Journal of Neurology
https://doi.org/10.1007/s00415-021-10823-z

ORIGINAL COMMUNICATION

Treatment response scoring systems to assess long-term prognosis in self-injectable DMTs relapsing–remitting multiple sclerosis patients

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Received: 2 June 2021 / Revised: 15 September 2021 / Accepted: 24 September 2021

Abstract

Background and objectives Different treatment response scoring systems in treated MS patients exist. The objective was to assess the long-term predictive value of these systems in RRMS patients treated with self-injectable DMTs.

Methods RRMS-treated patients underwent brain MRI before the onset of therapy and 12 months thereafter, and neurological assessments every 6 months. Clinical and demographic characteristics were collected at baseline. After the first year of treatment, several scoring systems [Rio score (RS), modified Rio score (MRS), MAGNIMS score (MS), and ROAD score (RoS)] were calculated. Cox-Regression and survival analyses were performed to identify scores predicting long-term disability.

Results We included 319 RRMS patients. Survival analyses showed that patients with RS > 1 and RoS > 3 had a significant risk of reaching an EDSS of 4.0 and 6.0 The score with the best sensitivity (61%) was the RoS, while the MRS showed the best specificity (88%). The RS showed the best positive predictive value (42%) and the best accuracy (81%).

Conclusions The combined measures integrated into different scores have an acceptable prognostic value for identifying patients with long-term disability.

Thus, these data reinforce the concept of early treatment optimization to minimize the risk of long-term disability.

Keywords Multiple sclerosis · Treatment response · Scores

Introduction

The increasing number of treatments for the management of multiple sclerosis (MS) makes it necessary to identify early factors that predict long-term outcomes with the objectives of optimizing therapy and of facilitating evidence-based therapeutic decision-making [1]. However, we lack appropriate consensus and algorithms for the management of treatment response.

Previous evidence indicates that clinical and MRI parameters during the first months of treatment are good predictors of either treatment response or early Expanded Disability Status Scale (EDSS) worsening in the short term [2, 3]. Based on these parameters, several score systems have been created. Although some of the best-known scores, such as the Rio score (RS), modified Rio score (MRS), MAGNIMS score (MS), or Risk of ambulatory disability score (RoAD), are used to predict short-term response, their long-term predictive value is currently unknown [4–7], Nevertheless, some data indicate that the presence of both early on-treatment MRI activity and relapses are strongly correlated with severe long-term disability [8]. Moreover, previous data from our cohort also demonstrated that scores based on the combination of clinical and MRI measures predict long-term EDSS worsening [9].

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Published online: 01 October 2021

On the other hand, current scoring systems for predicting treatment response are based solely on either clinical factors collected at MS onset [10–12] or clinical and MRI measures collected within the first year after disease-modifying therapies (DMTs) start [4–6], and provide information only about treatment response in the short term. The recent RoAD score demonstrated that the combination of baseline factors and 1 year factors was able to predict disability worsening after 10 years of follow-up [7].

Therefore, based on the above premises, the objectives were the following: 1/to compare different treatment response scoring systems and 2/to evaluate if these scores were able to predict long-term disability.

Patients and methods

Study design and patient disposition

This was a single-center, longitudinal, observational study based on a previously described prospective cohort of patients with MS who started treatment with injectable drugs (interferon beta or glatiramer acetate) (Fig. 1) from 2001 to 2008 [4]. All patients were treatment naive. We collected data of patients with RRMS according to the following criteria:

1. Subject received any formulation of IFNβ or glatiramer acetate as the first treatment.
2. Expanded Disability Status Scale (EDSS) [13] < 4.0 at treatment onset.
3. At least biannual follow-up visits from treatment initiation, including EDSS scoring performed by certified neurologists.
4. Complete data on brain MRI scans at baseline (within 1 month before starting treatment) and after 1 year (± 1 month) since treatment onset, acquired with the same protocol.
5. No concomitant participation in experimental trials.
6. At least 10 years of follow-up after treatment start.

Scores of early disease activity during treatment

Patients were classified according to their clinical and MRI activity in the first year of therapy, as previously described [4] (Fig. 1). We considered activity after 1 year based on the following: the presence of relapses, sustained and confirmed EDSS worsening and active MRI lesions [new T2 or contrast-enhancing lesions (CEL)]. Different scores were assigned and analyzed according to different combinations of these measures of activity, [11–14, 18] namely, RS, MRS MS, and RoAD score.

The RS was obtained after the first year of therapy as follows: 1 point for patients with ≥ 3 new T2 and/or CE lesions, 1 point for patients with ≥ 1 relapse, and 1 point for patients with an EDSS score increase in ≥ 1 point, sustained at the end of follow-up. A total score (0–3) was calculated for each scoring system, and patients were classified into one of two categories: low (score 0–1) or high (score 2–3) risk.

