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Flexible modeling of disease activity measures improved prognosis of disability progression in relapsing−remitting multiple sclerosis

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Abstract

Objectives: To illustrate the advantages of updating time-varying measures of disease activity and flexible modeling in prognostic clinical studies using the example of the association between the frequency of past relapses and occurrence of ambulation-related disability in multiple sclerosis (MS).

Study Design and Setting: Longitudinal population-based study of 288 patients from Burgundy, France, diagnosed with relapsing−remitting MS in 1990−2003. The end point was a nonreversible moderate MS disability (European Database for Multiple Sclerosis score $\geq$3.0 derived from Extended Disability Status Scale). Alternative time-varying measures of attacks frequency included (1) conventional number of early MS attacks in the first 2 years after diagnosis; and two new measures, continuously updated during the follow-up; (2) cumulative number of past attacks; and (3) number of recent attacks, during the past 2 years. Multivariate analyses used Cox proportional hazards model and its flexible generalization, which accounted for time-dependent changes in the hazard ratios (HRs) for different attack frequency measures.

Results: HRs for all measures decreased significantly with increasing follow-up time. The proposed updated number of recent attacks improved model's fit to data, relative to alternative measures of attack frequency, and was associated with a statistically significantly increased hazard of developing ambulation-related MS disability in the next 2 years during the entire follow-up period.

Conclusion: Updated measures of recent disease activity, such as frequency of recent attacks and modeling of their time-dependent effects, may substantially improve prognosis of clinical outcomes, such as development of MS disability.

Keywords: Prognostic studies; Multiple sclerosis; Disability; Attack frequency; Time-varying covariates; Time-dependent effects

1. Introduction

Modern clinical and epidemiological studies increasingly rely on longitudinal designs with repeated measurements of prognostic and risk factors during the follow-up, which imply more complex data structures. In the past decade, many studies have addressed various analytical challenges encountered in longitudinal studies [1−3]. Cox proportional hazards (PH) model, the most popular statistical model for the analyses of clinical prognostic studies [4], permits modeling repeated prognostic factor measurements through time-varying covariates [5]. Time-varying covariates are necessary to represent any information on prognostic factors or exposures that becomes available only during the follow-up, to avoid important ''immortal time'' or ''survival'' biases [6−8]. They should be also used to model those prognostic factors that change values during

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What is new?

Key findings

- We demonstrate how the results of longitudinal clinical studies of disease progression can be enhanced by both (1) updating prognostic factors during the follow-up and (2) flexible modeling of changes over time in their prognostic ability. These generic methodological issues are illustrated in the context of a longitudinal study of the evolution of relapsing−remitting multiple sclerosis (MS), where prognosis of disability was improved by (1) using a time-varying indicator of the updated number of recent attacks, in the last 2 years, and (2) accounting for a gradually decreasing strength of its impact with increasing disease duration.

What this adds to what was known?

- From the methodological perspective, our analyses and results add empirical evidence of the potential benefits of flexible analyses of time-varying covariates and time-dependent effects in clinical prognostic studies. Although similar advantages have been demonstrated, using mostly simulated data, in statistical literature, the use of flexible statistical models in real-life clinical research is still rare. From the substantive perspective, we have provided new insights into the dynamics of the evolution of relapsing−remitting MS. Published studies of MS typically use only early measures of disease activity, such as the number of attacks in the first 2 years or the interval between the first two attacks, and assume that their effects are constant during the entire disease evolution. In contrast, we demonstrate that updating the number of recent attacks during follow-up significantly improves prognosis of development of MS disability in the next 2 years, across the follow-up period, although the early measures of disease activity quickly lose their associations with the hazard. Moreover, we show that the short-term risks of disability evolution associated with increased recent disease activity are much higher than reported by most previous studies that used conventional statistical models.

What is the implication and what should change now?

