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ABSTRACT Objective: To develop covariate specific short-term disability curves to demonstrate the probability of progressing by Expanded Disability Status Scale (EDSS) at semiannual visits. **Methods:** Semiannual EDSS scores were prospectively collected in 218 relapsing-remitting (RR) and clinically isolated syndrome (CIS) patients as part of the Comprehensive Longitudinal Investigation of Multiple Sclerosis at the Brigham and Women's Hospital (CLIMB) study. Baseline brain parenchymal fraction (BPF) and T2 lesion volume were available on 205 patients. A partial proportional odds model determined the influence of covariates on the change in EDSS score at subsequent visits. A discrete second order Markov transitional model was fit and generated a probability matrix for each subject; the 6-month probabilities of EDSS change were graphically represented. **Results:** The univariate analysis demonstrated the lowest baseline BPF quartile (OR 1.99; $p = 0.0203$) and the highest T2 lesion volume quartile (OR 2.19; $p = 0.0130$) were associated with progression in EDSS. Covariate specific disability curves demonstrated the effect of BPF and T2 lesion volume on short-term progression. In subjects with a 6-month EDSS of 2, the probability of a sustained progression of an EDSS of 3 within 3 years was 0.277 for a subject with low BPF and a high T2 lesion volume vs 0.055 for a subject with high BPF and a low T2 lesion volume. **Conclusions:** Markov transitional models allow for the comparison of covariate specific short-term disability changes among groups of patients with multiple sclerosis. **NEUROLOGY 2007;68:2059–2065**

Clinical predictors of short-term progression in multiple sclerosis (MS) are similar to those influencing long-term disability.[1-6] However, the standard statistical methods of survival analysis used to create these predictive models fail to incorporate the ongoing fluctuating nature of the disease. In survival methods, patients who have not reached the target Expanded Disability Status Scale (EDSS)[7] before the end of the study are censored, thus any disease progression which may have occurred is not considered in the analysis and clinical information is lost. Markov transitional models incorporate the fluctuating nature of chronic diseases through the analysis of discrete states of progression and make use of all clinical information. To further develop our understanding of short-term disability changes in MS, we have applied our longitudinal data to a Markov transitional model.

In our model, the subject's previous disability history is used to predict subsequent short-term disability as measured by EDSS. Once the model is fit, the probability of progression over time is calculated and drawn based upon specific clinical and MRI covariates.

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METHODS **Clinical resources.** Data were collected from February 2000 to April 2005 as part of the Comprehensive Longitudinal Investigation of Multiple Sclerosis at the Brigham and Women's Hospital (CLIMB) study at the Partners Multiple Sclerosis Center in Boston, MA. CLIMB is an ongoing longitudinal cohort study that aims to understand the natural history of MS in the current era of Food and Drug Administration–approved disease-modifying therapies.[8] Subjects aged ≥18 years with a clinically isolated syndrome (CIS) or the diagnosis of relapsing-remitting (RR) MS may be enrolled within the CLIMB study and are monitored with annual neurologic examinations, MRI, immunologic, genetic, neuropsychological, and quality of life studies. Informed consent was obtained according to Institutional Review Board guidelines. A computerized database is used to store data on subjects enrolled in CLIMB; data collected include age, gender, date of onset of neurologic symptoms, date of diagnosis of clinically definite MS, medication history, relapse data, MRI data, and semi-annual EDSS examinations. A relapse in the CLIMB study is defined as a new or worsening neurologic symptom lasting for at least 24 hours in duration and is documented retrospectively at each 6-month visit.