The MRS was obtained after the first year of therapy as follows: 1 point for patients with ≥ 5 new T2 lesions, 1 point for patients experiencing 1 relapse, and 2 points for patients experiencing ≥ 2 relapses. A total score (0–3) was calculated for each scoring system, and patients were classified into one of two categories: low (score 0–1) or high (score 2–3) risk.

The MS was obtained after the first year of therapy as follows: 1 point for patients with ≥ 3 new T2 lesions, 1 point for patients experiencing 1 relapse, and 2 points for patients experiencing ≥ 2 relapses. A total score (0–2) was calculated for each scoring system, and patients were classified into one of two categories: low (score 0–1) or high (score 2) risk.

Taking into account that RoAD score is the only one that considers baseline variables, the score was constructed as

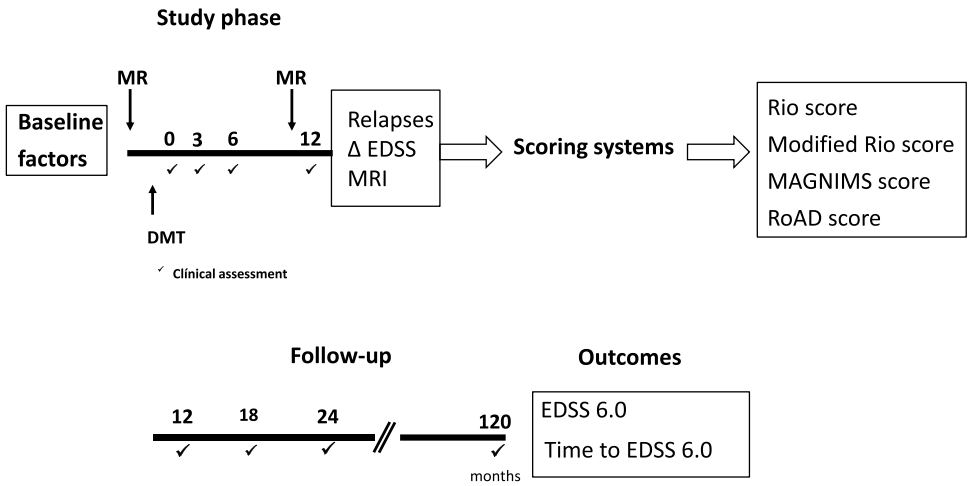

Fig. 1 Cohorts and study design

follows: Baseline factors; 1 point for patients ≥ 40 years, 1 point for patients with a disease duration ≥ 2 years, 1 point for patients with a baseline EDSS ranging from 1.5 to 2 or 2 points for patients with a baseline EDSS > 2, and 1-year factors; 1 point for patients with ≥ 3 new T2 lesions, 1 point for patients with ≥ 2 CEL lesions, 1 point for patients experiencing 1 relapse or 2 points for patients experiencing ≥ 2 relapses. A total score (0–8) was calculated and patients were classified into one of two categories: low (score 0–3) or high (score 4–8) risk.

Long-term disability outcomes

The study outcome was the time to reach the disability milestones of EDSS 4 and 6.0, corresponding to walking restriction and the ability to walk only with unilateral support and < 100 m without assistance and resting, confirmed in at least two consecutive visits and sustained (stable or higher) at the end of follow-up period.

We adopted such a combined outcome instead of the classical 0.5-point or 1.0-point EDSS worsening [13] to set a robust outcome based on a clinically significant milestone for patients with MS.

MRI protocol and assessment

All MRI scans were obtained on a 1.5 T magnet, using a standardized protocol that included at least the following sequences: 1/axial proton density-(PD) and T2-weighted turbo spin echo; 2/ axial T2-FLAIR (fluid attenuation inversion-recovery); and 3/axial T1-weighted spin echo before and after injection of 0.2 mmol/kg body weight (5–10 min delay). For each sequence, 44 contiguous, 3 mm-thick slices were obtained.

The number of active lesions (new T2 and CEL) on the 12 month MRI scan was visually assessed by two experienced neuroradiologists who were blinded to the patients' clinical data by direct comparison with the baseline scan, according to previously published guidelines [14].

Statistical analysis

Descriptive statistics were used to assess demographic and clinical data. We calculated the diagnostic properties [sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy] of each one of the treatment response scoring systems based on the number of patients who reached the pre-defined long-term outcomes. The 95% confidence intervals (CIs) of each of these indices for each parameter or scoring system were calculated.

Kaplan–Meier survival analyses were used to estimate the cumulative risk of developing the EDSS worsening endpoint according to the presence or absence of active disease based on the above-mentioned parameters and score systems after the beginning of therapy. We performed uni- and multivariable logistic regression and Cox proportional hazard regression analyses to study the prognostic value of early clinical disease activity for the prediction of long-term disability outcome with adjustment according baseline EDSS score. The multivariable logistic regression and Cox regression models included the following covariates: sex, age at DMT onset, disease duration, time to first DMT, relapses before DMT onset, and baseline EDSS.

