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Predicting the On-Study Relapse Rate for Multiple Sclerosis Patients in Clinical Trials

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Abstract

Background: The annual relapse rate has been commonly used as a primary efficacy endpoint in phase III multiple sclerosis (MS) clinical trials. The aim of this study was to determine the relative contribution of different possible prognostic factors available at baseline to the on-study relapse rate in MS. **Methods:** A total of 821 patients from the placebo arms of the Sylvia Lawry Centre for Multiple Sclerosis Research (SLCMSR) database were available for this analysis. The univariate relationships between on-study relapse rate and the baseline demographic, clinical, and MRI-based predictors were assessed. The multiple relationships were then examined using a Poisson regression model. Two predictor subsets were selected. Subset 1 included age at disease onset, disease duration, gender, Expanded Disability Status Scale (EDSS) at baseline, number of relapses in the last 24 months prior to baseline, and the disease course (RR and SP). Subset 2 consisted of Subset 1 plus gadolinium enhancement status in MRI. The number of patients for developing the models with no missing values was 727 for Subset 1 and 306 for Subset 2. **Results:** The univariate relationships show that the on-study relapse rate was higher for younger and for female patients, for RR patients than for SP patients, and for patients with positive enhancement status at entry (Wilcoxon test, $p<0.05$). A higher on-study relapse rate was associated with a shorter disease duration, lower entry EDSS, more pre-study relapses and more enhancing lesions in T1 at entry. The fitted Poisson model shows that disease duration (estimate=-0.02) and previous relapse number (estimate=0.59 for 1, 0.91 for 2 and 1.45 for 3 or more relapses vs 0 relapse) remain. We were able to confirm these findings in a second, independent dataset. **Conclusions:** The relapse number prior to entry into clinical trials together with disease duration are the best predictors for the on-study relapse rate. Disease course and gadolinium enhancement status, given the other covariates, have no significant influence on the on-study relapse rate.

Introduction

Since the results of the pivotal trial of interferon β-1b were reported in 1993,[1] the annual relapse rate has been commonly used as a primary efficacy endpoint in phase III clinical trials for relapsing-remitting (RR) and as secondary outcome for studies with secondary progressive (SP) multiple sclerosis (MS) patients.[2-10] These trials demonstrated a reduction of the annual relapse rate.[1-10] Most of the trials enrolled patients with a history of at least two relapses in the two years prior to entry,[1,3,4,6,7,9] being 15 – 64 years old,[1,2,4-10] having more than one year of disease duration,[1,2,7,10]and with Expanded Disability Status Scale (EDSS) scores within a range below 6.0 for RR patients[1-3,6,7,9,10] and 3.0 – 6.5 for SP patients.[4,5,8]

Several studies addressed the relationship between relapse rate and demographic and clinical factors. For subjects in natural history cohorts, Weinshenker[11] and Ebers[12] summarized the results from several studies which showed that the relapse rate was higher in younger patients, also higher for patients with a shorter disease duration, and was not correlated with the clinical course.[13] In a 9-month, placebo-controlled study[14] it was also found that the on-study relapse rate was correlated with the number of relapses during the two years before entry into study. However, the magnitude of the effects of these baseline demographic and clinical variables on the annual on-study relapse rate was only examined univariately.

It was assumed that it is the inflammatory aspect of the lesions as seen in magnetic resonance imaging (MRI) that is in closest relation to relapses.[15] In consequence the lesion numbers on MRI have been proposed as predictors for the occurrence of subsequent relapses.[16] However, studies showed that there was only a weak univariate correlation of MRI-based measures, especially gadolinium enhancing lesions at baseline and on-study relapse rate, visible in MS patients.[14,17]

The aim of this study was to determine the relative contribution of a large set of different possible prognostic factors for the on-study relapse rate in MS in a multiple regression model. This would help to select patients more efficiently for clinical trials that use relapse rate as a primary endpoint.

Methods

Patients and variables

A total of 821 RR and SP patients from the placebo arms of RCTs in the "open" part of the SLCMSR database were available for the analysis. Each release of the SLCMSR database is divided into an "open" and a "closed" : a working sample and a validation sample. The main hypotheses generated from an analysis of the "open" portion are then retested in a second, confirmatory validation step using the "closed" part of the database prior to submitting the results for publication.