MRI examinations and analysis. Subjects underwent MRI examination on a 1.5-T scanner (Signa, General Electric Medical Systems, Milwaukee, WI) and imaging sequences included dual echo (proton density [PD] and T2-weighted) axial images. The dual echo images were acquired using two interleaved (echo time, 30 and 80 msec), long repetition time (TR, 3,000 msec) sequences to generate 54 contiguous 3-mm-thick slices covering the whole brain from the foramen magnum to the superior convexity (in-plane resolution: 0.9375 × 0.9375 mm, 256 × 256 image matrix). Our MS Imaging laboratory has previously developed and validated a two-channel segmentation algorithm for the fully automated segmentation of white matter (WM), gray matter (GM), CSF, and white matter signal abnormalities/lesions (WMSA). Template-driven segmentation (TDS+) combines a statistical signal-intensity based classification algorithm with an anatomic context provided by a digital atlas of the brain. It produces segmentations with very high reproducibility and accuracy of WMSA segmentation.[9-11] Volumes for WM, GM, CSF, and WMSA and consequently normalized whole brain volume can be derived from this series. Reproducibility and accuracy of this pipeline has already been established by our previous work.[9] TDS+ is a fully automated image segmentation procedure[9] that can yield T2 burden of disease (lesion volume in ml), brain volume, and brain parenchymal fraction (BPF). BPF is defined as the ratio of brain parenchymal tissue volume (sum of T2 lesions, normal appearing white matter, and gray matter) to the intracranial cavity volume. MRI examinations were completed within 4 weeks of EDSS assessment.

Statistical analysis. Markov transitional models can be applied to regress the transitions of subjects from one state (level of EDSS) to another in subsequent visits on selected covariates.[12-14] Therefore, we analyzed our longitudinal clinical data collected through the CLIMB study to a second-order Markov model and determined the probability of short-term progression given an individual subject's covariates, current EDSS, and EDSS measured 6 months prior. Specifically, given the EDSS history of a patient and his or her covariates, we specified a partial proportional odds model to the probabilities of different possible values of the EDSS in the next visit (6 months). The model depends only on the two most recent EDSS values (current and previous 6-month EDSS), hence this is a Markov Model of order two. Markov model of the order one (dependent on only current EDSS) was initially attempted, but was rejected by a statistical goodness-of-fit test. The partial proportional odds model specifies the transition probabilities between EDSS values in consecutive visits and is an extension of the logistic model to ordinal response. Similar to logistic regression analysis, coefficients of covariates are interpreted as ORs. Model estimation was performed by solving generalized estimating equations after manipulation of the data using SAS proc genmod.[15]

Time to progression was defined as the time to sustained (two semi-annual visits) EDSS of 3, which signifies the start of moderate disability. Estimates of the probability of progression over time were calculated as follows. For each subject, the model results were translated to 6 months transition probabilities (between EDSS values). Subject specific probabilities were arranged in a transition matrix and by using simple matrix manipulations and multiplications, produced the probability curves of time to progression. Pointwise CIs were constructed using asymptotic normal theory and a resampling procedure. The curves were created up to 10 visits (5 years). A detailed description of the statistical methodology is currently in press.[16]

Due to the low range of EDSS scores in the cohort, three EDSS levels were created. The EDSS levels were defined as 1 (0 to 1.5), 2 (2 to 2.5), or 3 (≥3). Zero to 1.5 was considered one step due to the high rate of inter-/intrarater variability at this low range of the EDSS. In addition, due to the minimal disability of the cohort, an EDSS of 3 and higher were considered one state. Clinical and MRI measurements were analyzed as categorical covariates divided by quartiles with the exception of disease duration, in which the divisions were created to equally disperse the number of three sequential visits. The following baseline covariates obtained at the time of enrollment into CLIMB were included in the multivariate analysis: sex, age, disease duration from initial symptom, BPF, and T2 lesion vol-

Table 1 Subject demographic and disease characteristics

Characteristics	Values
Patients, n (%)	205
Female	159 (77.6)
Male	46 (22.4)
Age, y, mean ± SD (range)	38.79 ± 9.3 (19–62)
Diagnosis, n (%)	
CIS	19 (9.3)
RR	186 (90.7)
Disease duration from onset, y, mean ± SD (range)	4.90 ± 5.8 (0–29.0)
EDSS, mean ± SD (range)	1.41 ± 1.18 (0–6.5)
BPF, mean ± SD (range)	0.8829 ± 0.03750 (0.7542–0.9577)
T2 lesion volume, mL, mean ± SD (range)	4.394 ± 4.495 (0.78–34.57)
Disease-modifying therapy, n (%)	175 (85.4)

CIS = clinically isolated syndrome; RR = relapsing remitting; EDSS = Expanded Disability Status Scale; BPF = brain parenchymal fraction.

