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ORIGINAL COMMUNICATION

SMILE: a predictive model for Scoring the severity of relapses in MultIple scLErosis

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Abstract

Background In relapsing–remitting multiple sclerosis (RRMS), relapse severity and residual disability are difficult to predict. Nevertheless, this information is crucial both for guiding relapse treatment strategies and for informing patients.

Objective We, therefore, developed and validated a clinical-based model for predicting the risk of residual disability at 6 months post-relapse in MS.

Methods We used the data of 186 patients with RRMS collected during the COPOUSEP multicentre trial. The outcome was an increase of ≥ 1 EDSS point 6 months post-relapse treatment. We used logistic regression with LASSO penalization to construct the model, and bootstrap cross-validation to internally validate it. The model was externally validated with an independent retrospective French single-centre cohort of 175 patients.

Results The predictive factors contained in the model were age > 40 years, shorter disease duration, EDSS increase ≥ 1.5 points at time of relapse, EDSS = 0 before relapse, proprioceptive ataxia, and absence of subjective sensory disorders. Discriminative accuracy was acceptable in both the internal (AUC 0.82, 95% CI [0.73, 0.91]) and external (AUC 0.71, 95% CI [0.62, 0.80]) validations.

Conclusion The predictive model we developed should prove useful for adapting therapeutic strategy of relapse and follow-up to individual patients.

Keywords Multiple sclerosis · Relapse phenotype · Predictive model · Relapse recovery · EDSS

Introduction

Relapse severity and residual disability are highly variable in patients with relapsing–remitting multiple sclerosis (RRMS), and recovery remains difficult to predict [1, 2]. From experience, neurologists know that several clinical factors influence the risk of sequelae, and, thus, mid-term disability. Previous studies have shown that older age, relapse severity, and relapse phenotype (particularly

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motor, bowel/bladder, cognitive and cerebellar disorders) are associated with poor recovery [3–7].

However, clinicians do not yet have a validated predictive tool to help them estimate post-relapse residual disability. This information is of particular importance for informing patients about their relapse prognosis and for guiding relapse treatment strategies. The ability to identify relapses with a poor chance of recovery is crucial for planning adaptations to patient management. Recent studies have identified relapse phenotype as a potentially useful prognostic marker, insofar as it may distinguish between mild and severe demyelinating events in RRMS [8–10].

We, therefore, set out to develop and validate a clinical-based model for predicting the risk of disability accrual at 6 months post-relapse in patients with MS. We deliberately excluded MRI data, as they are rarely available at time of relapse. Based on the data from a previous multicentre clinical trial [11], the resulting "SMILE" model for *S*coring the severity of relapses and predicting residual disability in *M*ult*I*ple sc*LE*rosis contained six variables. We externally validated its predictive capacities using data from an independent single-center French cohort.

Materials and methods

Patients for learning and internal validation

We used data from the COPOUSEP study (Corticothérapie Orale dans les Poussées de Sclérose en Plaques, ClinicalTrials.gov number NCT00984984). The purpose of this multicentre randomized clinical trial was to establish non-inferiority between oral and intravenous administration of corticosteroids for the treatment of RRMS relapses [11]. Patients were included between January 2008 and June 2013. The baseline was defined by corticosteroid treatment onset.

Pre-relapse data were collected retrospectively from patients' files by the neurologist at the screening appointment. Relapse was defined as new or worsening neurological symptoms attributable to MS, lasting at least 24 h without pyrexia, responsible for an increase of at least 1 point in one or more of the Kurtzke Functional Systems Scores and resulting in a score of at least 2 on the most affected scale (≥ 3 on the sensory scale). For each relapse, a neurologist provided a clinical description in the case report form at the baseline appointment. All data concerning relapses were collected in a prospective way. Patients were followed regularly, and their EDSS score at 6 months post-relapse was recorded. DMT at relapse onset was allowed, except for natalizumab, mitoxantrone, and cyclophosphamide.

Patients for external validation

We used a distinct cohort of patients followed up at Bordeaux University Hospital (BUH), whose data were contained in the European Database for Multiple Sclerosis (EDMUS). Additional data, essential to our study were then retrospectively collected from the patients' files by three neurologists. All relapses occurred between January 2005 and December 2016. We selected the most recent relapse for each patient. Relapse was defined in the same way as in the COPOUSEP trial, except for the Kurtzke Functional Systems Scores, which were not available. Mild relapses with isolated worsening of paraesthesia were not included. All DMTs were allowed during the relapse.