The statistical analyses were performed with SPSS 20.0 (SPSS Inc., Chicago, IL, USA), SAS (SAS Institute Inc., Cary, NC, USA), and G-Stat (GlaxoSmithKline S.A., Madrid, Spain) statistical software packages. The level of statistical significance was set at $p < 0.05$.

Results

We studied 319 patients starting self-injectable DMTs who met the inclusion criteria (Fig. 2) (233 female, 86 male) who started subcutaneous GA 20 mg OD ($n = 24$), intramuscular IFNB-1a 30 mcg OW ($n = 120$), subcutaneous IFNB-1b 250 mcg EOD ($n = 72$), or subcutaneous IFNB-1a 22 or 44 mcg TPW ($n = 103$) from 2001 to 2008. The patients had a mean age of 33.9 (SD 9.1; range18–69) years at the beginning of treatment and a mean disease duration of 4 (SD 4.6) years. The median EDSS score at baseline was 1.5

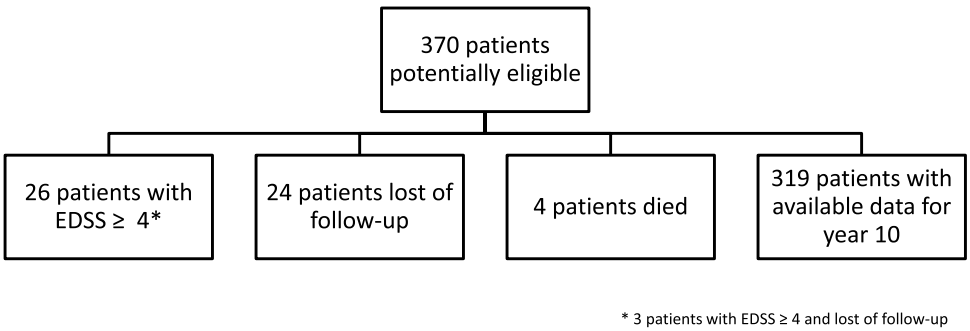

Fig. 2 Flowchart of the patients included in the study

(IQR 1–2). The annualized relapse rate was 1.5 (SD 0.7). The mean number of CEL lesions was 3.4 (SD 6.6). There were no significant baseline differences in terms of age, sex, disease activity, and EDSS between patients lost to follow-up and those who underwent a full assessment (data not shown).

A total of 86 (27%) patients required escalation to monoclonal antibodies (natalizumab = 41, rituximab = 13, alemtuzumab = 3) or were changed to oral "high efficacy" agents (fingolimod = 27, cladribine = 2) over the follow-up period.

Early disease activity (first year)

Eighty patients (25%) presented one or more relapses with an annualized relapse rate of 0.3 (SD 0.7), 195 (61%) presented new T2 lesions with a mean number of 3.3 (SD 5.3), 80 (25%) had one or more CEL lesions with a mean number of 0.8 (SD 2.5), and 39 (12%) suffered a confirmed EDSS worsening of ≥ 1 point. The number of patients scored as having low and high risk was 251 (79%) and 67 (21%) according to the RS, 271 (85%) and 47 (15%) according to the MRS, 264 (83%) and 55 (17%) according to the MS and 226 (71%), and 94 (29%) according to the RoAD score, respectively.

Long-term disability by different scores

During the follow-up period, 78 (24%) and 51 patients (16%) reached an EDSS score of 4.0 and 6.0, respectively. Table 1 shows the proportion of patients with an EDSS score of 4.0 and 6.0 for the different categories of the different scores.

After the first year of treatment, 18 (11%) patients with RS = 0 (reference category), 5 (6%) with a RS = 1 (HR = 0.5, 95% CI 0.2–1.1, $p = 0.5$), and 28 (42%) with a high score (HR = 5.0, 95% CI 3.2–7.9, $p < 0.001$) reached an EDSS ≥ 6.0 over the follow-up. 21 (11%) patients with an MRS = 0 (reference category), 14 (19%) with an MRS = 1 (HR = 2.2, 95% CI 1.2–4.1, $p = 0.01$), and 16 (34%) with a high score (HR = 4.1, 95% CI 2.3–7,5, $p < 0.001$) reached an EDSS ≥ 6.0 over the follow-up. 18 (10%) patients with a MS = 0 (reference category), 15 (16%) with an MS = 1 (HR = 2.2, 95% CI 1.2–4.1, $p = 0.015$), and 18 (33%) with high score (HR = 4.3, 95% CI 2.3–7.9, $p < 0.001$) reached an EDSS ≥ 6.0 over the follow-up. 20 (9%) patients with RoAD = 0–3 (reference category) and 31 (33%) with RoAD = 4–8 (HR = 6.2, 95% CI 3.5–10.8, $p = 0.001$) reached an EDSS ≥ 6.0 over the follow-up. As showed in Table 1, similar results were obtained for EDSS 4.0 as outcome measure.