Table 2 Description of sequential Expanded Disability Status Scale (EDSS) levels collected from the cohort

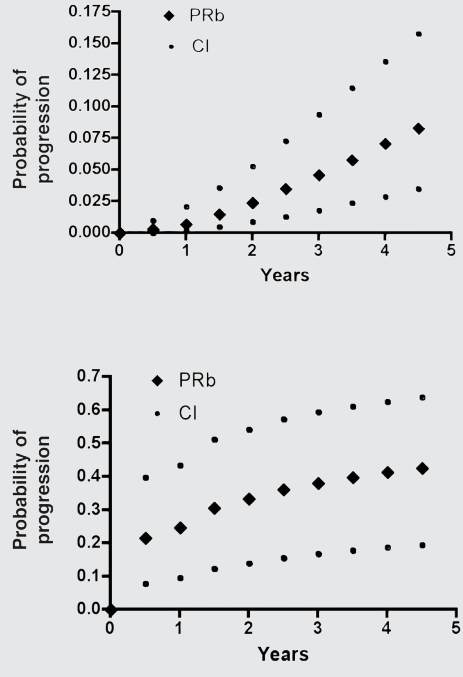
Third visit EDSS level; first two EDSS levels	Number			Proportion, %		
	1	2	3	1	2	3
1,1	363	33	2	91.2	8.3	0.5
2,1	45	16	2	71.4	25.4	3.2
3,1	3	2	1	50.0	33.3	16.7
1,2	29	18	3	58.0	36.0	6.0
2,2	20	63	11	21.3	67.0	11.7
3,2	2	11	10	8.7	47.8	43.5
1,3	2	3	5	20.0	30.0	50.0
2,3	1	8	9	5.6	44.4	50.0
3,3	1	12	50	1.6	19.0	79.4

The first and second 6-month EDSS levels of a set of three consecutive visits created the EDSS profile, which together with the third visit EDSS were applied to the second order Markov model to calculate the transition probabilities. The EDSS levels observed at the third of three sequential visits arranged by EDSS profile are represented as an absolute number and a proportion.

ume. Age and disease duration were the only covariates considered as time dependent. The MRI covariates used in the model were the baseline values (fixed in time) since their pattern of future change is not predictable.

RESULTS A total of 218 RR and CIS patients were enrolled in CLIMB study between April 2000 and April 2005 and had 725 sets of three sequential visits; 205 of these patients had available covariate data for the multivariate analysis and 669 sets of three sequential visits. Baseline demographic and disease characteristics of the 205 subjects upon enrollment are presented in table 1. The first and second 6-month EDSS levels of a set of three consecutive visits created the EDSS profile, which together with the third visit EDSS were applied to the second order Markov model to calculate the transition probabilities. The EDSS levels observed at the third of three sequential visits arranged by EDSS profile are shown in table 2. This table demonstrates that patients with an EDSS profile (1,1) have a small probability to progress to an EDSS of 3 and people with an EDSS profile of (3,3) have a small probability to improve to an EDSS of 1, however these probabilities still exist. If the one-order Markov model were appropriate for these data then the proportions of third visit EDSS levels would be equal among those patients with the same second visit EDSS levels. Table 2 clearly reveals that the one order model would fail. Due to the low occurrences of some EDSS profiles, combinations of selected profiles were used in the model. The EDSS profiles (1,3) and (2,3) were combined, and similarly, (2,1) and (3,1) were combined; this grouping was based upon having improvement or worsening over a 6-month period. Thus, there were a total of seven EDSS profiles used for the analysis.

