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Original Research Paper

Long-term disability trajectories in primary progressive MS patients: A latent class growth analysis

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Abstract

Background: Several natural history studies on primary progressive multiple sclerosis (PPMS) patients detected a consistent heterogeneity in the rate of disability accumulation.

Objectives: To identify subgroups of PPMS patients with similar longitudinal trajectories of Expanded Disability Status Scale (EDSS) over time.

Methods: All PPMS patients collected within the MSBase registry, who had their first EDSS assessment within 5 years from onset, were included in the analysis. Longitudinal EDSS scores were modeled by a latent class mixed model (LCMM), using a nonlinear function of time from onset. LCMM is an advanced statistical approach that models heterogeneity between patients by classifying them into unobserved groups showing similar characteristics.

Results: A total of 853 PPMS (51.7% females) from 24 countries with a mean age at onset of 42.4 years (standard deviation (SD): 10.8 years), a median baseline EDSS of 4 (interquartile range (IQR): 2.5–5.5), and 2.4 years of disease duration (SD: 1.5 years) were included. LCMM detected three different subgroups of patients with a mild ($n = 143$; 16.8%), moderate ($n = 378$; 44.3%), or severe ($n = 332$; 38.9%) disability trajectory. The probability of reaching EDSS 6 at 10 years was 0%, 46.4%, and 81.9% respectively.

Conclusion: Applying an LCMM modeling approach to long-term EDSS data, it is possible to identify groups of PPMS patients with different prognosis.

Keywords: Primary progressive multiple sclerosis, disability, long-term, trajectories, clinical trials, heterogeneity

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Introduction

Primary progressive multiple sclerosis (PPMS) is observed in 10%–15% of patients with multiple sclerosis (MS) and has the worst prognosis of all MS subtypes.

In contrast to the relapsing-remitting (RR) form of the disease, for which several disease-modifying drugs are now available, to date, no effective therapy has been approved for use in PPMS. Two clinical trials of glatiramer acetate[1] and fingolimod[2] failed to demonstrate efficacy of these drugs on disability progression in patients with PPMS. Recently, a new drug (ocrelizumab) gave positive results in two phase III trials,[3] showing the ability to reduce of more than 20% the risk of 12- and 24-week confirmed disability

progression. Ocrelizumab received the "Breakthrough therapy designation" from the US FDA in February 2016, and it will be soon approved for the treatment of PPMS. The treatment of PPMS remains a hot topic of MS research. Despite active efforts to identify new biomarkers and define sensitive clinical outcome measures, the time course of disability accumulation remains the main clinical outcome measure in PPMS clinical trials.

Several PPMS natural history studies[4–11] have been published demonstrating a large degree of heterogeneity in time from disease onset to Expanded Disability Status Scale (EDSS) 4 (with the median ranging between 5 and 8.1 years) and EDSS 6 (with the median ranging between 7.1 and 14 years).

The main aim of this study was to investigate the reported heterogeneity of long-term disability accumulation in an independent large cohort of PPMS patients and to determine whether distinct PPMS trajectories can be detected by applying advanced statistical modeling techniques based on latent class analysis.

Methods

PPMS patient clinical data contained within the International MSBase registry were extracted in November 2015. The MSBase registry has been previously described.[12] Briefly, it is a longitudinal, prospective, international, and web-based database collecting standardized clinical outcomes in MS patients using a minimal dataset. The minimal dataset consists of patient date of birth, sex, MS center, date of disease onset, disease phenotype, and disability measures. Information on disease-modifying treatment exposure (with start and end dates) and on clinical relapses were also extracted. Patients originally classified as PPMS but with relapses during follow-up, defined as active PPMS according to the newly published definition,[13] were not excluded from the main analysis. However, a subgroup analysis involving only non-active PPMS was planned.

Data were recorded as part of routine clinical practice using the offline medical record iMed and then uploaded to the MSBase web portal.