Inclusion criteria

The following inclusion criteria were applied to patients in both the COPOUSEP trial and the BUH cohort: (1) age 18–55 years, (2) RRMS diagnosed according to 2005 McDonald criteria [12], (3) relapse with available data about its clinical presentation, (4) EDSS score ≤ 5 before relapse and (5) pre- and post-relapse EDSS scores available.

Collected data

The minimum dataset requirements included several candidate predictive factors at relapse: sex, age, disease duration, DMT, EDSS score 3–6 months before relapse during a stable period, EDSS score at relapse, and relapse phenotype. Relapses were divided into nine phenotypes according to the presenting symptoms and signs: (1) motor (motor disorders or isolated irritative pyramidal signs), (2) sensory (subjective sensory disturbances corresponding to paraesthesia, objective sensory disturbances corresponding to anaesthesia/hypoesthesia), (3) gait/balance disorder related to proprioceptive ataxia, (4) visual, (5) bladder/bowel, (6) cerebellar, (7) brainstem, (8) cognitive disorders, and (9) multifocal symptoms.

Outcome

We deemed that an increase of at least 1 EDSS point compared with the pre-relapse EDSS score attested to the persistence of a residual deficit at 6 months after the relapse of interest.

Statistical methods

The logistic regression was used. From the COPOUSEP data, univariate analyses were performed to validate

the log-linearity assumptions. If the log linearity did not hold, the variable was transformed to minimize the Akaike information criterion. The predictive factors were selected using lasso penalization [13], because several problems can occur with a variable selection based on the *p* value, such as multiple testing, colinear predictors or dependence with the sample size [14, 15]. Since there is no consensus on a valid method for obtaining confidence intervals or standard errors for lasso prediction [16], the standard deviation indicated is that of a classical logistic regression. The tuning parameter was estimated by fivefold cross-validation. No interaction was tested to respect the recommended number of events-per-variable for a parsimonious model [15]. For internal validation and correction of the overoptimistic discriminative accuracy, bootstrap cross-validation was used to estimate the area under the receiver operating characteristic curve (AUC).

For the external validation, the model was applied to the BUH cohort. The 95% confidence interval (95% CI) of the AUC was non-parametrically obtained by 1000 bootstrap replications. The calibration was evaluated by comparing the observed and expected probabilities of disability worsening and computing the Hosmer–Lemeshow statistic.

All analyses were performed using R version 3.4.3 [17] with the penalized [18] and ROCt [19] packages.

Results

Patients at baseline

The COPOUSEP trial included 199 patients. We excluded 13 patients from the learning and internal validation (one owing to missing baseline EDSS score, and 12 owing to missing 6-month EDSS score) (Fig. 1). The resulting COPOUSEP dataset included 186 patients with RRMS (mean age 35.3 ± 9.43 years; 142 women). We included 175 patients from the BUH cohort (mean age 36.2 ± 8.12 years; 134 women) for the external validation. A total of 102 (54.8%) patients in the COPOUSEP trial and 102 (58.6%) patients in the BUH cohort were on DMTs at baseline. All patients received a high dose of corticosteroids to treat the baseline relapse (1 g per day for 3 or 5 days). As illustrated in Table 1, baseline characteristics were similar across the two datasets, except for the EDSS score at relapse, which was higher in the COPOUSEP trial (3.45 ± 0.96 vs. 2.93 ± 1.00, $p < 0.001$).

