Modeling the course and outcomes of MS is statistical twaddle—No

Roberto Bergamaschi and Cristina Montomoli

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References


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patients on the basis of observations taken during an early stage of the disease. A reliable and personalized model of MS course could be extremely valuable for everyone concerned with the disease: (a) for the patient who wants to be informed about his or her prospects to plan their future and therapeutic approaches, (b) for the clinician who needs to identify early-stage patients who warrant early aggressive intervention before their disease reaches a phase where treatment may no longer be effective, and (c) for the researcher who needs to improve the design of clinical therapeutic trials by the selection of more homogeneous sets of patients who start treatment with a similar risk of failure.

Before trying to model the natural history of MS, an essential point to determine is the choice of the outcome, which must be “strong” enough to distinguish an unfavorable from a favorable disease evolution. In literature, the most used outcomes are the time to reach (a) secondary progressive MS (SPMS) and (b) major clinical disability milestones (e.g., Expanded Disability Status Scale (EDSS) \( \geq 6.0 \)). However, these endpoints are influenced by biases. Progression of disability must be confirmed over time in order to prove a progressive course but, as Kalincik et al. suggest, the disability outcomes based on 3- to 6-month confirmed disability progression overestimate the accumulation of permanent disability, thus observations should be extended for up to 12–24 months. The crude evaluation of the EDSS value is biased because the clinical impact of MS is determined both by the neurological disability caused by the disease and by the timing of its occurrence. As a matter of fact, the same patient can be considered as having a “mild” disease course or an “aggressive” course if the same level of neurological disability has been reached after decades or within months of clinical onset. Therefore, it is necessary to adjust disability for disease duration. The multiple sclerosis severity score (MSSS), which corrects EDSS for disease duration using an arithmetically simple method, is a good indicator of clinical disease impact, allowing comparison of individual disability with the distribution of scores in cases having equivalent disease duration.

A second relevant point is how to analyze the vast amount of the collected data that can be utilized for modeling the natural course of the disease, and whether we have to take into account of only the onset/early or also include the intermediate events.

In Tintore’s study, a multivariate analysis incorporating demographic, clinical, radiological and biological data available at baseline was performed, demonstrating that it is possible to predict MS development and disability accumulation using a multivariate approach based on a large prospective cohort. This and previous studies are based on statistical models which relate the baseline/early manifestations of the disease to the time at which a specified endpoint event occurs. In those works, the statistical analysis often ignores the uncertainty affecting pre-baseline information, and it also ignores the rich wealth of information available from post-baseline observations, which may be used as a surrogate for the censored failure times. The use of Bayesian methodology and Markov chain Monte Carlo (MCMC) simulation technology overcomes these aforementioned limitations. In the Bayesian graphical model\(^4\) that allowed the identification of early clinical variables significantly associated with an increased risk of developing SPMS, the intermediate indicators were treated as a surrogate response event of unobserved failures in censored patients.

Finally, prognostic factors relating to an unfavorable disease course must be combined with synthetic scores, applicable in the early phase of disease, at a single patient level, in order to personalize the forecast. The following scores have been demonstrated to be reliable enough.

The propensity score\(^5\) indicates the susceptibility of a single patient to be treated with disease modifying immune therapies on the basis of his or her early clinical variables, allowing grouping of patients with a similar likelihood of receiving therapy. The BREMSO score,\(^6\) derived from a framework based on Bayesian predictive model of the natural history of MS, indicates the propensity of an individual patient, at disease onset, of having an unfavorable long-term disease evolution (expressed as high MSSS). The predictive algorithm EBDiMS\(^7\) estimates the risk of disease progression in individual MS patients by analyzing a large natural history cohort; the consistency of EBDiMS has been tested by comparing its predictions with those of neurologists with renowned expertise in the field of MS.

The above-mentioned individual scores may be useful (a) to identify high-risk patients who require early or more aggressive therapies, (b) to identify low-risk patients who could use relatively less effective but safer therapies, (c) to favor a more homogeneous selection of patients for clinical therapeutic trials, (d) to evaluate the effect of therapies in the field of observational studies, facilitating an a posteriori subdivision of non-randomized patients on the basis of their different “propensity” to be treated or to reach a poor endpoint.

In conclusion, modeling the course and outcomes of MS is a difficult but not an impossible endeavor, provided that

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The definition and choice of endpoints are made with care.

Statistical methods are appropriate.

Full use of available information is made by the incorporation in the model of several clinical aspects of the disease and of paraclinical information, in order to minimize the margin of error in the forecast.

Individualized predictive scores are calculable early determining the degree of disability that the single patient is likely to develop over the mid- to long-term for sustaining more personalized treatment decisions.

**Conflict of interest**

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**References**


**Modeling the course and outcomes of MS is statistical twaddle—Commentary**

**Michael Hutchinson**

It is in the nature of human enquiry to try to establish rules by which we might determine the likelihood of future outcomes. One such rule, now never referred to, was Kurtzke’s ‘Five-year rule’: minimal disability at 5 years predicted better long-term outcomes. In the examination of the natural history of multiple sclerosis (MS), there is an important corpus of population-based studies, in particular from Lyon, London Ontario and Rennes among others. These studies, by examining large cohorts of MS patients, established some indices of early disease activity, which might be applied in a predictive manner in the clinic, such as the relatively milder course following onset with optic neuritis, being female, the importance of the first inter-attack interval and the characteristic ‘amnesic’ nature of secondary progressive MS at Expanded Disability Status Scale (EDSS) levels of 3.0 or 4.0. While these population-based indices might be of general utility in individual patients, to extrapolate them in formulae, using markers of early disease activity, to predict long-term outcomes is erroneous.

**The fallacy of ‘benign’ MS**

One particular preoccupation has been repeated attempts at defining and predicting ‘Benign MS’. At one stage when counselling patients, I used to employ this term quite frequently when, after 15 or more years of illness, the patient had minimal disability with EDSS scores of 3.0 or less. On following the patient for a further 5–10 years, unfortunately the