Scler 18(1):90–97. https://doi.org/10.1177/1352458511416487
45. Kister I, Caminero AB, Monteith TS, Soliman A, Bacon TE, Bacon JH, Kalina JT, Inglese M, Herbert J, Lipton RB (2010) Migraine is comorbid with multiple sclerosis and associated with a more symptomatic MS course. J Headache Pain 11(5):417–425. https://doi.org/10.1007/s10194-010-0237-9
46. Pakpoor J, Handel AE, Giovannoni G, Dobson R, Ramagopalan SV (2012) Meta-analysis of the relationship between multiple sclerosis and migraine. PLoS ONE 7(9):e45295. https://doi.org/10.1371/journal.pone.0045295
47. Wijnands JM, Zhu F, Kingwell E, Zhao Y, Ekuma O, Lu X, Evans C, Fisk JD, Marrie RA, Tremlett H (2019) Five years before multiple sclerosis onset: phenotyping the prodrome. Mult Scler 25(8):1092–1101. https://doi.org/10.1177/1352458518783662
48. Calabrese M, Gasperini C, Tortorella C, Schiavi G, Frisullo G, Ragonese P, Fantozzi R, Prosperini L, Annovazzi P, Cordioli C, Di Filippo M, Ferraro D, Gajofatto A, Malucchi S, Lo Fermo S, De Luca G, Stromillo ML, Cocco E, Gallo A, Paolicelli D, Lanzillo R, Tomassini V, Pesci I, Rodegher ME, Solaro C, Group R (2019) "Better explanations" in multiple sclerosis diagnostic workup: a 3-year longitudinal study. Neurology 92(22):e2527–e2537. https://doi.org/10.1212/WNL.0000000000007573
49. Solomon AJ, Bourdette DN, Cross AH, Applebee A, Skidd PM, Howard DB, Spain RI, Cameron MH, Kim E, Mass MK, Yadav V, Whitham RH, Longbrake EE, Naismith RT, Wu GF, Parks BJ, Wingerchuk DM, Rabin BL, Toledano M, Tobin WO, Kantarci OH, Carter JL, Keegan BM, Weinshenker BG (2016) The contemporary spectrum of multiple sclerosis misdiagnosis: a multicenter study. Neurology 87(13):1393–1399. https://doi.org/10.1212/WNL.0000000000003152
50. Kaisey M, Solomon AJ, Luu M, Giesser BS, Sicotte NL (2019) Incidence of multiple sclerosis misdiagnosis in referrals to two academic centers. Mult Scler Relat Disord 30:51–56. https://doi.org/10.1016/j.msard.2019.01.048
51. Cools N, Ponsaerts P, Van Tendeloo VF, Berneman ZN (2007) Regulatory T cells and human disease. Clin Dev Immunol 2007:89195. https://doi.org/10.1155/2007/89195
52. Marrie RA, Reider N, Cohen J, Stuve O, Trojano M, Sorensen PS, Reingold SC, Cutter G (2015) A systematic review of the incidence and prevalence of cancer in multiple sclerosis. Mult Scler 21(3):294–304. https://doi.org/10.1177/1352458514564489
53. International Multiple Sclerosis Genetics C (2011) Genome-wide association study of severity in multiple sclerosis. Genes Immun 12(8):615–625. https://doi.org/10.1038/gene.2011.34
54. Baranzini SE, Wang J, Gibson RA, Galwey N, Naegelin Y, Barkhof F, Radue EW, Lindberg RL, Uitdehaag BM, Johnson MR, Angelakopoulou A, Hall L, Richardson JC, Prinjha RK, Gass A, Geurts JJ, Kragt J, Sombekke M, Vrenken H, Qualley P, Lincoln RR, Gomez R, Caillier SJ, George MF, Mousavi H, Guerrero R, Okuda DT, Cree BA, Green AJ, Waubant E, Goodin DS, Pelletier D, Matthews PM, Hauser SL, Kappos L, Polman CH, Oksenberg JR (2009) Genome-wide association analysis of susceptibility and clinical phenotype in multiple sclerosis. Hum Mol Genet 18(4):767–778. https://doi.org/10.1093/hmg/ddn388
55. George MF, Briggs FB, Shao X, Gianfrancesco MA, Kockum I, Harbo HF, Celius EG, Bos SD, Hedstrom A, Shen L, Bernstein A, Alfredsson L, Hillert J, Olsson T, Patsopoulos NA, De Jager PL, Oturai AB, Sondergaard HB, Sellebjerg F, Sorensen PS, Gomez R, Caillier SJ, Cree BA, Oksenberg JR, Hauser SL, D'Alfonso S, Leone MA, Martinelli Boneschi F, Sorosina M, van der Mei I, Taylor BV, Zhou Y, Schaefer C, Barcellos LF (2016) Multiple sclerosis risk loci and disease severity in 7,125 individuals from 10 studies. Neurol Genet 2(4):e87. https://doi.org/10.1212/NXG.0000000000000087
56. Crielaard L, Kavaliunas A, Ramanujam R, Olsson T, Hillert J, Stridh P, Kockum I, Manouchehrinia A (2019) Factors associated with and long-term outcome of benign multiple sclerosis: a nationwide cohort study. J Neurol Neurosurg Psychiatry 90(7):761–767. https://doi.org/10.1136/jnnp-2018-319913
57. Healy BC, Liguori M, Tran D, Chitnis T, Glanz B, Wolfish C, Gauthier S, Buckle G, Houtchens M, Stazzone L, Khoury S, Hartzmann R, Fernandez-Vina M, Hafler DA, Weiner HL, Guttmann CR, De Jager PL (2010) HLA B*44: protective effects in MS susceptibility and MRI outcome measures. Neurology 75(7):634–640. https://doi.org/10.1212/WNL.0b013e3181ed9c9c
58. Lysandropoulos AP, Perrotta G, Billiet T, Ribbens A, Du Pasquier R, Pot Kreis C, Maggi P, Theaudin M (2020) Human leukocyte antigen genotype as a marker of multiple sclerosis prognosis. Can J Neurol Sci 47(2):189–196. https://doi.org/10.1017/cjn.2019.329
59. Horton M, Rudick RA, Hara-Cleaver C, Marrie RA (2010) Validation of a self-report comorbidity questionnaire for multiple sclerosis. Neuroepidemiology 35(2):83–90. https://doi.org/10.1159/000311013