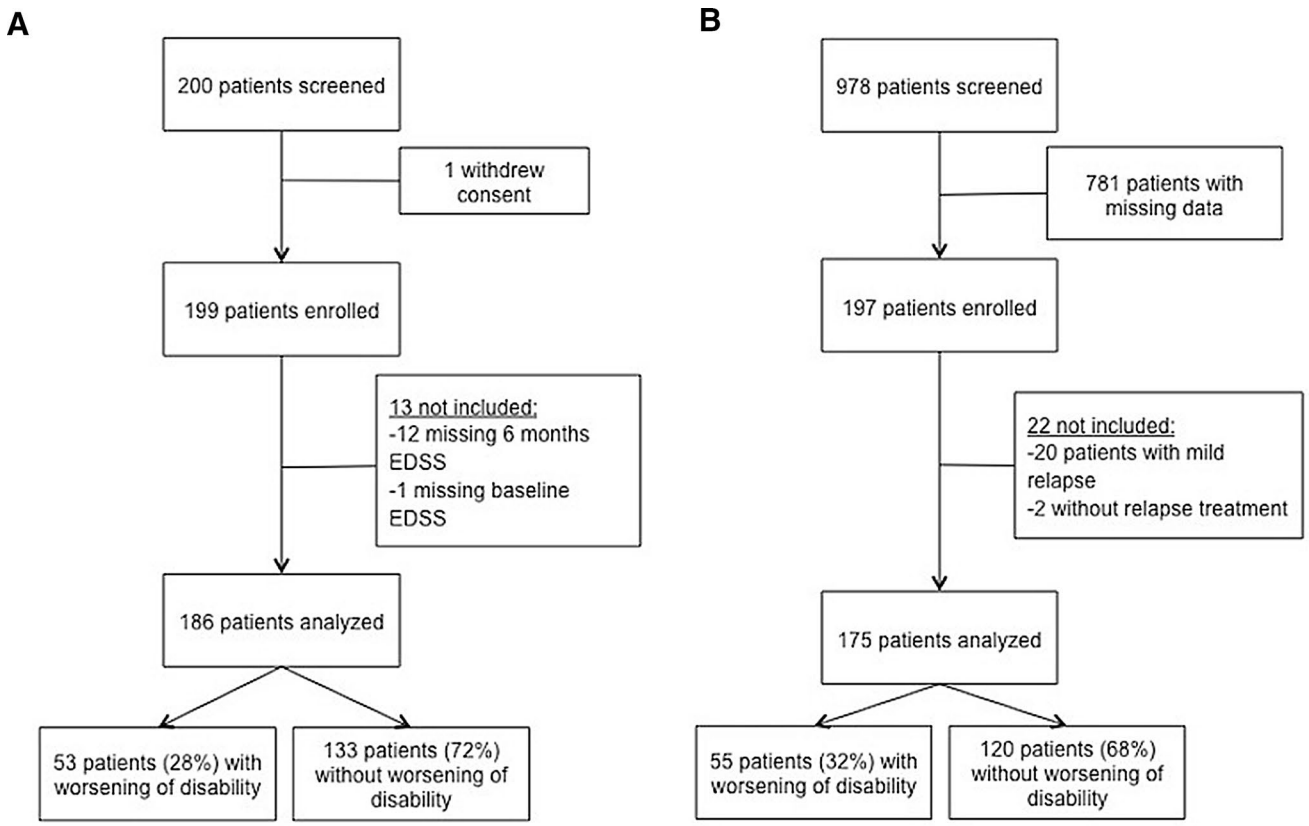

Fig. 1 Flowchart. **a** Patients from COPOUSEP trial for learning and internal validation. **b** Patients from Bordeaux University Hospital cohort for external validation

Table 1 Patients' characteristics and relapse phenotypes according to the learning (COPOUSEP trial) and external (BUH cohort) datasets

	COPOUSEP ($n=186$)		BUH ($n=175$)		p value
	Mean ± SD	Missing data	Mean ± SD	Missing data	
Disease duration (years)	7.32 ± 5.5	1	7.62 ± 6.56	1	0.638
Age (years)	35.3 ± 9.43	0	36.2 ± 8.12	0	0.323
EDSS score 3–6 months before relapse	1.42 ± 1.13	0	1.45 ± 1.18	0	0.758
EDSS score at baseline	3.45 ± 0.96	0	2.93 ± 1.00	0	< 0.001
	n (%)		*n* (%)		
Female	142 (76.3%)	0	134 (76.6%)	0	1.000
Disease-modifying therapy at relapse time					
No treatment	84 (45.2%)	0	72 (41.4%)	0	0.537
First line	95 (51.1%)	0	59 (33.9%)	1	
Second line	7 (3.8%)	0	43 (24.7%)	0	
Relapse phenotypes					
Visual disorders	30 (16.4%)	3	31 (17.7%)	0	0.848
Proprioceptive ataxia	30 (16.4%)	3	37 (21.1%)	0	0.310
Objective sensory disorders	74 (40.4%)	3	95 (54.3%)	0	0.012
Subjective sensory disorders	60 (32.8%)	3	93 (53.1%)	0	< 0.001
Motor disorders	71 (38.8%)	3	63 (36.0%)	0	0.662
Isolated irritative pyramidal signs	2 (1.1%)	3	7 (4.0%)	0	< 0.001
Vertigo and cerebellar disorders	39 (21.3%)	3	21 (12.0%)	0	0.027
Brainstem disorders	29 (15.8%)	2	24 (13.7%)	0	0.691
Cognitive disorders	1 (0.5%)	3	7 (4.0%)	0	0.033
Bowel/bladder disorders	15 (8.2%)	3	25 (14.3%)	0	0.097
Multifocal disorders	22 (12.9%)	16	Unknown	Unknown	Unknown

Student's t test was performed for quantitative variables. Kruskal–Wallis test or Chi-square test was performed for binary variables. $p < 0.05$ was considered statistically significant

BUH Bordeaux University Hospital, *EDSS* Expanded Disability Status Scale, *SD* standard deviation

Relapses at baseline

Baseline relapse phenotypes are shown in Table 1. In the two datasets, patients mostly experienced relapses that included sensory and/or motor disorders (40.4% and 38.8% for COPOUSEP trial vs. 54.3% and 36.0% for BUH cohort). Visual and cerebellar disorders, proprioceptive ataxia, cranial nerve, bowel/bladder disorders, and cognitive impairments were less frequent. Subjective sensory disturbances were significantly more frequent in the BUH dataset than in the COPOUSEP one (53.1% vs. 32.8%; $p < 0.001$).