Survival curves showing time to EDSS ≥ 6.0 according to the level of disease activity after the first year of treatment are shown in Fig. 3.

Finally, Table 2 shows the diagnostic properties of the highest categories of different scores in identifying patients who reached (or not) an EDSS ≥ 6.0. The RoAD score showed the best sensitivity (61%, 95% CI 46–74), the MRS the best specificity (88%, 95% CI 84–92), and the RS the best PPV (42%, 95% CI 33–51) and accuracy (81%, 95% CI 76–85).

Discussion

The positive impact of treatments on the natural history of MS is becoming increasingly clear [15, 16]. However, to optimize this influence is necessary to identify those patients who will have an inadequate response to injectable treatment at an early stage [2]. Our data demonstrate that patients with clinical and radiological activity during the first year

Table 1 Cox regression models for the risk of reaching the disability milestones of EDSS 4.0 and 6.0 over 10 years of follow-up by level of risk after the first year of treatment according to the different score systems

Score	Reaching EDSS 4	HR	95% CIs	*p* value	Reaching EDSS 6	HR	95% CIs	*p* value
RS 0	29/165 (18%)	1.00			18/165 (11%)	1.00		
RS 1	11/86 (13%)	0.69	0.33–1.46	0.7	5/86 (6%)	0.51	0.24–1.11	0.5
RS 2–3	38/67 (57%)	6.45	3.43–12.14	< 0.001	28/67 (42%)	5.00	3.18–7.86	< 0.001
MRS 0	34/197 (17%)	1.00			21/197 (11%)	1.00		
MRS 1	21/74 (28%)	1.83	0.98–3.42	0.6	14/74 (19%)	2.24	1.21–4.12	0.01
MRS 2–3	23/47 (49%)	4.59	2.33–9.08	< 0.001	16/47 (34%)	4.13	2.26–7.53	< 0.001
MS 0	30/173 (17%)	1.00			18/173 (10%)	1.00		
MS 1	24/91 (26%)	1.72	0.93–3.16	0.8	15/91 (16%)	2.18	1.15–4.09	0.015
MS 2	24/55 (44%)	3.72	1.92–7.20	< 0.001	18/55 (33%)	4.25	2.28–7.90	< 0.001
RoAD 0–3	29/224 (13%)	1.00			20/224 (9%)	1.00		
RoAD 4–8	49/94 (52%)	7.40	4.22–12.97	< 0.001	31/94 (33%)	4.48	2.6–7.9	< 0.001

RS Rio Score, *MRS* Modified Rio Score, *MS* MAGNIMS Score, *RoAD* Risk of ambulation disability