The use of MSBase as a research platform was approved by the Melbourne Health Human Research Ethics Committee as well as local ethics committees at each participating center. Signed informed consent or waivers were obtained from each participant as per local regulations.

Patients with only one EDSS assessment or with the first EDSS assessment performed later than 5 years from MS onset and those not fulfilling minimal dataset requirements were excluded from the analysis. To ensure data quality, only information from centers contributing at least 10 active records (cases with regular annual updates of clinical information) to the Registry were included.

To ensure consistency of EDSS evaluations, the Neurostatus certification at all participating centers was required.

Statistical methods

We used the latent class growth curve mixture models (LCMM) to model longitudinal EDSS scores. LCMM is an advanced statistical approach that models heterogeneity between patients by classifying them into unobserved groups (latent classes); the classes are distinct from each other, but patients in each class show similar within-class characteristics. The time from MS onset (years) and age were considered as possible time indicators.

Models with increasing numbers of latent classes were fitted to the data and the best model (lower values better fit) was selected according to both Akaike information criterion (AIC) and Bayesian information criterion (BIC) fit indices, and to parsimony, clinical interpretability of the data and according to the posterior probability of classification to the correct latent class.[14] The same indices (AIC, BIC) were used to determine which time indicator (time since onset or age) and which time function (linear, quadratic, square root, logarithm) best fit the EDSS trajectories over time.

To address this last issue, fractional polynomials (FP)[15,16] were used; these automatically detect which powers of time (i.e. $time^{-2}$, $time^{-1}$, $time^{-0.5}$, time, $time^{2}$) can be combined to obtain the best longitudinal fit of the dependent variable (i.e. EDSS).

In addition to AIC and BIC, to assess the goodness of the fit, the root mean square errors (RMSE) were calculated, defined as the differences between the predicted and observed EDSS, and the proportion of these differences that were less than 0.5 points.

All models were unconditional models, with latent class probabilities independent from covariates.

Membership of a patient to a specific class (trajectory) was determined by calculating the posterior

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probability of belonging to one class and assigning the patient to the class with the highest probability. The average posterior probability for patients assigned to each class is reported as a measure of goodness of discrimination.

To check the stability of results, a cross-validation approach was used: the dataset was split into a training and a validation set (50:50), repeating the procedure 100 times. The LCMM was independently applied in each training and validation set and the predicted trajectories were compared at defined time points; the percentage of patients classified in each group was compared by a chi-square test. Additional methodological details are reported in the supplementary material.

As a further step, only observations within 1, 3, and 5 years from first visit were used to classify patients using a leave-one-out procedure, and the results were compared with the correct classification based on the whole follow-up time. The aim of this final analysis was to establish the length of observation time needed for a PPMS subject to be assigned with high confidence to his or her prognostic group.

Demographic and clinical characteristics were compared among classes using univariable and multivariable logistic regression models (multinomial and ordinal), with class as the dependent variable.

The number of relapses was analyzed by a negative binomial regression model with follow-up duration as an offset indicator.

Latent class analysis was rerun in subgroups according to the presence/absence of relapses during the follow-up.

Stata (v.13; StataCorp), with the function "fp" and "gllamm," was used for the latent class analysis.

Results

Patient characteristics

A total of 853 PPMS patients from 24 countries (Italy: 21.5%; Spain: 15.9%; The Netherlands: 15.9%; Canada: 11.8%; Australia: 8.2%; others 26.7%) were included. Data on ethnicity were present in 491 patients with a large prevalence of Caucasians (76.8%). Demographic and clinical characteristics are reported in Table 1.

A male:female ratio of 1:1.07 and an age at onset of 42.4 years were calculated.

Patients had a mean follow-up duration of 8.1 years (standard deviation (SD): 5.5 years), with a median number of EDSS observations of 10 (range, 2–52) during the follow-up. The first EDSS assessment was reported at a mean of 2.4 years from disease onset (SD: 1.5; range, 0–5 years).

Mean frequency of EDSS assessments was every 273 days with a median of 174 days (interquartile range (IQR): 91, 302 days).