The on-study relapse rate as response variable was referred to as the number of relapses during the first year of the study. The lower boundary for the first year was fixed at 330 days, which means that patients observed shorter than 330 days were excluded from the analysis. For some patients we have information only about the number of relapses in a certain time interval which does not necessarily coincide with the one year observation period we are interested in. Therefore, these relapses were counted proportionally and as a consequence some of the relapse rates are non-integers.

If the follow-up period is extended from one to two years (lower boundary 690 days), the number of patients drops to 620 (256 RR and 364 SP). However, as the 2-year follow-up on relapse rate

is relevant for phase III trials, we will report on the corresponding results along the lines of the one year analyses.

Variables selected as possible predictors at baseline for the on-study relapse rate include continuous variables (age at disease onset, disease duration (time since first symptom), T2 lesion volume), ordinal variables (EDSS, number of relapses in the 12 and 24 months prior to entry into the study, number of enhancing lesions in T1), and binary variables (gender, disease course (RR vs SP) and gadolinium enhancement status in T1). All patients had to be free of relapses at entry into the study.

Statistical methods

The univariate relationships between the on-study relapse rate and baseline explanatory variables were assessed by the Wilcoxon rank sum statistic for binary predictors and Spearman's rank correlation coefficient for continuous and ordinal predictors.

Next, the multiple relationships were examined using a Poisson regression model. The non-integer on-study relapse numbers were rounded. To check if overdispersion was present, a quasi-likelihood model was fitted with all covariates. The estimated overdispersion parameter was close to 1, hence it seemed appropriate to use regular Poisson regression and Akaike's information criterion (AIC) to develop the model,[18,19] and then obtain the final estimates by a quasi-Poisson model.[18] Initial models with all covariates were developed with a stepwise model selection procedure based on minimizing the AIC. To limit the tendency of this automatic procedure to favour a complex model, the stepwise procedure was terminated if selected predictors failed to achieve significance at a 5% level. Predictor subsets were selected based on statistical, clinical, and data availability considerations. Subset 1 initially included age at disease onset, disease duration, gender, EDSS at baseline, number of pre-study relapses in the last 24

months, and the disease course (RR or SP). Data on gadolinium enhancement status was not included in this subset for maintaining the sample size, but the potential importance of this predictor was considered in Subset 2, consisting of all predictors in Subset 1 plus gadolinium enhancement status. Considering the high variability between individual raters and image analysis centres[20] (personal communication with Prof. Schach about heterogeneity in pooled MS trials which cannot be explained by clinical and demographic differences alone) for determining the number of enhancing lesions we have condensed this information to enhancement status. Both EDSS scores and the number of relapses in the last 24 months prior to entry into the trials were treated as categorical variables (three categories with similar number of patients for EDSS: 0-3.0, 3.5-5.0, and 5.5 or above; four categories for prior relapse number: 0, 1, 2, and 3 or more). The number of patients with complete observations for all of these variables was 727 (332 RR and 395 SP patients) for Subset 1 and 306 (174 RR and 132 SP patients) for Subset 2. The 2-year analysis included 585 patients in Subset 1, and 183 patients in Subset 2.

Expansions of these initial models were considered allowing interactions between included predictors. Following the final fitted models, the confidence intervals for the predicted mean on-study relapse rate were computed.

The original set of 821 patients decreased quite considerably when fitting the predictors in the multiple models, especially for Subset 2. In order to address the question of selection bias, we performed a homogeneity analysis and compared the patients of Subset 1 and Subset 2 with their missing counterparts from the total of 821 patients (94 for Subset 1 and 515 for Subset 2, respectively). We compared the patient groups with respect to the distribution of the variables age at onset, disease duration, gender, EDSS, pre-study relapses, enhancement status, disease course and the on-study relapse rate, and found no major differences. The only discrepancies we found were in the 94 patients corresponding to Subset 1. They seemed to have somewhat shorter

disease duration (8.16 years versus 10.77 years), a slightly higher previous relapse rate (2.67 versus 1.94), and a larger percentage of RR patients (70.21% versus 45.67%).

Following completion of the analyses in the "open" part of the database, a summary of the major findings was prepared. A detailed proposal for specific analyses required to confirm these findings was approved by the SLCMSR Publication Committee. The SLCMSR data trustees then executed these analyses in the "closed" part of the database.

Results

Descriptive statistics

The "open" part of the dataset available for the analysis was derived from nine different image analysis centres. The inclusion criteria were not identical among the clinical trials, however, we expect the potential heterogeneity in mean age, duration of the disease, EDSS scores, and relapse rate prior to entry to study to be captured by the multiple regression models. The on-study relapse rate was available for a total of 821 placebo patients, where 398 patients were diagnosed with RRMS and 423 patients with SPMS. As the individual trials differed in entry criteria and variables collected, the number of patients with data available differed depending on the particular explanatory variables being studied. The descriptive statistics are shown in Table 1.