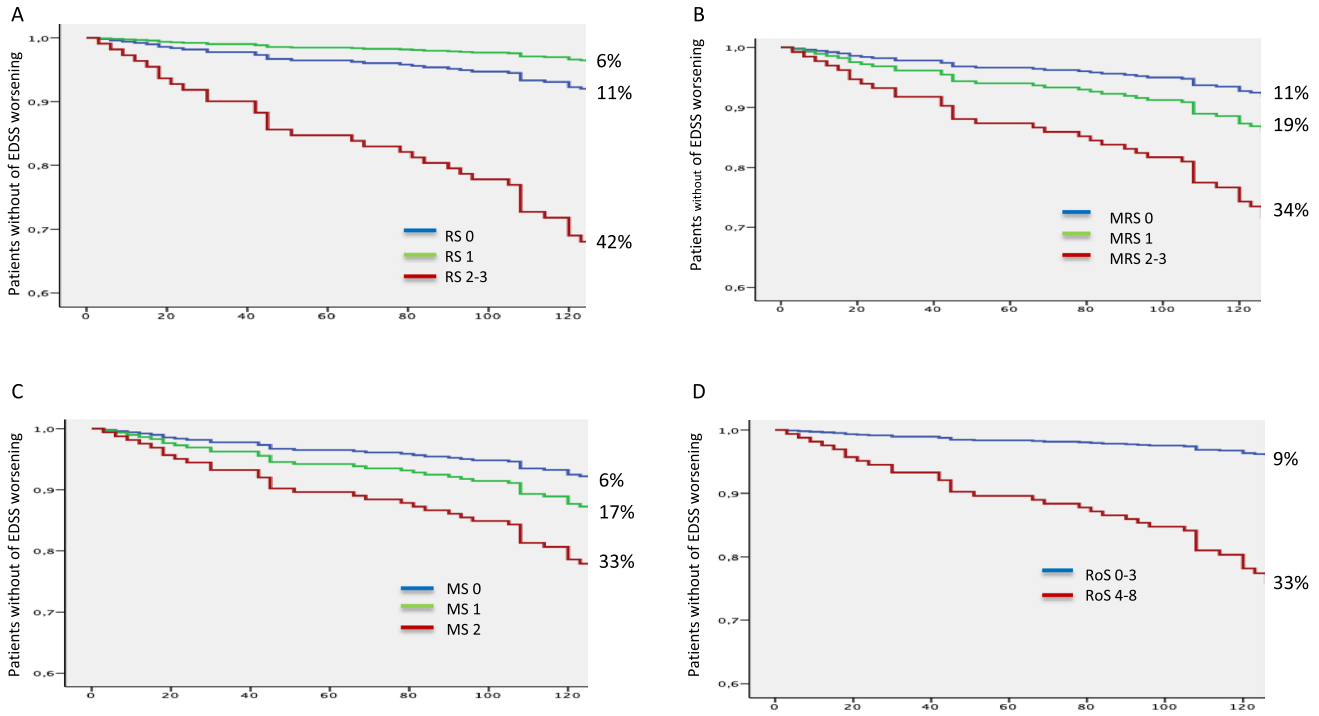

Fig. 3 Time to reach the disability milestone of EDSS ≥ 6.0 over 10 years of follow-up by risk category after the first year of treatment according to the different score systems. EDSS, Expanded Disability Status Scale. **A**. Rio score. **B**. Modified Rio score. **C**. MAGNIMS score. **D**. RoAD score

Table 2 Diagnostic properties of the scoring systems after 1 year of treatment for the risk of reaching the disability milestone of EDSS ≥ 6.0 over 10 years of follow-up

	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Accuracy (%)
Rio score (2–3)	55 (40–69)	85 (81–89)	91 (88–93)	42 (33–51)	81 (76–85)
Modified Rio score (2–3)	31 (19–46)	88 (84–92)	87 (85–89)	34 (23–47)	79 (74–84)
MAGNIMS score (2)	34 (21–49)	86 (82–90)	87 (85–89)	33 (23–44)	78 (73–82)
RoAD score (4–8)	61 (46–74)	77 (71–82)	91 (88–94)	33 (27–40)	74 (68–79)

NPV Negative predictive value, *PPV* Positive predictive value

of therapy have a significant risk of accruing disability in the long term.

The concepts of responder or non-responder patients and when the response is established are not well defined and nowadays are still arbitrary [17]. In clinical practice, the lack of response is defined based on the presence of clinical (relapses and/or disability worsening) and/or MRI activity, defined by the presence of new T2 or CEL lesions [4–7, 18, 19]. Nevertheless, there is no consensus about the number of relapses or active lesions needed to define a confirmed poor response. With the above-mentioned variables, different score systems of response have been created. The main objective of these scores is to facilitate the evidence-based decision-making process to determine the best treatment option for a particular patient.

Most scores have been created in cohorts with a relatively short follow-up period and the outcomes were generally based on one point of EDSS worsening. By contrast, there is little information in the literature on the prognostic role of these scores on severe long-term disability (i.e., the milestone of reaching EDSS ≥ 6.0 after longer periods of follow-up). In this regard, our results demonstrate that clinical and radiological activity (RS 2–3, HR = 5.0, 95% CI 3.2–7.9, $p < 0.001$; MRS = 2–3, HR = 4.1, 95% CI 2.3–7.5, $p < 0.001$; MS = 2–3, HR = 4.3, 95% CI 2.3–7.9, $p < 0.001$; and RoAD score = 4–8, HR = 4.5, 95% CI 2.6–7.9, $p = 0.001$) during the first year of immunomodulatory treatment is a clear indicator of poor long-term prognosis (EDSS 6.0 after 10 years of follow-up) regardless of the score used during the first year of treatment.

The MEDA concept (minimal evidence of disease activity) has aroused interest as a composite outcome measure that is easily accessible in the clinical practice setting and has a good predictive value in identifying patients without

a long-term unfavorable outcome [2, 9]. Nevertheless, the degree of early disease activity that confers a potential risk for a poor long-term prognosis is currently unknown. Recently, Prosperini et al. analyzed whether the MAGNIMS low score, that is, no relapses and < 3 new T2 lesions, can be considered as MEDA, i.e., minimal disease activity which does not imply a risk of future disability [20]. In fact, patients with one relapse and < 3 new T2 lesions were patients with a risk of long-term disability, therefore; not fulfilling the MEDA definition. On the contrary, our data show that patients with RS = 1, which includes patients with one relapse without EDSS worsening and < 3 active lesions, are patients without a significant risk of long-term disability (HR 0.5, 95% CI 0.24–1.11). Thus, we can include under the category MEDA those patients with one relapse without EDSS worsening and no evidence of significant radiological activity (< 3 active lesions).