Figure 1 Crude probability curves to sustained disability of an Expanded Disability Status Scale (EDSS) of 3



Upper panel: Patient with an EDSS of 1 at time 0 and an EDSS of 1 at −0.5 years. Lower panel: Patient with an EDSS of 2 at time 0 and an EDSS of 3 at −0.5 years. PRb = probability.

The crude probability for subsequent EDSS progression at 6-month intervals was calculated from a transition matrix similar to that shown in table 2 after combining the EDSS profiles and is represented by probability curves (figure 1). The probability curves shown in figure 1 demonstrate a comparison of two patients with different 6-month EDSS levels and their individual probability to reach a sustained EDSS of 3 (note that the scale of the Y axis differs). A patient with a sustained EDSS of 1 over the past 6 months has the probability of 0.046 of a sustained EDSS of 3 at 3 years as compared to 0.382 for a patient with a current EDSS of 2 and an EDSS of 3 6 months prior.

Controlling for EDSS over the past 6 months, the ORs for a change in subsequent 6-month EDSS based on specific covariates were calculated using the partial proportional odds model and are given in table 3. The univariate analysis demonstrated a significant association within specific MRI quartiles. The lowest BPF quartile (OR 1.99; $p = 0.0203$) compared to the highest quartile and the highest T2 lesion volume quartile (OR 2.19; $p = 0.0130$) compared to the lowest quartile were associated with subsequent progression in EDSS. These quartile associations were not significant in the multivar-

Table 3 Results of the partial proportional odds model

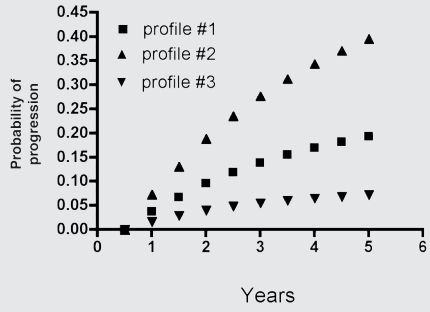
Covariate	OR	CI	*p* (Quartile)	*p* (Category)
Univariate analysis				
Sex				
Female	0.67	0.41–1.11		0.1201
Male (reference)				
Age, y				0.4261
≤32 (reference)				
33–38	0.89	0.46–1.73	0.7373	
39–46	0.85	0.45–1.59	0.6062	
≥47	1.27	0.68–2.35	0.4489	
Disease duration, y				0.2161
≤3 (reference)				
3.5–6	1.56	0.88–2.76	0.1260	
6.5–10	1.80	0.996–3.26	0.0516	
≥10.5	1.76	0.93–3.32	0.0825	
BPF				0.0917
≤0.8598	1.99	1.11–3.55	0.0203	
0.8599–0.8837	1.23	0.64–2.36	0.5320	
0.8838–0.9117	1.09	0.57–2.07	0.7931	
≥0.9118 (reference)				
T2 lesion volume, mL				0.0565
≤1.81 (reference)				
1.82–2.95	1.27	0.64–2.49	0.4926	
2.96–5.08	1.45	0.75–2.80	0.2757	
≥5.08	2.19	1.18–4.06	0.0130	
Current EDSS profile†				<0.0001
Multivariate analysis				
Covariate				
Sex				0.3568
Age				0.5879
Disease duration				0.4703
BPF				0.5805
T2 lesion volume				0.5545
Current EDSS profile				<0.0001

*Division not by quartiles.
†Current Expanded Disability Status Scale (EDSS) and EDSS 6 months prior.
BPF = brain parenchymal fraction.