Table 1 about here.

The demographic and clinical data of patients in the two subsets are shown in Table 2.

Table 2 about here.

Univariate analysis

The Spearman rank correlation coefficient (r) for the continuous variables and the Wilcoxon rank sum statistic for the binary predictors were used to assess the relationship with on-study relapse rate, which is shown in Table 3.

Table 3 about here.

The results show that the on-study relapse rate was larger for RR patients than for SP patients, also for younger and for female patients, and for patients with positive enhancement status at entry. A higher on-study relapse rate was associated with a shorter disease duration, and lower entry EDSS. Patients who had more previous relapses or more enhancing lesions in T1 tended to have a higher on-study relapse rate. There was no significant relationship between on-study relapse rate and T2 lesion volume at entry. Thus, this predictor was not considered any further in the multiple regression models.

In Table 4, the on-study relapse rate was then compared between RR and SP patients stratified by the previous relapses (0, 1, 2, and 3 or more relapses).

Table 4 about here.

None of the between-group comparisons was significant at a 5% level, i.e. given the number of relapses in the last 24 months, the on-study relapse rate did not significantly differ for RR and SP patients.

We also compared the on-study relapse rate between patients with no or at least one enhancing lesion for 0, 1, 2, 3 or more previous relapses. The results are described in Table 5, and again we found no significant difference between gadolinium status groups.

Table 5 about here.

Poisson regression analysis

The initial fit of the model for Subset 1 with all the covariates returned an overdispersion parameter of 1.10. This shows that the estimated standard errors for the effects are slightly too small. Then the stepwise model selection procedure based on the AIC criterion included disease duration, relapse number in the last 24 months, and age at onset into the model, in which disease duration and relapse number in the last 24 months were significant at a 5% level. The model with the three predictors was not significantly better than the model with the two significant predictors as described above (the likelihood ratio test statistic was 2.99 with 1 degree of freedom, p=0.08). Adding an interaction between disease duration and previous relapse number into the model did not improve the model fit significantly (p=0.65). And there was no enlargement in sample size when refitting the model only with these two predictors.

For Subset 2, which includes gadolinium enhancement status, the overdispersion parameter in the initial model with all the covariates was 1.13, then the stepwise selection procedure based on the AIC criterion was used for model development. Only relapse number in the last 24 months was significant at a 5% level. Thus given the pre-study relapse number, no significant effect of Gadolinium enhancement status could be shown in this smaller subset. On the other hand, if gadolinium enhancement was the only predictor for modeling on-study relapse rate, then the p-value was found to be 0.030. However, when using the predictors identified in Subset 1 (relapse number in last 24 months and disease duration) the additional inclusion of the variable gadolinium enhancement led to a p-value of 0.152, thus no longer significant. Therefore, the final model could only be based on Subset 1. The fitted model is described in Table 6, where the standard errors were adjusted for the estimated overdispersion.

Table 6 about here.

The results show that a longer disease duration is associated with a lower on-study relapse rate; the more relapses were observed prior to entry to the study, the higher is the on-study relapse rate.

The model selection on Subset 1 for the 2-year follow-up arrived at the same final model: the relapse number in prior 24 months and disease duration are the best clinical predictors, and both are significant at a 5% level. The effect sizes and p-values of the predictors are nearly identical to the ones obtained for the 1-year analysis. The estimate of the intercept changed from -0.93 in the 1-year follow up to -0.22 for the 2-year results to explain the higher relapse rate level when considering the extended observation period.

In Subset 2, the univariate influence of enhancement status on the 2-year on-study relapse rate yields a p-value of 0.07, and thus the final model can be based on Subset 1.

Predicted on-study relapse rate

The predicted on-study relapse rate and corresponding 95% confidence intervals for the mean were calculated based on the fitted Poisson regression model with overdispersion. These are shown in Table 7.

Table 7 about here.

Validation results

The "closed" part of the SLCMSR database release that was held back for confirmation of hypotheses contained 1047 RR and SP patients with information on the relapse rate for the first year on trial. Distribution with respect to disease course, on-study relapse rate, attack number in

24 months prior to study entry, baseline EDSS and enhancement status were very similar in the "open" and "closed" parts, indicating they were comparable and suitable for the purpose of validation.