- Our substantive findings are relevant for the clinical management of MS patients over time, implying that a continuous reassessment of the recent disease activity may improve prognosis and help adapting the treatment to the current needs of individual patients. On the other hand, our generic methodological conclusions should contribute to an increased use of flexible modeling of time-varying covariates in a wide range of clinical prognostic studies.

the follow-up, especially if the updated, more recent values are expected to be prognostically more relevant than the baseline values [9]. Several recent clinical epidemiology articles have illustrated the potential advantages of time-varying covariates and called for their more frequent use in prospective or retrospective cohort studies [10−13] and even in cross-sectional analyses [14]. However, many clinical studies with repeated measurements of prognostic factors do not use time-varying covariates, possibly due to the uncertainty regarding how to accurately model longitudinal changes in the prognostic factor values [9]. This challenge can be addressed by estimating models with alternative, clinically plausible representations of a time-varying prognostic factor, including, for example, its most recent value and some cumulative measures of past values, and then comparing the goodness of fit of different models [13,15].

Furthermore, the accuracy of the results and conclusions based on the Cox PH model depends on the validity of the underlying assumptions [5]. In particular, (1) the PH assumption constrains the estimated covariate effects [hazard ratios (HRs)] to be constant over time, whereas (2) the log-linearity assumption implies a linear relationship between each continuous prognostic factor and the logarithm of the hazard [5]. These conventional assumptions are seldom tested in clinical prognostic studies [4] and are often accepted a priori. Yet, several flexible models were proposed, in statistical literature, to test these restrictive conventional assumptions, and their applications in prognostic studies revealed frequent, statistically significant and clinically important violations of both the PH [16−19] and/or the log-linearity hypotheses [20,21]. Indeed, both assumptions may be simultaneously violated by the same continuous prognostic factor of mortality, for example, age at diagnosis in different cancers [22−24] or albumin in non−small-cell lung cancer [25]. Accounting for such violations of the conventional assumptions may be essential to both avoid biased estimation and detect a statistically significant association [20,25,26]. Flexible modeling of the effects of prognostic factors has been advocated in several methodological articles in major epidemiology journal [16,20,27,28]. However, in spite of high relevance of, on one hand, (1) modeling of time-varying covariates and, on the other hand, accounting for possible violations of (2) the PH and/or (3) the log-linearity assumptions; to date, only few prognostic studies have simultaneously addressed all these issues.

We illustrate the practical importance of the previously mentioned ‘‘generic’’ methodological considerations in a prognostic study of the evolution of multiple sclerosis (MS). MS is the most common chronic disabling disease of the central nervous system in young adults of Western countries, with a standardized prevalence of 40 to 200 cases per 100,000 inhabitants [29,30]. The disease affects mainly

young women and can lead to a wheelchair dependence and cognitive decline [31]. Initial disease course involves episodes of relapsing and remitting (RR) neurologic dysfunction [32], followed by a progressive phase with slowly increasing impairment and disability [33,34]. Individual patterns of MS evolution are highly variable [35,36], even if global disease course is now well described [37]. An accurate description of the role of prognostic factors associated with MS progression will help better to inform patients about likely future evolution of their disease, allow the clinicians to identify the patients who need immune treatments, and improve the design of new therapeutic trials [38].

Initially, relapsing−remitting form of MS, male gender, older age at onset, cerebellar and sphincter involvement at onset, and incomplete recovery after the first MS attack are all associated with worse disease course [39−41]. In addition, two measures of early disease activity (1) the number of attacks in the first 2 years after diagnosis and (2) the length of the interval between the first two MS attacks were also suggested to be useful prognostic factors [40,42], but their actual impact remains controversial [40,42,43], and it is unclear which has higher prognostic utility [8]. Some discrepancies in results can be partly explained by between-studies differences in: patient populations (unselected vs. specialized reference centers) [44], inclusion of patients with different forms of MS [40,45], definitions of the beginning of follow-up [46], choice of the specific level of disability as the end point, and follow-up duration [47,48]. Finally, the differences between statistical models used and limitations of some published analyses might also have led to different results.

Similar to other prognostic studies, most analyses of the MS evolution rely now on the popular Cox PH model [48−50]. However, most prognostic studies of MS progression use only early disease activity measures, in the first 2 years after diagnosis and ignore all information collected later during the follow-up [51,52]. Yet, continuous reassessment of the frequency of MS attacks during the follow-up could help to understand the dynamic of the MS evolution and to improve prognosis. Indeed, we have previously demonstrated that including, in the Cox PH model, time-varying covariates representing updated measures of disease activity improves the accuracy and the power of the analyses [8].