iate analysis. The strongest association with subsequent progression in both the univariate and multivariate analysis was EDSS over the past 6 months. The coefficients for all of the specific EDSS profiles provide minimal information and therefore are not listed in table 3. The multivariate estimates calculated from the proportional odds model were incorporated into the transitional matrix to calculate covariate specific probabilities. These covariate specific probabilities are represented graphically in figure 2 wherein three different patient profiles were created to represent the influence of various clinical and MRI characteristics on subsequent progression. A patient with profile 1 (an average person) has a 0.139 probability of progressing to a sustained EDSS of 3 within 3 years, whereas profile 2 (high atrophy, high lesion burden) patients will have a probability of 0.277 and 3 (low atrophy, low lesion burden) patients will have a 0.055 probability of progressing.

DISCUSSION A Markov transitional model was considered for our MS clinical data due to the discrete nature of progression through the various EDSS levels. The Markov model incorporates the

Figure 2 Covariate specific probability curves to sustained Expanded Disability Status Scale (EDSS) of 3



All patients with a sustained EDSS of 2 over past 6 months. Profile 1: MRI and clinical values based on means: female, 39 years of age, disease duration of 5 years, brain parenchymal fraction (BPF): 0.882, T2 LV: 4.4 mL. Profile 2: BPF lowest quartile and LV in highest quartile: female, 39 years of age, disease duration of 5 years, BPF: 0.8525, T2 LV: 10.83 mL. Profile 3: BPF highest quartile and LV in lowest quartile: female, 39 years of age, disease duration of 5 years, BPF: 0.9209, T2 LV: 1.03 mL.

ongoing fluctuating nature of the disease to calculate the probability of subsequent disability; therefore we were able to gain clinical information that would have been lost from censored patients in a traditional survival analysis. For example, in a survival analysis, when estimating the time to an EDSS of 6, patients without disability (EDSS of 0) at the end of the study are treated equally to patients with severe disability (EDSS of 5). Another important feature of the Markov model is that it can be used to estimate various outcome measures such as sustained or non-sustained one-point increase in EDSS and as longitudinal data are collected, traditional outcomes such as an EDSS of 6 or higher may be used. Others have also considered the application of a Markov model to MS data. Markov transitional models were previously applied to experimental allergic encephalomyelitis to determine the probability of transitioning from a relapse to a remission and provided measures for the mean time occupied in each state, mean time to first relapse/remission, and steady-state probabilities.[12] In addition, a continuous Markov model was applied to clinical MS data to describe the movement between a relapsing state into a progressive disease state.[17] Further work expanding upon this allowed for a time estimate of the transitions as a function of multiple clinical variables using a survival model.[18] However, this approach requires continuous information in regard to the clinical outcome of each subject and it is best suited to progressive processes. A discrete Markov model was chosen for this analysis since EDSS data are collected at discrete time intervals within the CLIMB study as well as in the clinical practice of MS. Furthermore, a discrete Markov model incorporates clinical improvement as well as progression to calculate the probability of future disability, as opposed to a continuous model, which assumes only a forward movement through the disease states.

The use of longitudinal disability curves is helpful to visualize the probability of progression in MS and has been traditionally represented as Kaplan Meier survival curves. A recently published study presented an approach to MS disability curves[19] based upon percentiles of EDSS scores at specific disease durations. Interestingly, patients with MS were compared through the use of percentiles and the average expected pattern of patients falling within specific percentiles could be ascertained. Although this methodology can provide information regarding where a patient with MS may fall within a distribution, it does not represent a mechanism to incorporate covariates that may potentially influence future progression. Our methodology allows for a comparison of patients but with the ability to incorporate both clinical and MRI data to create covariate specific probability curves. The interpretation of our results should be similar to a survival analysis in that the covariate specific probabilities represent the average behavior of a patient within a specific profile. The curves in figures 1 and 2 demonstrate the usefulness of this method wherein the probabilities derived from the matrix can create survival-type disability curves that provide a method to compare patients. The associations found within the univariate analysis between specific MRI quartiles and subsequent EDSS progression were apparent among the three different covariate specific curves in figure 2. In patients with a 6-month sustained EDSS of 2, the probability of a sustained progression to an EDSS of 3 in patients within the lowest BPF quartile and highest T2 lesion volume quartile was five times that of a patient within the highest BPF and lowest T2 lesion volume quartiles and two times that of a patient at the mean. Dividing the covariates into quartiles was used as an aid to interpret the model results; quartiles were used since there are no clear cutoffs in the literature.