EDSS trajectories

Time from disease onset was superior to age when fitting EDSS trajectories over time, with lower AIC and BIC values, a lower RMSE (time from onset: 0.55; age: 0.67), and a higher proportion of prediction within 0.5 EDSS points from observed (time from onset: 92.2%; age: 86.6%). Patients were therefore classified into groups using time from disease onset as the preferred time indicator. An adjustment for center did not affect the results, so we presented unadjusted results. The analysis was adjusted for center, and the optimum number of classes describing groups of patients with different trajectories of EDSS over time was 3 (RMSE = 0.86). The longitudinal EDSS time course in PPMS is therefore best described by three distinct trajectories, with patients in each group sharing similar characteristics. Further the best function describing the trajectories of EDSS had a square root, a linear, and a quadratic component of time from onset.

A total of 143 patients (16.8%) were classified in the first "mild" class (Figure 1; mild in panel (a) and blue line in panel (b)). Patients in the mild class had a median baseline EDSS of 2, with a median time from onset to reach a confirmed EDSS = 3 of 10.4 years (95% confidence interval (CI) = 8.2–12.4) and a confirmed EDSS = 4 of 13.9 years (95% CI: 11.6–21.3 years; Figure 2).

Median time to reach a confirmed EDSS = 6 was more than 20 years.

Median age at EDSS = 4 for patients in this class was 64.7 years (95% CI: 58.5–67.2 years).

The mean posterior probability for a subject to be classified in this class was high (92.4%), indicating that patients assigned to this class had a very high probability of belonging to this class.

The second class (Figure 1: moderate panel in Figure 1(a) and red line in Figure 1(b)) was an intermediate

Table 1. Characteristics of patients included in the analysis.

Characteristics	$N = 853$
Age at onset	42.4 (10.8)
Males, *n* (%)	412 (48.3)
EDSS at first visit, median (IQR)	4 (2.5–5.5)
Time to diagnosis from onset, years (mean (SD); range)	2.2 (1.8)
Disease duration at first EDSS assessment, mean (SD)	2.4 (1.5)
Country	
Italy	22%
Spain	15.9%
The Netherlands	15.9%
Canada	11.8%
Australia	8.2%
Turkey	6%
Others	20.2%
Ethnicity ($n = 491$), n/N (%)	
Caucasian	377 (76.8)
Asian	56 (11.4)
Turkish	27 (5.5)
Other	31 (6.3)
Year of entry in registry	
<1980	0.6%
1980–1989	0.9%
1990–1999	13.1%
2000–2009	60.9%
2010–2015	24.5%

EDSS: Expanded Disability Status Scale; IQR: interquartile range; SD: standard deviation.

class with a "moderate" disability trajectory. A total of 378 patients (44.3%) were assigned to this class.

Median EDSS at baseline was 3.5, median time to confirmed EDSS = 4 was 5.3 years (95% CI: 4.9–5.7 years; Figure 2), and median time to EDSS = 6 was 10.4 years (95% CI: 9.6–11.4).

Median age at EDSS = 4 was 52.5 years (95% CI: 50.8–54.5 years) and median age at EDSS = 6 was 60.5 years (95% CI: 58.3–63.4 years).

The mean posterior probability to be classified in class 2 was 90%, with 5.6% of probability to be classified in class 1 ("mild") and 4.4% in class 3 ("severe").

The third, "severe" class (Figure 1: severe panel (a) and green line in (b)) comprised 332 patients (38.9%). A median baseline EDSS of 5.5, a median time to reach a confirmed EDSS = 6 of 4.8 years (95% CI: 4.3–5.1 years; Figure 2), and a median age at EDSS = 6 of 53.1 years (95% CI: 50.6–54.3 years) characterized this trajectory.

The mean posterior probability to be classified in the class was 94.2%.

Cross-validation

The same procedure was run in 100 random split of the dataset (50:50) and EDSS trajectories obtained in each couple of training and validation sets for the first 20 repetition are reported in the supplementary material (Figure 1S) together with the frequencies of patients assigned to each class (Table 1S).