Although patients with MRS and MS = 1 are classified as low risk, according to our data, these patients may have a significant risk of disability during a follow-up period of 10 years [HR 2.2; (95% CI 1.2–4.1) for MRS and HR 2.2 (95% CI 1.5–4.1) for MS]. These findings demonstrate one of the fundamental problems of MRS and MS, which is their low ability to discriminate patients with high and low risk of long-term disability. Possibly, the explanation of this phenomenon is related to the fact that neither the MRS nor the MS include EDSS worsening during the first year as a variable of the score. Thus, these scores do not differentiate relapses with or without EDSS worsening, while it may occur in the RS. As previously mentioned, the presence of an isolated relapse with no EDSS worsening or MRI activity is not associated with long-term disability. From the foregoing, it is clear that the use of EDSS worsening during the first year of treatment helps to discriminate those patients at risk of long-term disability. The practical issue is that there are protocols in which the possibility of a therapeutic switch or escalation is performed in the presence of an isolated relapse [21]. Thus, it is important to consider the radiological activity and/or EDSS worsening before considering a treatment change in these patients.

The RoAD score differs from previous scores in that this score is the only one using baseline clinical and demographic variables. It ranges from 0 to 8, and patients with a score of > 3 are at risk of long-term disability. It has the advantage that a score of > 3 can be achieved only with baseline clinical and demographic variables. Thus, in these patients with poor prognosis before the start of the DMD, the initiation of induction or intensive treatment could be considered to minimize the risk of long-term disability [22].

As previously described, the MRS and MS have the highest specificity (88% and 86%) but with a very low sensitivity compared to the RS and RoAD score [23]. The MRS and MS (pure activity-based measure) do not perform as well as the RS and RoAD score (a combination of activity and EDSS worsening), in predicting a future increase of disability [24].

Although sensitivity and specificity are the parameters of most interest from a statistical point of view, PPV and NPV are the parameters of most interest from a clinical point of view. In this case, the NPV should be prioritized, since it maximizes the "true negatives" (i.e., "true" optimal responders), and minimizes the "false negatives" (i.e., suboptimal responders in whom treatment is not switched and therefore not receives therapy that might be helpful). Overall, the predictive value of all criteria was limited. Overall, the PPV of the different scores is quite poor, since none of them exceeds 50%; however, the NPV is quite good mainly for the RS and RoAD score with values above 90%. As previously reported, the criterion with a best-balanced accuracy was an RS ≥ 2 [17].

Our paper has several limitations. First of all, the influence of different treatment strategies as therapy switching or escalation during follow-up has not been studied. However, the number of patients who required therapeutic escalation in this cohort was relatively low probably due to the fact that therapeutic options were scarce during the study period. In fact, the proportion of patients who reached an EDSS of 4 or 6 is higher in patients who escalate. Therefore, there is a modest impact of escalation in this cohort for the above-mentioned reasons. Second, other factors different from relapses, MR activity, and EDSS worsening, such as adherence, presence of neutralizing antibodies, oligoclonal bands, or lesion topography, also can be related to long-term disability [25–28]. Third, our findings are limited to patients initially treated with GA and IFNs. Regardless of the fact that it is likely that these scores can be used in patients treated with other first-line drugs, studies to validate this aspect are needed.

By contrast, our study has several strengths. First, because long-term data are so critical for obtaining valid and accurate information on a therapeutic effect, we used very strict long-term outcomes, that is, the disability milestones of EDSS 4.0 and 6.0. Second, the study has been developed in a real-life setting following a standardized clinical and MRI follow-up protocol, and finally, the study had a low rate of patients lost to follow-up. Therefore, and taking into account that it is important to identify non-responders patients as soon as possible to introduce high-efficacy therapies for minimizing early disability (29–33), our data may be useful in the management of MS patients in daily clinical practice.

In summary, the data reported in this study demonstrate that in RRMS patients treated with self-injectable DMTs, the combined clinical–radiological activity measures integrated into different scores during the first year of treatment have an acceptable prognostic value for identifying patients at risk of long-term disability. Furthermore, scores which include early EDSS worsening in the first year of treatment

seem to be better at discriminating patients with a greater risk of disability worsening. Thus, these data reinforce the concept of early treatment optimization to minimize the risk of long-term disability.