Furthermore, the effects of different measures of disease activity on the hazard of MS disability may not be consistent with the conventional PH hypothesis, which implies that, for example, number of attacks in the first 2 years is equally useful for prognosticating disease evolution in the early years of MS course as many years later. On the other hand, the log-linearity hypothesis would imply that the HR associated with increasing the number of attacks, for example, (1) from two to four and (2) from six to eight, is the same. Both hypotheses may not be consistent with the true unknown effects of the number of previous attacks on MS evolution. First, the impact of early disease activity markers on the MS evolution may decrease with increasing time since diagnosis [37,48], which would invalidate the PH assumption. Furthermore, to avoid the potentially implausible log-linearity assumption, most previous studies of MS prognosis categorized the number of attacks and the time between the first two attacks, although imposing the PH assumption [8,36,39,53]. However, categorization of quantitative prognostic factors may induce loss of statistical power and bias in the estimated effects [54]. In addition, to ensure accurate estimation and tests regarding the effects of a continuous prognostic factor on the hazard, both the PH and the log-linearity hypotheses have to be simultaneously tested and their possible violations have to be accounted [24,25,55,56].

To address these limitations of previous prognostic studies, we rely on flexible modeling to assess and account for possible changes over time in both the values of a prognostic factor and its impact on the outcome of interest. We then illustrate the potential benefits of flexible modeling and its ability to yield new clinical insights, by applying this approach to reassess the role of the frequency of past attacks as a prognostic factor for time to ambulation-related disability in MS.

2. Methods

2.1. Study population

Study population was derived from the patients followed either at the University Hospital, in Dijon, France, or by a neurologist from the Burgundy Multiple Sclerosis Network, a part of the European Database for Multiple Sclerosis (EDMUS) [57,58]. The network includes all the neurologists in the region of Burgundy and prospectively follows the patients from the onset of their disease, defined as the first MS attack. In the analyses, we have included all 288 patients diagnosed with a confirmed relapsing−remitting multiple sclerosis (RR-MS), according to the Poser's classification [59], diagnosed between January 1, 1990, and November 15, 2003.

2.2. Data collection

Clinical, biological, radiological, and therapeutic information collected at each visit or hospitalization was recorded in a standardized MS database [60,61]. For patients first seen after the disease onset, previous data were entered retrospectively, based on a structured interview, which permits identifying each step of MS evolution [62]. The French commission for data protection (Commission National Informatique et Liberté) approved the study. All patients gave written consent to be included in the database.

Individual case reports included demographics, medical history, biological, electrophysiological and neuroimaging data, and treatments, as well as the dates of key episodes in the MS course [relapses, occurrence of the secondary progressive multiple sclerosis (SP-MS), and of successive

levels of irreversible disability]. An MS attack was defined as an acute flair-up of symptoms lasting more than 24 hours [37]. Only attacks separated by at least 1 month were counted as separate events [37].

Patient's disability was scored using the EDMUS Grading Scale (EGS) [62], a validated ambulatory scale, which can be easily scored retrospectively based on an interview. Retrospective EGS scores agree well with the "gold standard" of the Extended Disability Status Scale scores [62]. EGS scores range from 0 (no neurologic abnormality) to 10 (death from MS). A disability level was defined as irreversible if it had persisted for at least 6 months [63].

In our analyses, the end point was defined as the first occurrence of an EGS score $\geq$3, often considered a threshold of "moderate disability," corresponding to the beginning of ambulation-related problems [39,64]. This disability level was also used as the primary end point in previous studies of MS evolution [65,66].

2.3. Statistical methods

The statistical methods described in the following can be easily adapted to other prognostic studies, which involve time-to-event analyses and repeated over time measures of some prognostic factors.

2.3.1. Alternative time-dependent measures of MS attacks frequency

Time-to-event methods were used to investigate time from the disease onset (first MS attack) to the first occurrence of EGS score $\geq$3. Follow-up continued until April 2004. Subjects who had an EGS score $<$3 at their last follow-up assessment were censored at that time. All multivariate models were adjusted for patient's age at onset and gender [8].