The mean percentage relative difference between training and validation sets in the predicted probability to have an EDSS progression at 5 years was 9% (95% CI: 5.4–12.7%) for class 1, 4.2% (95% CI: 2.8–5.6%) for class 2, and 2.3% (95% CI: 1.2–3.3%) for class 3.

The median chi-square testing the differences of frequency of patients in each class was 3.92 (2 degree of freedoms, $p = 0.14$).

Prediction for new patients based on short-term EDSS observation

After defining the above three classes, we determined the class that each patient would have been assigned if he or she had just 1, 3, or 5 years of follow-up from their first EDSS visit. In Table 2, the classification after 1, 3, and 5 years is compared to the classification of the patient using his or her entire follow-up. Using a 1-year follow-up time, we were able to predict the correct long-term trajectory in 77.5% of the patients; this increased to 86.9% when using a 3-year follow-up period and to 93.8% when using a 5-year follow-up period.

Baseline characteristics

In Table 3, baseline demographic and clinical characteristics of patients are compared among the three classes. Diagnosis delay from onset decreases with the increase of severity class ($p < 0.001$). A higher rate of superimposed relapses during follow-up was observed in the more severe class ($p_{adjusted} = 0.054$). The number of relapses experienced in each class is reported in the supplementary material.

Differences among countries ($p_{adjusted} = 0.026$) were also found. While Australia showed a higher prevalence of