Significant univariate relationships were confirmed for the important predictors selected in the multiple regression analyses for Subset 1. These included the correlation of disease duration, and attack number last 24 months with the on-study relapse rate, and the comparison of the relapse rate of patients with and without positive enhancement status.

Validation of the multiple Poisson regression model for Subset 1 revealed a significant effect of disease duration, and attack number in the last 24 months. On Subset 2, we first fitted a Poisson model with the predictor enhancement status alone, which gave $p=0.005$. Along the lines of the analyses in the "open" part, we assessed the importance of enhancement status if it enters as an additional predictor given disease duration and prior attack number. The resulting p-value for enhancement status in the multiple Poisson model was then 0.09, which corresponds exactly to the results obtained in the "open" part.

In summary, we were able to validate all findings in the "closed" portion of the data release, including the result that gadolinium enhancement status alone is a significant predictor for the on-study relapse rate in the first year. However, when it enters in the multiple model, its significance diminishes compared to the clinical predictors disease duration and attacks prior 24 months.

Discussion

Although only a part of the entire database could be used for this study, the number of 821 placebo patients studied was still a magnitude larger than that seen in a typical phase III clinical trial (commonly 100-500 patients per arm). Additionally, in using data from several trials, the possibility of selection bias is reduced.

The results revealed modest but nevertheless significant relationships between on-study relapse rate and various clinical and MRI-based determinants including disease course, disease duration, gender, age at disease onset, EDSS at baseline, relapse rate prior to entry into the study, and enhancing lesion numbers in T1.

Some variables retained considerable prognostic value even in a multiple regression approach including number of relapses in the last 24 months and disease duration, and these findings were unequivocally confirmed in the "closed" part of the SLCMSR database. As such, the utility of the Poisson regression model would be primarily in defining the expected on-study relapse rate in groups of patients considered for clinical trials. The mean on-study relapse rate could therefore be predicted by pre-study relapse number and disease duration. This is illustrated in Table 6: if we take a patient with 10 years of MS, the predicted on-study relapse rate for the patients with 0, 1, 2 and 3 or more relapses in the previous two years would be 0.33, 0.60, 0.83, and 1.43, respectively.

The results for a 2-year follow-up are very similar to the ones obtained in the first year – even though they are based on 25% less patients: model selection on Subset 1 arrived at the same model for the 2-year rates including disease duration, and number of relapses in last 24 months as best clinical predictors. The effect sizes and p-values corresponded well to the results for the

first year. However, for Subset 2, even the univariate contribution of enhancement status is not significant.

Another implication of these findings includes the role of relapse number prior to study entry and disease duration as stratification criteria for the randomization of the patients in placebo and treatment arms of a clinical trial. If not used as such, they should alternatively be adjusted for as covariates in the statistical analysis when demonstrating the treatment effect.

Furthermore, we found that the disease course does not have a significant contribution to the multiple model although its contribution appears as significant in the univariate analysis. This is due to the association of disease course and previous relapse number (the correlation coefficient between these two variables is 0.59). The effect of the disease course is captured by the pre-study relapse number, which can be seen in Table 4. This implies for future trials, that the enrolment should rather be based on the relapse number in the last 24 months than on the disease course.

The value of enhanced MRI for predicting clinical outcomes has not been well established. A longitudinal study found a correlation between enhanced MRI lesions at entry and the relapse rate in the next year.[21] However, another meta-analysis from five natural course studies and four placebo groups of clinical trials showed that the relationship between gadolinium enhancement status at baseline and relapse rate was only marginal.[17] In the current study, in the univariate comparison gadolinium enhancement was significantly correlated with on-study relapse rate. The trend towards an increase of the on-study relapse rate in patients with enhanced lesions is depicted in Table 5. However, in the multiple model the predictive value decreased when the other clinical covariates entered. Several reasons for this finding are possible. Enhanced MRI is able to detect the inflammatory activity of the disease with high sensitivity. But, some lesions might be clinically silent, i.e., damage to the central nervous system pathways is not reflected in

the clinical symptoms or signs. About 50 percent of the patients will have at least one gadolinium-enhancing lesion at any given time. However, different patients contribute at different time points and a large proportion of these lesions are not associated with clinical manifestations. Gadolinium-enhancing lesions occur up to ten times more often than clinical relapses.[22] Another reason for this lack of relationship may be related to the pathology of MS lesions. Gadolinium enhancement depicts local breakdown of the blood-brain barrier and to some extent inflammatory infiltration. When taking recent evidence about a more complex role of the immune system in the pathogenesis of MS into account[23], this may or may not be followed by demyelination and axonal injury and clinically detectable deficits.