To account for the temporal relationship between MS attacks and the outcome (EGS score $\geq$3) and avoid using information on the future attacks [8], all models relied on time-dependent measures of the number of past MS attacks, updated during the follow-up [8,67]. At time t during the follow-up, a time-dependent covariate represents the relevant information on the past attacks observed, for a given subject, only until time t. Thus, the resulting values of time-dependent covariates for all subjects in the risk set are comparable and independent of the duration of their future individual follow-up (after time t).

We estimated four Cox PH models, each using a different time-dependent measure of the frequency of past MS attacks. Similar to previous studies [67–70], model 1A focused on the number of early attacks, during the first 2 years of MS evolution. To avoid biased estimation and include patients followed for less than 2 years, at any time t $<$ 24 months, the updated time-dependent measure counted only those attacks which had already occurred, until time t, whereas at t $>$ 24 months, all attacks recorded in the first 2 years were counted [8]. Thus, for example, for a patient with consecutive attacks at 0 (MS onset), 12, 17, and 32 months, the assigned "number of early attacks" was "1" until 12 months, "2" between 12 and 17 months, and "3" at any time thereafter. Model 1 B was similar except it counted all past attacks, which occurred during the first 5 years (rather than 2 years used in model 1A). Model 2 relied on a "cumulative number of all past attacks." Accordingly, at any time t during the follow-up, the corresponding time-dependent measure represented the total number of past attacks, accumulated from the disease onset ($t = 0$) until current time t. Finally, model 3 used the time-dependent measure that represented the continuously updated "number of recent attacks," which occurred in the two previous years of follow-up. At t years after the MS onset, the updated time-dependent "number of recent attacks" represented the number of attacks observed in the 2-year interval between ($t - 2$) and t years of follow-up. Thus, depending on the temporal variation in a patient's disease activity, the values of time-dependent covariate in model 3 could either increase or decrease from one interval to the next one, in contrast to nondecreasing functions of time used in the three other models.

2.3.2. Flexible modeling of time-dependent and nonloglinear effects

All models discussed above imposed a priori conventional PH and log-linearity assumptions. To test whether these assumptions are valid for the effects of the frequency of past MS attacks, we relied on likelihood ratio tests (LRT), based on a flexible spline-based extension of Cox's model [26,55,71]. For each Cox model of Section 2.3.1, we estimated a flexible model with the same measure of attacks frequency. If the PH or the log-linearity hypothesis was rejected ($P < 0.05$ for LRT), we used regression splines [72,73] to estimate, respectively, the time-dependent function that described how the effect of a corresponding measure changes during the follow-up or how the logarithm of the hazard varies with increasing frequency of attacks [55,71]. To avoid overfit bias and ensure model parsimony, the final flexible model included only statistically significant time-dependent and/or nonloglinear effects, selected by the backward elimination procedure, recently adapted, and validated for flexible modeling of event times [71,74] (Online Appendix at www.jclinepi.com provides details). All flexible analyses were implemented with a customized program in R (R Core Team, Vienna, Austria) language [71], available on request.

3. Results

3.1. Descriptive statistics

Table 1 summarizes the characteristics of the 288 study participants. Most were women (73.3%), and the

Table 1. Baseline demographic and disease-related characteristics

Characteristics	Values
Gender, *n* (%)	
Male	77 (26.7)
Female	211 (73.3)
Age at onset of disease (yr) mean (SD)	32.3 (10.3)
Age at onset of disease in classes, *n* (%)	
<20	30 (10.4)
20–40	189 (65.6)
≥40	69 (25.0)
Initial symptoms, *n* (%)	
Isolated optic neuritis	57 (19.8)
Isolated brain-stem dysfunction	48 (16.7)
Isolated dysfunction of long tracts	103 (35.8)
Other symptoms	5 (1.7)
Unknown symptoms	6 (2.1)
Combination of symptoms	69 (23.9)
Number of attacks in the first 2-year mean (IQR)	2.1 (1–3)
Interval between the first and second attack (yr) mean (IQR)	1.9 (1–2)

Abbreviations: SD, standard deviation; IQR, interquartile range.