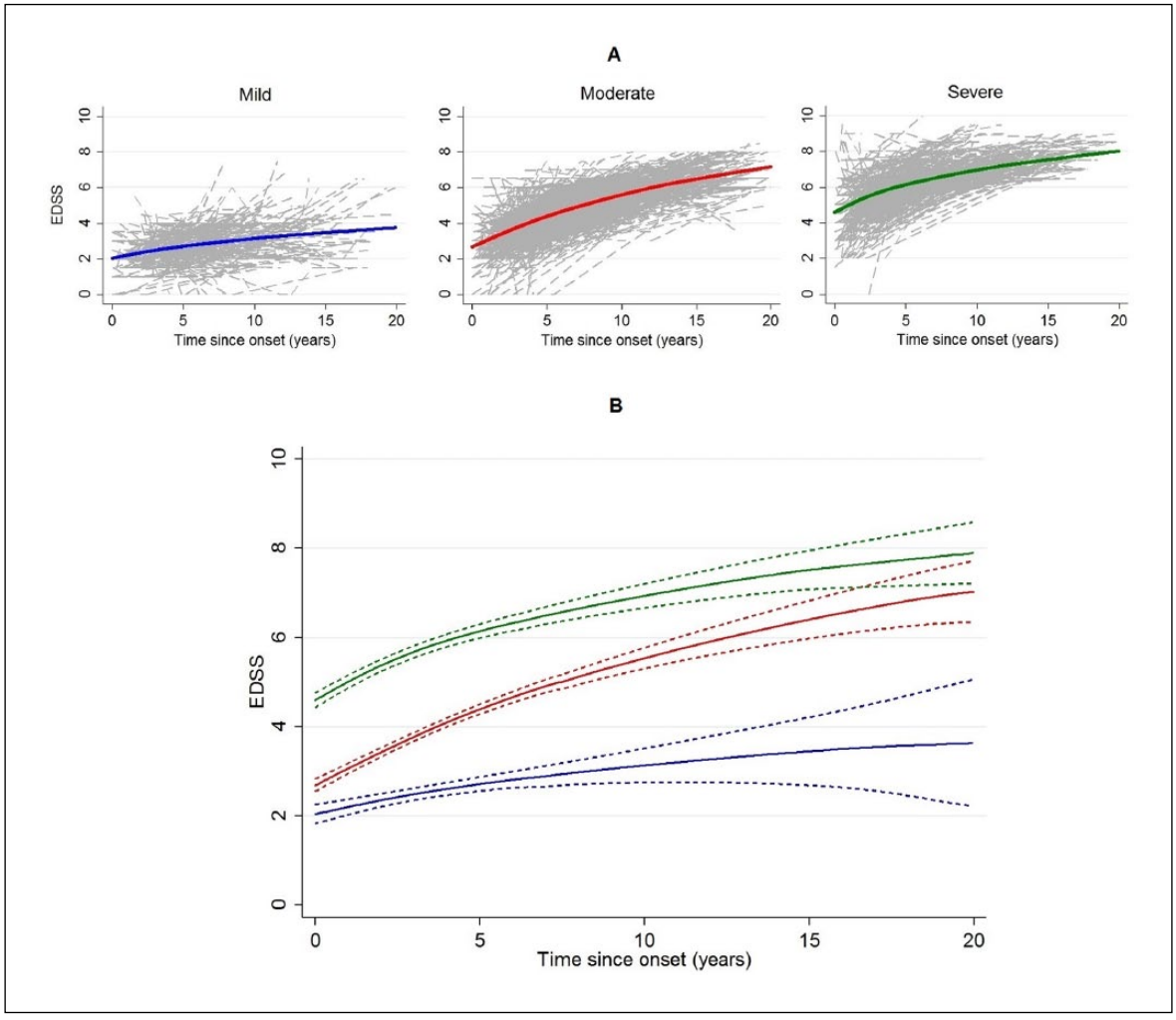

Figure 1. Typical disability trajectories since disease onset in PPMS patients as identified by latent class analysis.
The top panels (a) show individual disability trajectories (Spaghetti-plot) together with the estimated class trajectory. Below (b), disability trajectories of the three classes are plotted together with the 95% confidence intervals.
The mean trajectories are defined as follows:
Class mild (blue curve) equation: $EDSS = 1.99 + 0.032 \times \sqrt{time\ since\ onset} + 0.12991 \times (time\ since\ onset) - 0.0026 \times time\ since\ onset^2$;
Class moderate (red curve) equation: $EDSS = 2.54 + 0.205 \times \sqrt{time\ since\ onset} + 0.32 \times (time\ since\ onset) - 0.007 \times time\ since\ onset^2$;
Class severe (green curve) equation: $EDSS = 4.24 + 0.87 \times \sqrt{time\ since\ onset} + 0.016 \times (time\ since\ onset) - 0.001 \times time\ since\ onset^2$.

severe patients (54.3%), Italy had more patients assigned to the moderate class (49.5%).

A trend for a higher frequency of males and older patients with increasing class severity was observed.

Subgroup analysis

A total of 595 patients did not show superimposed relapses during the whole follow-up (Table 3) and were considered in the subgroup analysis (Table 2S-Supplementary material). Using the same approach previously described, three latent classes resulted to be the best model.

A total of 98 patients (16.5%) were classified in the "mild" class, 280 patients (47.1%) were assigned to the intermediate class with a "moderate" disability trajectory, while the third, "severe" class comprised 217 patients (36.5%).

The tree trajectories (Figures 2S and 3S—Supplementary material) did not show consistent differences compared with those previously reported on the whole sample.

Median time to a confirmed EDSS = 4 was, respectively, of 13.9 years (95% CI: 10.5–21.3 years), 5.1 years (95% CI: 4.4–5.7), and 2.7 years (95% CI: 2.2–3.6 years; calculated on 39 patients that had not still