This study provides information about the predictive role of demographic, clinical, and MRI-based parameters on the on-study relapse rate. The benefit of the model fitted in this study is that inclusion or exclusion of a patient into a clinical trial could be based on a predicted relapse rate rather than on a single demographic or clinical characteristic. In particular, patients selected for relapse intervention trials should usually meet a relapse rate criterion which depends on the number of relapses in the two years pre-trial and disease duration.

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Table 1. Descriptive statistics of the predictor variables

Variable	Statistic	Total	RRMS	SPMS
On-study relapse rate	N	821	398	423
	Mean (SD)	0.88 (1.16)	1.12 (1.23)	0.65 (1.05)
	Median	0	1	0
	Range	0 – 7	0 – 7	0 – 6
Gender	N	821 (100.00%)	398 (100.00%)	423 (100.00%)
	Male	292 (35.57%)	115 (28.89%)	177 (41.84 %)
	Female	529 (64.43%)	283 (71.11%)	246 (58.16 %)
Age at onset (years)	N	815	394	421
	Mean (SD)	29.37 (7.87)	28.61 (7.22)	30.08 (8.38)
	Median	29	28	29
	Range	4 – 57	10 - 53	4 – 57
Disease duration (years)	N	815	394	421
	Mean (SD)	10.49 (7.65)	7.14 (6.10)	13.61 (7.65)
	Median	8.50	5.42	12.50
	Range	0.50 – 40.92	0.50 - 37.67	1.33 - 40.92
EDSS	N	821	398	423
	0.0 – 3.0	262 (31.91%)	253 (63.57%)	9 (2.13%)
	3.5 – 5.0	290 (35.32%)	122 (30.65%)	168 (39.72%)
	5.5 – 8.0	269 (32.77%)	23 (5.78%)	246 (58.15%)
Relapses during last 12 months	N	672	302	370
	Mean (SD)	0.90 (0.98)	1.46 (0.98)	0.44 (0.70)
	Median	1	1	0
	Range	0 – 5	0 - 5	0 - 3
Relapses during last 24 months	N	733	336	397
	Mean (SD)	1.95 (1.69)	2.93 (1.47)	1.12 (1.40)
	Median	2	3	1
	Range	0 – 9	0 - 9	0 - 8

T2 lesion volume (cm^3)	N	554	206	348
	Mean (SD)	21.24 (19.69)	17.81 (18.06)	23.27 (20.35)
	Median	16.02	12.68	18.37
	Range	0.07 – 135.44	0.07 – 128.60	0.20 – 135.44
Number of enhancing lesions in T1	N	382	232	150
	Mean (SD)	2.45 (4.84)	2.81 (5.57)	1.88 (3.35)
	Median	1	1	0
	Range	0 – 47	0 - 47	0 - 16
Gd. Enh. lesions	N	382	232 (100.00%)	150 (100.00%)
	At least one/	210 (54.97%)	133 (57.33%)	77 (51.33%)
	None	172 (45.03%)	99 (42.67%)	73 (48.67%)

SD=standard deviation, Gd. enh. lesions=Gadolinium enhancing lesions

Table 2. Demographics of patients in the two subsets

Variable	Statistic	Subset 1		Subset 2	
		RRMS (N=332)	SPMS (N=395)	RRMS (N=174)	SPMS (N=132)
On-study relapse rate	Mean (SD)	1.17 (1.23)	0.62 (0.98)	1.10 (1.22)	0.70 (1.15)
	Median	1	0	1	0
	Range	0 – 6	0 – 6	0 – 5	0 – 6
Age at onset (years)	Mean (SD)	28.25 (6.92)	30.07 (8.38)	28.39 (7.28)	29.63 (8.33)
	Median	28	29	28	29
	Range	13 – 48	4 – 57	13 – 48	4 – 48
Disease duration (years)	Mean (SD)	7.27 (6.10)	13.71 (7.67)	7.85 (6.56)	13.61 (8.07)
	Median	5.50	12.67	5.92	12.21
	Range	0.67 – 34.83	1.33 – 40.92	0.67 – 34.83	1.67 – 40.92
EDSS	0.0 – 3.0	219 (65.96%)	8 (2.03%)	112 (64.73%)	2 (1.52%)
	3.5 – 5.0	96 (28.92%)	164 (41.52 %)	46 (26.44%)	49 (37.12%)
	5.5 – 8.0	17 (5.12%)	223 (56.46%)	16 (9.20%)	81 (61.36%)
Number of relapses last 24 months	Mean (SD)	2.93 (1.48)	1.11 (1.40)	2.74 (1.53)	0.98 (1.47)
	Median	3	1	2	0
	Range	0 – 9	0 – 8	0 – 9	0 – 8
Gender	Male	94 (28.3%)	163 (41.3%)	49 (28.2%)	61 (46.2%)
	Female	238 (71.7%)	232 (58.7%)	125 (71.8%)	71 (53.8%)
Gd. Enh. lesions	At least one / none	_	_	111 (63.8%) 63 (36.2%)	66 (50.0%) 66 (50.0%)