The median follow-up time, that is, the time between the disease onset and the last consultation, was 6.4 years (SD = 3.7, IQR 3–9). During the follow-up, 108 patients (37.5%) reached an EDMUS Grading Scale score equal to or higher than 3.

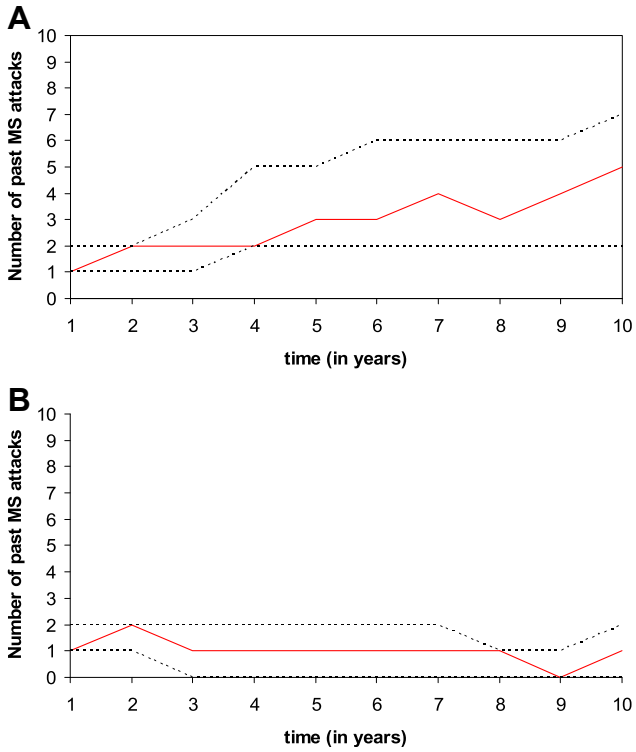

Fig. 1. (A) Cumulative number of attacks until the end of year (solid red curve: median; dotted curves: 25th and 75th percentiles) (B) Number of attacks in the last 2 years until the end of year (solid red curve: median, dotted curves: 25th and 75th percentiles). MS, multiple sclerosis. (For interpretation of references to color in this figure legend, the reader is referred to the Web version of this article.)

mean age at MS onset was 32.3 years (standard deviation = 10.3 years). Isolated dysfunction of long tracts was the most frequent symptom at onset (35.8%).

During the first 2 years after the MS onset, the median number of "early" attacks was 2 [interquartile range (IQR) 1–3] with the maximum of 11 attacks. There was a very strong relationship between a higher number of attacks within the first 2 years and a shorter interval between the first and the second attack (which might have occurred after 2 years), with the negative Spearman rank correlation of −0.79 [95% confidence intervals (CI): −0.84, −0.75] for 269 (93.4%) patients who had at least two attacks during the follow-up. Thus, the number of early attacks, used in model 1A, accounts well for the variation in the length of the first interattack interval.

Figures 1A and 1B show how the median and the IQR of, respectively, cumulative and recent number of attacks change during follow-up. Both IQRs reflect a substantial between-patient variation, which is accounted for in our models 2 and 3 (Section 2.3.1).

3.2. Comparison of the alternative models for the number of past attacks

Table 2 lists that adjusted HRs for all time-varying measures of the number of attacks, used in alternative Cox models, are above 1.0, with the 95% CIs which exclude 1.0. Thus, all measures of the MS attack frequency are associated with a statistically significantly accelerated occurrence of an EGS score ≥3. However, model 2 and, especially, model 3 fit the data considerably better than model 1, as indicated by much lower Akaike information criterion (AIC) values (Table 2). Thus, the new measure that continuously, during the entire follow-up, updates the information about the recent attacks, in the last 2 years, improves considerably the prognosis of MS evolution relative to the previously used number of early attacks, in the first 2 years of follow-up. This difference underlines further the fact that, in the later years of follow-up, the recent disease activity is more relevant than the activity observed much earlier, closer to the disease onset.