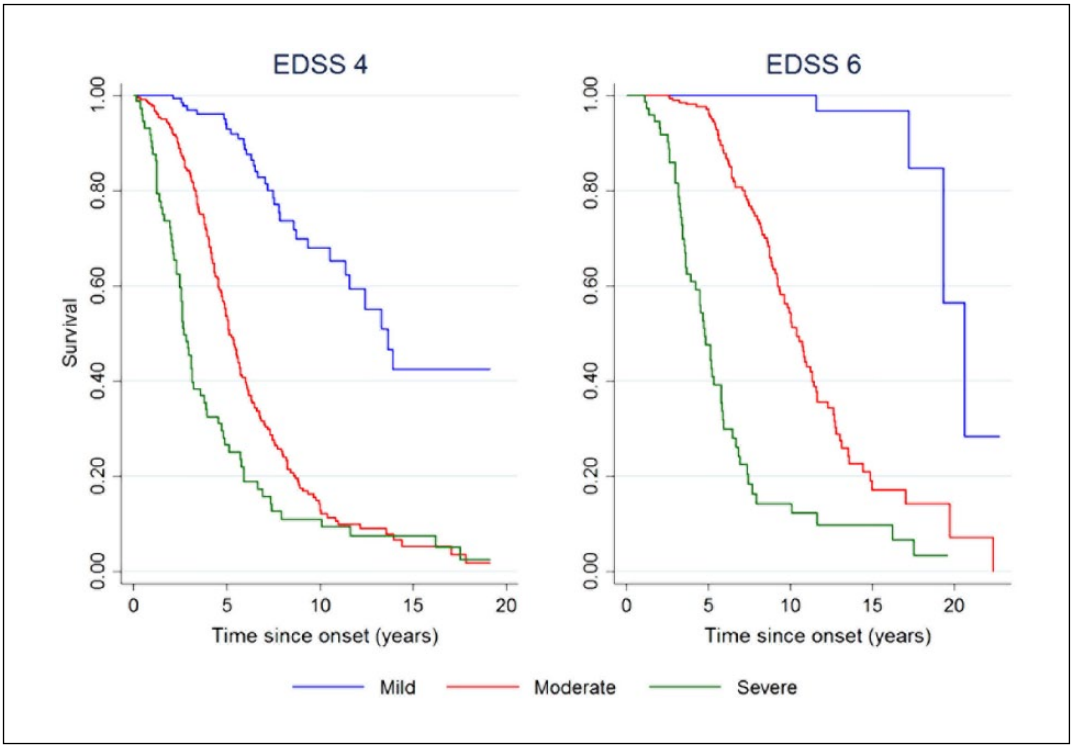

Figure 2. Time to 12-month confirmed EDSS of 4 and 6 according to different classes of disability. The blue, red, and green line represent, respectively, the mild, moderate, and severe disability class.

Table 2. Classification of patients according to 1-, 3-, and 5-year follow-up and comparison with their trajectory assigned after their entire follow-up.

	Final classification on the entire follow-up			Total
	Mild	Moderate	Severe	*n* = 853
	n = 143	*n* = 378	*n* = 332	
Classification after 1 year				
Mild	93 (65)	47 (12.4)	3 (0.9)	143
Moderate	50 (35)	306 (81)	67 (20.2)	423
Severe	0	25 (6.6)	262 (78.9)	287
	Misclassification rate: 192/853 (22.5%)			
Classification after 3 years				
Mild	115 (80.4)	38 (10.1)	1 (0.3)	154
Moderate	28 (19.6)	324 (85.7)	29 (8.7)	381
Severe	0	16 (4.2)	302 (91)	318
	Misclassification rate: 112/853 (13.1%)			
Classification after 5 years				
Mild	123 (86)	20 (5.3)	1 (0.3)	144
Moderate	20 (14)	348 (92.1)	19 (5.7)	387
Severe	0	10 (2.6)	312 (94)	322
	Misclassification rate: 70/853 (8.2%)			

Results are reported as *N* (%) with % calculated on total number of patients assigned to the class at the end of follow-up (column). The misclassification rate was calculated summing the patients not correctly classified.

Table 3. Demographic and clinical characteristics according to classes of disability.