SD=standard deviation, Gd. enh. lesions=Gadolinium enhancing lesions

Table 3. Univariate relationships between the explanatory variables and on-study relapse rate

Predictor	Relationship	p-value
Disease course	RR > SP	<0.001
Gender	Female > Male	0.048
Age at onset	r = -0.07	0.048
Duration of disease	r = -0.23	<0.001
EDSS	r = -0.18	<0.001
Number of relapses in last 12 months	r = 0.39	<0.001
Number of relapses in last 24 months	r = 0.42	<0.001
T2 lesion volume	r = -0.01	0.785
Number of enhancing lesions in T1	r = 0.15	0.003
Enhancement status	At least 1 lesion > No lesion	0.011

Table 4. On-study relapse rate for RR and SP patients stratified by previous relapses

Relapses in last 24 months	Disease course		
	Statistic for on-study relapse rate	RR	SP
0	**N**	5	182
	Mean (SD)	0.40 (0.89)	0.31 (0.63)
1	**N**	28	83
	Mean (SD)	0.43 (0.69)	0.61 (0.82)
2	**N**	121	82
	Mean (SD)	0.92 (1.02)	0.74 (0.98)
3 or more	**N**	182	50
	Mean (SD)	1.48 (1.32)	1.58 (1.51)

SD=standard deviation

Table 5. On-study relapse rate for enhancement status stratified by previous relapses

Relapses in last 24 months	Enhancement status at baseline		
	Statistic for on-study relapse rate	**No enhancing lesion**	**At least 1 lesion**
0	**N**	39	34
	Mean (SD)	0.33 (0.62)	0.5 (0.86)
1	**N**	25	26
	Mean (SD)	0.44 (0.77)	0.58 (0.86)
2	**N**	31	53
	Mean (SD)	0.71 (0.83)	0.91 (1.10)
3 or more	**N**	38	66
	Mean (SD)	1.42 (1.29)	1.65 (1.53)

SD=standard deviation

Table 6. Fitted Poisson regression model to predict on-study relapse rate

Predictor	Estimate	Std. Error	P-value
Disease duration (years)	-0.02	0.01	0.015
Relapse number last 24 months*			
(1 vs 0 relapse)	0.59	0.20	0.003
(2 vs 0 relapse)	0.91	0.17	<0.001
(3 or more vs 0 relapse)	1.45	0.16	<0.001

* 187 (25.7%) patients had 0 relapse; 111 (15.3%) patients had 1 relapse; 200 (27.5%) patients had 2 relapses; 229 (31.5%) patients had 3 or more relapses.

Table 7. Predicted mean relapse rate for Model 1

Relapses in prior 24 months	Disease duration (years)	Predicted mean	95% Confidence interval
0	0	0.40	[0.28 ; 0.56]
	5	0.36	[0.27 ; 0.49]
	10	0.33	[0.25 ; 0.45]
	15	0.31	[0.23 ; 0.41]
	20	0.28	[0.21 ; 0.38]
1	0	0.71	[0.51 ; 0.98]
	5	0.65	[0.49 ; 0.88]
	10	0.60	[0.46 ; 0.79]
	15	0.55	[0.42 ; 0.72]
	20	0.51	[0.38 ; 0.68]
2	0	0.99	[0.80 ; 1.21]
	5	0.91	[0.76 ; 1.08]
	10	0.83	[0.70 ; 0.98]
	15	0.76	[0.63 ; 0.92]
	20	0.70	[0.56 ; 0.88]
3 or more	0	1.69	[1.46 ; 1.96]
	5	1.55	[1.38 ; 1.75]
	10	1.43	[1.26 ; 1.62]
	15	1.31	[1.11 ; 1.54]
	20	1.20	[0.97 ; 1.50]