On the other hand, the estimates obtained with the conventional Cox PH models are not accurate because the underlying PH assumption is systematically violated ($P < 0.05$) for all the measures of the attacks frequency we considered (Table 2). Indeed, the flexible models that account for time-dependent effects fit the data systematically much better than the corresponding PH models, with the AIC values lower by at least 6 points (Table 2). This pattern of results provides a strong evidence that the associations of all attack frequency measures change over time. On the other hand, the log-linearity hypothesis was never rejected (all P-values > 0.05) indicating that the risks of occurrence of an EGS score ≥3 increase gradually with increasing attack frequency, across the range of observed values. Comparison of the AIC values confirms that flexible time-dependent model 3, which relies on the updated

Table 2. Results of different conventional Cox PH models and flexible time-dependent models, with alternative time-varying measures of the frequency of past MS attacks

Model	Measure of the number of MS attacks	Conventional Cox PH model		Flexible Cox model	
		HR (95% CI)[a]	AIC[b]	*P*-values[c]	AIC[b]
Model 1A	Number of early attacks	1.190 (1.015, 1.395)	1,026.739	0.004	1,018.4
Model 1B	Cumulative number of past attacks up to 5 years	1.121 (1.026, 1.226)	1,025.207	0.002	1,015.9
Model 2	Cumulative number of past attacks	1.133 (1.052, 1.220)	1,021.159	0.002	1,011.1
Model 3	Number of recent attacks	1.408 (1.246, 1.592)	1,007.306	0.013	1,001.4

Abbreviations: PH, proportional hazards; MS, multiple sclerosis; HR, hazard ratio; CI, confidence interval; AIC, Akaike information criterion.
[a] Adjusted HR for one additional MS attack with the corresponding 95% CI of conventional Cox PH model.
[b] AIC with lower values indicating a better fit to data.
[c] *P*-values for testing the PH assumption. (Time-dependent effects are shown in Fig. 2).

number of recent attacks, in the past 2 years, fits the data better than any other model shown in Table 2.

Fig. 2 shows the estimated, statistically significant time-dependent effects of alternative measures of attack frequency. The solid curves show how the logarithm of the hazard associated with one additional attack in the respective time window changes with increasing time since MS onset. For comparison, the dashed lines represent the (constant over time) log HR estimated by the corresponding Cox PH model, with the 95% CIs. All four time-dependent curves indicate that the log HRs for all measures decrease sharply in the two to 3 years after the onset. This implies