Characteristics	Mild (n = 143)	Moderate (n = 378)	Severe (n = 332)	Univariable (p)	Multivariable (p)^
Age at onset, mean (SD)	41.3 (11.1)	42.6 (10.3)	42.8 (11.3)	0.24*	
30 and younger, *n* (%)	24 (16.8)	51 (13.5)	45 (13.5)	0.17	
30–40, *n* (%)	37 (25.9)	83 (22)	81 (24.4)		
40–50, *n* (%)	46 (32.2)	158 (41.8)	110 (33.1)		
50 and older, *n* (%)	36 (25.1)	86 (22.7)	96 (29)		
Males	64 (44.8)	180 (47.6)	168 (50.6)	0.22*	
Country, *n* (%)				0.035	0.026
Australia	10 (14.3)	22 (31.4)	38 (54.3)		
Canada	15 (14.9)	41 (40.6)	45 (44.5)		
Italy	36 (19.2)	93 (49.5)	59 (31.4)		
The Netherlands	20 (14.7)	60 (44.1)	56 (41.2)		
Spain	16 (11.8)	63 (46.3)	57 (41.9)		
Turkey	10 (19.6)	18 (35.3)	23 (45.1)		
Others	36 (21.1)	81 (47.4)	54 (31.6)		
Ethnicity, *n* (%)				0.21	
Caucasian	74 (81.3)	172 (80)	131 (70.8)		
Asian	11 (12.1)	21 (9.8)	24 (13)		
Turkish	3 (3.3)	9 (4.2)	15 (8.1)		
Other	3 (3.3)	13 (6)	15 (8.1)		
Time to diagnosis from onset, years (mean (SD); range)	2.7 (2.2; 0.1–11)	2.3 (1.8; 0–12.7)	1.6 (1.4; 0–10)	<0.001	<0.001
Disease duration at first EDSS assessment, mean (SD)	2.3 (1.5)	2.5 (1.4)	2.3 (1.5)	0.39	
Year of first visit, median (IQR)	2006 (2001–2010)	2007 (2002–2010)	2007 (2003–2010)	0.22	
Relapse status during follow-up, *n* (%)				0.052	
0	90 (62.9)	271 (71.7)	234 (70.5)		
1	40 (28)	82 (21.7)	62 (18.7)		
⩾2	13 (9.1)	25 (6.6)	36 (10.8)		
Relapse rate from onset to last follow-up, mean (SD)	0.10 (0.2)	0.10 (1.6)	0.16 (0.6)	<0.001	0.054
Treated, *n* (%)	79 (55.2)	197 (52.1)	184 (55.4)	0.64	
Percent of time on treatment over all follow-up, mean (SD)	20 (26.7)	14.9 (22.9)	14.9 (24.1)	0.10	
Number of annual visits, median (IQR)	1.43 (0.78–2.39)	1.53 (0.72–2.38)	1.48 (0.67–2.46)	0.93	
Follow-up from onset, years; median (IQR)	7.6 (4.6–11.3)	7.3 (4–12)	6.1 (3.9–9.4)	0.0018	0.16
Gd lesions first visit (n = 141), n/N (%)	8/28 (28.6)	18/57 (31.6)	15/56 (26.8)	0.85	
T2 lesions first visit (n = 231), mean (SD; range)	9.6 (11; 0–41)	7.6 (9.5; 0–50)	9.6 (12; 0–60)	0.28	

SD: standard deviation; EDSS: Expanded Disability Status Scale; IQR: interquartile range (25th–75th %).
*Test for trend with ordinal logistic regression.
^Multinomial logistic regression.

reached this threshold at first visit) in mild, moderate, and severe class.

Similarly, median time to EDSS = 6 was 10.4 years (95% CI: 9.6–11.7) in moderate and 4.8 years (95% CI: 4.2–5.2) in severe class while in mild class no patients reached EDSS 6 before 16 years from onset.

The mean posterior probability for a subject to be classified respectively in mild, moderate, and severe class was 96.7%, 96.1%, and 96.8%.

Performing the analyses on the subgroup of patients (n = 258) with at least one superimposed relapse during follow-up, the three classes model resulted again to be the best one.

The model assigned 40 patients (15.5%) in mild, 97 (37.6%) in moderate, and 121 (46.9%) in severe class (Figures 2S and 3S).