Brain atrophy has emerged as a potential marker of tissue destruction in MS with a cross-sectional correlation with disability which is stronger than that of T2 lesion load/volume.[20-22] There is evidence that brain atrophy begins early within the disease; however, its relationship with T2 lesion burden is still unclear.[23] In an 8-year longitudinal study, the change in brain atrophy over the initial 2 years was independently associated with long-term disability at 8 years.[24] Patients within the largest quartile of change had nearly a four times higher rate of progression to an EDSS ≥6 at 8 years compared to those in the lowest quartile, indicating that the rate of atrophy may have a strong influence on long-term disability. Although the cross-sectional corre-

lation of T2 lesion load and disability has been disappointing, the long-term potential of early T2 lesion burden was found to be significantly associated with long-term disability.[25] Thus, the incorporation of longitudinal MRI data including the rate of atrophy and T2 lesion accumulation may strengthen the predictive potential of MRI in this model. We will be able to formally test this hypothesis as more data are collected in the CLIMB study. Most importantly, a patient's clinical history as represented by EDSS over the past 6 months compared to the MRI or demographic features remained as the most significant factor for future progression.

Relapse data are collected retrospectively in our study as in most observational studies without an accurate documentation of specific EDSS changes as compared to clinical trials in which patients are evaluated at the time of a relapse. Due to these limitations, the second order model was developed in attempt to minimize the effect of relapses, since a single EDSS measurement may represent a relapse. As the CLIMB study continues, this model can be expanded to the third order, which depends upon the current EDSS and last two semi-annual EDSS, to further minimize the effect of relapses and offering another advantage to this methodology when analyzing data from observational studies. Since the effect of relapses on long-term disability remains unclear and their effect may be dependent upon the stage of the disease,[1,26,27] we will continue to collect this data and add it to the model as another covariate. At the time of this analysis, the relapse data from the CLIMB study were incomplete.

In addition, based upon this work, we have the opportunity to assess various treatment regimens. The majority of the patients included in the analysis were treated with one of the currently available injectable treatments; therefore, it was assumed that all patients were maximally treated. The decision to initiate or change treatment is most often based upon the progression of the disease; as a consequence, the incorporation of treatment as a covariate into predictive models is a significant challenge. A comparison of untreated patients to treated patients was completed and revealed that the former were older, had longer disease duration, and had a lower EDSS at baseline, revealing that these patients may have a more benign course of the disease. Therefore, until the factors that influence treatment decisions are collected, treatment cannot be accurately assessed with data from observational studies and if included will be biased and possibly not valid. However, the Markov model provides a framework to integrate therapy and to compare groups of patients on different regimens.

Therefore, now that we have established this new method, we can further assess its value in the progressive stage of MS and its ability to evaluate the influence of additional covariates such as specific treatments, relapses, new MRI metrics, as well as immunologic and genetic markers on subsequent disability. The curves presented in this article were calculated for up to 5 years; extending this to long-term prediction would be dependent on the assumptions of the model. In our case, accurate prediction is dependent upon the Markov assumption (the association of a patient's 6-month EDSS and future EDSS) as well as the covariates, and the error of this prediction accumulates over time; thus an approximate model yields good prediction for the short term, but less so for the long term. As the CLIMB study continues to enroll and follow patients, data will be available for the expansion of this model and at that time the validation of the results will be completed on a separate dataset. Thus, we believe that the Markov model represents a novel approach to short-term prediction in MS and provides an advantageous alternative to the traditional survival methods.

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