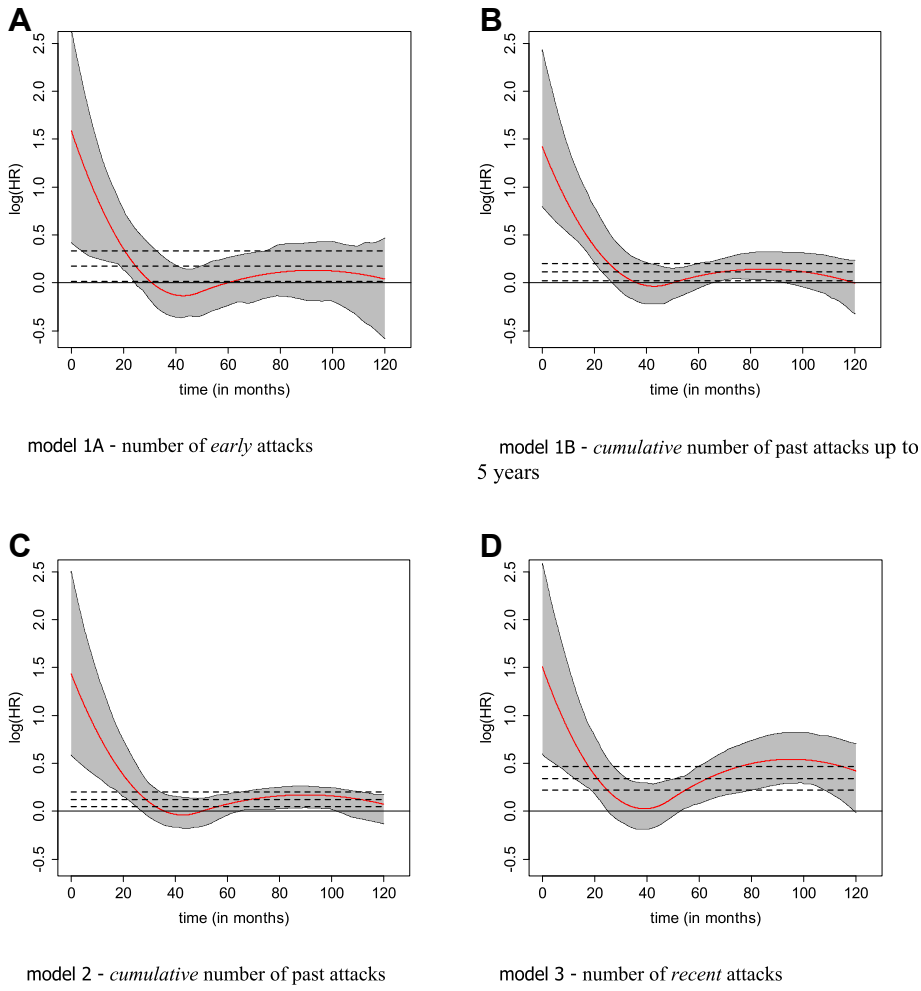

Fig. 2. Time-dependent effects (solid red curve) and 95% confidence interval (CI) (gray area) of alternative measures of attack frequency: (A) model 1A, (B) model 1B, (C) model 2, and (D) model 3. The three horizontal dashed lines indicate the effect and 95% CI of these alternative measures from the conventional Cox PH model. (For interpretation of references to color in this figure legend, the reader is referred to the Web version of this article.)

that the conventional Cox PH model that a priori restricts these effects to be constant over the entire follow-up duration and, thus, estimates the average-overtime HR, produces two types of biases [16,26]. Firstly, it largely overestimates the strength of the impact of higher frequency of attacks on the hazard of developing MS-related disability later than 2−3 years after the disease onset. For example, the Cox PH model 1A suggests that each additional ''early'' attack during the first 2 years of follow-up is associated with a 19% increase in the hazard (Table 2), at any time during the follow-up. In contrast, the flexible model indicates that the number of early attacks is not associated with the hazard after about 3 years of follow-up (Fig. 2A). Secondly, the average-over-time effects estimated by the conventional Cox PH models actually seriously underestimate the early risks, associated with higher frequency of attacks in the few first years of MS evolution. Indeed, in the first few years of follow-up, even the upper bounds of the 95% CI of the Cox model-based log HR (upper dashed lines in Figs. 2A−2D) are much lower than the time-dependent estimates (solid red curves) from the corresponding flexible models.

The dotted curves represent the 95% CI for the time-dependent effects. If the 95% CI at a given time t (shown on the horizontal axis) excludes 0, then the respective measure of attacks frequency has a statistically significant association with the hazard at time t. Interestingly, the 95% CIs for time-dependent effects in Figs. 2A−2C include 0 for later follow-up times. This suggests that, respectively, the number of attacks in the first 2 or 5 years and the cumulative number of past attacks are associated with significantly higher risks only during the 2−3 years after the MS onset. In contrast, the best-fitting flexible model 3 suggests that the higher updated number of recent attacks, in the last 2 years, may be still associated with significantly increased risks in the later stages of disease evolution, even 5−10 years after the MS onset, when the 95% CI in Fig. 2D excludes 0.

4. Discussion

In this article, we reassessed the role of the frequency of past and recent attacks as prognostic factors for disability progression in MS. Our results suggest that the analyses of MS progression may be enhanced by addressing two methodological limitations of the previous analyses that are common in clinical prognostic studies [4]. Firstly, we demonstrated the advantages of using time-varying covariates to account for changes in the values of prognostic factors during the follow-up. Indeed, compared with the number of attacks in the first 2 years, used in previous studies of MS evolution [67−70], both proposed time-varying measures, based on updated numbers of either cumulative or, especially, recent attacks in the past 2 years, improved substantially the models fit to data. Secondly, our flexible analyses confirmed the importance of assessing the validity of the conventional PH assumption, which constraints the estimated HRs to remain constant over time [5]. Although this important assumption is seldom tested in clinical applications of Cox's PH model [4], it is violated by several important prognostic factors [16,24,25,56]. In fact, our results consistently indicated that the prognostic ability of all measures of attack frequency in RR MS decreased significantly with increasing follow-up duration. However, in contrast to the other measures, the updated number of recent attacks, in the previous 2 years, retained, until the end of follow-up, a statistically significant short-term association with the hazard of developing an irreversible moderate MS disability, in the next 2 years. In other words, at any time during the follow-up, patients with higher number of recent attacks had statistically significant higher risks of developing moderate disability in the next 2 years. Importantly, in the flexible time-dependent model, risk of developing irreversible disability associated with increased frequency of recent MS attacks was much higher than suggested by the conventional Cox PH model, used in most previous studies [37,58,68,75].