The mean posterior probability for a subject to be classified, respectively, in mild, moderate, and severe class was 93.4%, 90.9%, and 97.3%.

Discussion

In the present analysis of the MSBase dataset, we were able to detect heterogeneity in the disability trajectories of patients with PPMS. Our findings are in agreement with previous natural history studies reporting a median time to EDSS = 6 ranging between 7.1[5] and 14 years[6] from disease onset.

Our modeling approach identified three distinct patterns of disability progression among PPMS patients. The EDSS time course of patients grouped in the milder class is represented by a trajectory that never reaches an EDSS 6 during the course of 20 years of follow-up available for analysis after the onset of disease; while the most severe trajectory begins with a high EDSS and reaches EDSS 6 within 5 years from onset. It is important to note that the classification of these trajectories of EDSS accumulation was performed according to an "unsupervised" approach. After classification, it was possible to examine whether the three groups, characterized by different EDSS accumulation patterns, had any differences in baseline characteristics. The most important predictor of disability severity was the time elapsing between clinical onset of MS and the diagnosis, with a shorter period between the onset symptoms and diagnosis predicting more aggressive disease. This could possibly be explained by an earlier presentation of patients with relatively more severe MS onset. Also in other neurological diseases, such as amyotrophic lateral sclerosis, time to diagnosis was a predictor of disease severity.[17]

Previous studies reported age at onset as a prognostic factor in PPMS[4,6,9,10] while no consistent differences were observed in our cohort. The London-Ontario study[18] did not detect differences between relapse-free and active patients in the time to reach disability milestones. In this study, patients within the most severe trajectory class had the highest rate of superimposed relapses. While patients who experience superimposed relapse activity are more likely to respond to therapies,[19,20] our study demonstrates that ongoing relapse activity seems to represent a negative prognostic factor in untreated PPMS patients. Previously male sex was reported as a potential negative prognostic factor,[21] but in our cohort of PPMS patients we detected only a small relative increase in the proportion of males in the intermediate and the severe disability classes. A global female:male ratio around 1 as observed in other natural history studies[5,16,21,22] was confirmed here.

The lack of clearly distinct baseline characteristics among the three classes possibly reflects the inability to identify clear prognostic classes using baseline variables alone and highlights the presence of distinct but not predictable prognostic patterns using the set of baseline parameters used here. However, the lack of a range of magnetic resonance imaging (MRI) predictors must be considered as a factor limiting the baseline prognostic ability.

Furthermore, our analysis has some practical implications. The presence of three classes of PPMS patients characterized by distinct EDSS accumulation trajectories over time is important to consider when designing clinical trials in PPMS. Our analysis suggests that it is important to take into account the EDSS course from onset: after just 1 year of observation we can correctly classify a PPMS patient in his or her correct prognostic group with a 77.5% probability, which increases to 86.9% when using a 3-year follow-up and to 91.8% when using a follow-up of 5 years. This means that if we enroll a PPMS patient with 1 or 3 years of disease duration, we can predict with high confidence his or her EDSS course in the subsequent follow-up period in the absence of therapeutic intervention. Our classifications may further be used as an inclusion/exclusion criterion or a parameter on which to be matched in different treatment groups.

Even if this is a very large and heterogeneous database coming from different countries and centers, these findings should be validated on an independent external cohort to generalize the results. Furthermore, since MSBase participants are more represented by MS specialist centers, we could postulate a larger frequency of more rapidly progressing patients than in a truly population-based cohort. This possibility should not impact the trajectories estimation when run in different population-based cohorts, but just the relative frequencies in the three classes, with a lower number of patients in the worst prognosis group and a higher frequency of subjects in the more benign category.

In conclusion, a longitudinal mixed model with latent classes applied to a large cohort of PPMS patients with long-term follow-up has allowed us to build a model to predict the future disability trajectory of PPMS subjects, after short-term follow-up. An

integrated dynamic approach, including in the model baseline prognostic factors but also time-dependent predictors, can be investigated as a future development to further improve the ability to predict the time course of disability progression in progressive MS.

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