Declarations

Conflicts of interest **J Río** has received speaking honoraria and personal compensation for participating on Advisory Boards from Almirall, Bayer-Schering Healthcare, Biogen-Idec, Genzyme, Merck- Serono, Novartis, Teva, and Sanofi-Aventis. A Rovira serves on scientific advisory boards for Novartis, Sanofi-Genzyme, SyntheticMR, Biogen and OLEA Medical, and has received speaker honoraria from Bayer, Sanofi-Genzyme, Merck-Serono, Teva Pharmaceutical Industries Ltd, Novartis, Roche and Biogen. C Gasperini has received fee as speaker or advisory board by Merck, Bayer, Biogen, Novartis, Teva, Genzyme. M Tintore has received compensation for consulting services and speaking honoraria from Almirall, Bayer Schering Pharma, Biogen-Idec, Genzyme, Merck-Serono, Novartis, Roche, Sanofi-Aventis, Viela Bio and Teva Pharmaceuticals. MT is co-editor of Multiple Sclerosis Journal- ETC. L Prosperini has received fee as speaker or advisory board by Merck, Bayer, Biogen, Novartis, Teva, Genzyme. S Otero-Romero has received speaking and consulting honoraria from Genzyme, Biogen-Idec, Novartis, Roche, Excemed and Merk; and research support from Novartis. M Comabella has received compensation for consulting services and speaking honoraria from Bayer Schering Pharma, Merk Serono, Biogen-Idec, Teva Pharmaceuticals, Sanofi-Aventis, and Novartis. C Nos has received compensation as steering committee member of clinical trials from Hoffmann-La Roche, and funding for registration in scientific meetings from Novartis. A Vidal-Jordana receives support for contracts Juan Rodes (JR16/00024) from Fondo de Investigaciones Sanitarias, Instituto de Salud Carlos III, Spain; and has received speaking honoraria and travel expenses from Novartis, Roche, Teva, Biogen and Sanofi-Genzyme. C Tur is currently being funded by a Junior Leader La Caixa Fellowship. The project that gave rise to these results received the support of a fellowship from "la Caixa" Foundation (ID 100010434). The fellowship code is LCF/BQ/PI20/11760008. She has also received the 2021 Merck's Award for the Investigation in Multiple Sclerosis (*Ayudas para la Investigación en Esclerosis Múltiple*, 2021), awarded by the Merck Foundation. In 2015, she received an ECTRIMS Post-doctoral Research Fellowship and has received funding from the UK MS Society. She has also received honoraria and support for traveling from Merck Serono, Sanofi, Roche, TEVA Pharmaceuticals, Novartis, Biogen, Bayer and Ismar Healthcare. G. Arrambide has received compensation for consulting services or participation in advisory boards from Sanofi and Merck; research support from Novartis; travel expenses for scientific meetings from Novartis, Roche, and ECTRIMS; and speaking honoraria from Stendhal, Sanofi, Merck. G. Arrambide is a member of the executive committee of the International Women in Multiple Sclerosis (iWiMS) network. A. Cobo-Calvo has received grant from Instituto de Salud Carlos III, Spain; JR19/00007. Breogán Rodríguez-Acevedo has received honoraria for consulting services from Wellspect. C Auger has received speaking honoraria from Novartis, Biogen and Stendhal. J Sastre-Garriga has received compensation for participating on Advisory Boards, speaking honoraria and travel expenses for scientific meetings, consulting services or research support from Celgene, Novartis, Biogen, Teva, Merck, Almirall, and Genzyme. X Montalban has received speaking honoraria and travel expenses for participation inscientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past with Actelion, Amirall, Bayer, Biogen, Celgene, Genzyme, Hoffmann-La Roche, Novartis, Oryzon Genomics, Sanofi-Genzyme, and Teva Pharmaceutical. L Midaglia, I Galán, J Castilló, and A Zabalza report no disclosures.

Ethical standard statement The local ethical committee approved the study, and all patients provided their informed consent.