Some limitations of our study have to be recognized. Most of our subjects were recruited before the introduction of immunomodulatory treatments. However, we do not think that the impact of the number of MS attacks would be so different nowadays. For example, even if immunomodulatory treatments reduce the disease activity, some variation between the number of recent attacks experienced by different patients remains and is likely to be associated with their short-term risks of disability progression. Furthermore, although our study population is limited to the Burgundy region of France, demographic characteristics (age at MS onset, sex ratio) and the distribution of initial symptoms are comparable to the well-known and validated French MS population reported by Confavreux et al. [37]. One challenge, common to longitudinal studies of MS evolution, was how to define the outcome. Similar to some previous studies [37,58,67], based on both statistical power and clinical relevance considerations, we have chosen EGS score $\geq$3 as the end point for our time-to-event analyses. EGS score of 3 indicates an unlimited walking distance without rest, but unable to run, or a significant not ambulation-related disability and, as such, may be considered as the lowest level of irreversible disability, which may limit activities of daily living [62]. It should be noticed that either EGS score of 3 or any other EGS score does not depend on or account for MS attacks and is not affected by transient increases in recent disease activity or temporary worsening of symptoms [62]. Finally, to keep our multivariate models parsimonious, given rather limited number of events in our data set, we adjusted the effects of attack frequency only for age and gender, as in some other studies of MS prognosis [37,66]. Future research should assess the robustness of our findings with

respect to adjusting for additional characteristics (neuroimaging and cerebrospinal fluid data).

We focused on the number of MS attacks rather than the length of the first interattack interval, which is commonly used in prognostic studies of MS disability progression [40,42]. One reason was that there is often some ambiguity regarding the temporal sequence of the occurrence of disability vs. the timing of the second attack, which determines the length of the first interattack interval [37,67,68,76]. We have previously demonstrated that, in such situations, complex modeling, with two separate time-dependent covariates [8], is necessary to avoid biases that occur if future information is used to predict past outcomes [6,7]. From this perspective, our choice of the number of attacks simplifies both the analyses and interpretation of the estimate effects. On the other hand, very high correlation between the number of early attacks and the length of the first interattack interval suggests that the latter measure is also unlikely to perform as well as the updated number of recent attacks.

Previous prognostic studies of MS disability (1) were limited to the role of attacks, in the first 2 years after diagnosis [58,65,66,68−70,77], and (2) relied on conventional Cox's PH model [37,68,78,79]. In contrast, by using more flexible statistical methods, we have demonstrated that (1) prognosis of MS disability occurrence is improved by using updated information on the number of recent attacks and (2) the PH assumption is incorrect as the prognostic value of all attack frequency measures decreases with increasing follow-up duration. The latter finding, concordant with a recent report by Tremlett et al. [48], may partially explain the contradictory results regarding the effect of the number of early attacks in previous publications, which assumed this effect was constant during the entire follow-up [68,77]. These new insights may be relevant for the clinical management of MS. They indicate that a continuous reassessment of recent disease activity throughout the follow-up will help dynamically adapt the treatment to current needs of individual MS patients, to reduce disease activity and its impact on long-term disability.

In conclusion, our analyses illustrate the potential advantages of flexible modeling that accounts for changes over time in both values of prognostic factors and their impact on future outcomes, in clinical prognostic studies. Our results provide new insights about the role of the frequency of past and recent relapses in the evolution of relapsing−remitting MS. Future applications of similar methods may enhance the accuracy of findings in prognostic studies of different diseases and outcomes, which increasingly involve repeated measures of prognostic factors during the follow-up.

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Supplementary data

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