References

1. Rotstein D, Montalban X (2019) Reaching an evidence-based prognosis for personalized treatment of multiple sclerosis. Nat Rev Neurol 15(5):287–300
2. Gasperini C, Prosperini L, Tintoré M et al (2019) Unraveling treatment response in multiple sclerosis: a clinical and MRI challenge. Neurology 92:180–192
3. Sormani MP, De Stefano N (2013) Defining and scoring response to IFN-β in multiple sclerosis. Nat Rev Neurol 9:504–512
4. Río J, Castilló J, Rovira A et al (2009) Measures in the first year of therapy predict the response to interferon beta in MS. Mult Scler 15(7):848–853
5. Sormani M, Signori A, Stromillo M, De Stefano N (2013) Refining response to treatment as defined by the Modified Rio Score. Mult Scler 19(9):1246–1247
6. Sormani MP, Gasperini C, Romeo M et al (2016) Assessing response to interferon-β in a multicenter dataset of patients with MS. Neurology 87(2):134–140
7. Gasperini C, Prosperini L, Rovira A et al (2021) Scoring the 10 year risk of ambulatory disability in DMD-treated multiple sclerosis patients: the RoAD score. Eur J Neurol 28(8):2533–2542
8. Bermel RA, You X, Foulds P et al (2013) Predictors of long-term outcome in multiple sclerosis patients treated with interferon beta. Ann Neurol 73:95–103
9. Río J, Rovira A, Tintoré M et al (2018) Disability progression markers over 6–12 years in interferon-β-treated multiple sclerosis patients. Mult Scler 24:322–330
10. Bergamaschi R, Berzuini C, Romani A, Cosi V (2001) Predicting secondary progression in relapsing–remitting multiple sclerosis: a Bayesian analysis. J Neurol Sci 189(1–2):13–21
11. Bergamaschi R, Quaglini S, Trojano M et al (2007) Early prediction of the long-term evolution of multiple sclerosis: the Bayesian Risk Estimate for Multiple Sclerosis (BREMS) score. J Neurol Neurosurg Psychiatry 78(7):757–759
12. Bergamaschi R, Montomoli C, Mallucci G et al (2015) BREMSO: a simple score to predict early the natural course of multiple sclerosis. Eur J Neurol 22(6):981–989
13. Kurtzke JF (1983) Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33:1444–1452
14. Wattjes MP, Rovira À, Miller D et al (2015) Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis–establishing disease prognosis and monitoring patients. Nat Rev Neurol 11(10):597–606
15. Brown JWL, Coles A, Horakova D et al (2019) Association of initial disease-modifying therapy with later conversion to secondary progressive multiple sclerosis. JAMA 321(2):175–187
16. Harding K, Williams O, Willis M et al (2019) Clinical outcomes of escalation vs early intensive disease-modifying therapy in patients with multiple sclerosis. JAMA Neurol 76(5):536–541
17. Río J, Ruiz-Peña JL (2016) Short-term suboptimal response criteria for predicting long-term non-response to first-line disease modifying therapies in multiple sclerosis: a systematic review and meta-analysis. J Neurol Sci 361:158–167
18. Río J, Comabella M, Montalban X (2009) Predicting responders to therapies for multiple sclerosis. Nat Rev Neurol 5(10):553–560
19. Prosperini L, Gallo V, Petsas N, Borriello G, Pozzilli C (2009) One year MRI scan predicts clinical response to interferon beta in multiple sclerosis. Eur J Neurol 16(11):1202–1209

20. Prosperini L, Mancinelli C, Haggiag S et al (2020) Minimal evidence of disease activity (MEDA) in relapsing–remitting multiple sclerosis. J Neurol Neurosurg Psychiatry 91:271–277
21. Rae-Grant A, Day GS, Marrie RA et al (2018) Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis neurology. Neurology 90:777–788
22. Rush CA, MacLean HJ, Freedman MS (2015) Aggressive multiple sclerosis: proposed definition and treatment algorithm. Nat Rev Neurol 11(7):379–389
23. Romeo M, Martinelli V, Rodegher M et al (2015) Validation of 1-year predictive score of long-term response to interferon-β in everyday clinical practice multiple sclerosis patients. Eur J Neurol 22:973–980
24. Rio J, Nos C, Tintoré M et al (2006) Defining the response to interferon-beta in relapsing–remitting multiple sclerosis patients. Ann Neurol 59:344–352
25. Filippi M, Rocca MA (2010) Multiple sclerosis: monitoring long-term treatments in multiple sclerosis. Nat Rev Neurol 6:421–422
26. Alenda R, Costa-Frossard L, Alvarez-Lafuente R et al (2018) Blood lymphocyte subsets identify optimal responders to IFN-beta in MS. J Neurol 265:24–31
27. Tintoré M, Rovira A, Río J et al (2008) Do oligoclonal bands add information to MRI in first attacks of multiple sclerosis? Neurology 70(13 Pt 2):1079–1083
28. Galassi S, Prosperini L, Logoteta A et al (2016) A lesion topography-based approach to predict the outcomes of patients with multiple sclerosis treated with Interferon Beta. Mult Scler Relat Disord 8:99–106
29. Iaffaldano P, Lucisano G, Butzkueven H et al (2021) Early treatment delays long-term disability accrual in RRMS: results from the BMSD network. Mult Scler. https://doi.org/10.1177/13524585211010/28
30. Kalincik T, Diouf I, Sharmin S et al (2021) Effect of disease-modifying therapy on disability in relapsing–remitting multiple sclerosis over 15 years. Neurology 96:e783–e797
31. He A, Merkel B, Brown JWL et al (2020) Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. Lancet Neurol 19:307–316
32. Buron MD, Chalmer TA, Sellebjerg F et al (2020) Initial high-efficacy disease-modifying therapy in multiple sclerosis: a nationwide cohort study. Neurology 95:e1041–e1051
33. Iaffaldano P, Lucisano G, Caputo F et al (2021) Long-term disability trajectories in relapsing multiple sclerosis patients treated with early intensive or escalation treatment strategies. Ther Adv Neurol Disord 14:1–10