Disease worsening

Six months after the relapse, 28.5% of patients from the COPOUSEP trial and 31.6% of patients from the BUH cohort had a persistent increase of ≥ 1 point compared with their pre-relapse EDSS score. Patients whose EDSS score was worse at 6 months post-relapse had fewer subjective sensory symptoms (19.2% vs. 38.2%; $p = 0.014$), and their pre-relapse EDSS score was lower (0.80 ± 0.97 vs. 1.66 ± 1.11; $p < 0.001$) than that of patients who remained stable after their relapse. Differences between these two datasets are shown in Table 2. In the COPOUSEP cohort, there were no significant differences in the percentage of patients with a worsening EDSS at 6 months, according to DMT at relapse time (29.8% for patients without treatment, 27.4% for patients with first line and 28.6% with a second line, $p = 0.939$).

Modification of disease modifying therapy after relapse

As illustrated in Table 1, in the COPOUSEP and the BUH cohorts, respectively, 45.2% ($n = 84$) and 41.4% ($n = 72$) patients did not have any DMT at relapse time, 51.1% ($n = 95$) and 33.3% ($n = 58$) patients had a first line and 3.8% ($n = 7$) and 24.7% ($n = 43$) of patients had a second line. Six months after the relapse, there were no DMT change for 59.1% ($n = 110$) of patients in the COPOUSEP study and for 49.1% of patients ($n = 86$) in the BUH cohort; whereas, therapeutic escalation was decided for

Table 2 Patients' characteristics and relapse phenotypes in the learning (COPOUSEP trial) dataset according to disability worsening

	Missing data	Worsening ($n=53$) Mean ± SD	Unaltered ($n=133$) Mean ± SD	p value
Disease duration (years)	1	6.24 ± 5.99	7.76 ± 5.28	0.091
Age (years)	0	34.53 ± 10.08	35.57 ± 9.18	0.500
EDSS score 3–6 months before relapse	0	0.80 ± 0.97	1.66 ± 1.11	< 0.001
EDSS score at baseline	0	3.61 ± 1.03	3.39 ± 0.93	0.156
		n (%)	*n* (%)	
Female	0	37 (69.8%)	105 (78.9%)	0.186
Disease-modifying therapy	0	28 (52.8%)	74 (55.6%)	0.728
Relapse phenotypes				
Visual disorders	*3*	11 (21.1%)	19 (14.5%)	0.273
Proprioceptive ataxia	*3*	10 (19.2%)	20 (15.3%)	0.514
Objective sensory disorders	*3*	19 (36.5%)	55 (42.0%)	0.498
Subjective sensory disorders	*3*	10 (19.2%)	50 (38.2%)	0.014
Motor disorders	*3*	22 (42.3%)	49 (37.4%)	0.539
Isolated irritative pyramidal signs	*3*	2 (3.8%)	0 (0.0%)	0.098
Vertigo and cerebellar disorders	*3*	11 (21.1%)	28 (21.4%)	0.974
Brainstem disorders	*2*	11 (21.1%)	18 (13.6%)	0.208
Cognitive disorders	*3*	1 (1.9%)	0 (0.0%)	0.033
Bowel/bladder disorders	*3*	4 (7.7%)	11 (8.4%)	0.875
Multifocal disorders	*16*	5 (10.4%)	17 (13.9%)	0.538

Student's t test was performed for quantitative variables. Fisher's exact test or Chi-square test was performed for binary variables. $p < 0.05$ was considered statistically significant

EDSS Expanded Disability Status Scale, *SD* standard deviation

32.8% ($n=61$) and 48% ($n=84$) of patients in COPOUSEP study and BUH cohort, respectively.

Predictive model

By analyzing the COPOUSEP data, we retained six variables in the SMILE model to predict the probability of disability worsening at 6 months post-relapse. Some factors were associated with poorer disease outcome: increase ≥ 1.5 points in the EDSS score during the baseline relapse (OR 1.08 ± 1.58 if increase of 1.5–2.5 points and OR 4.98 ± 9.23 if increase of ≥ 3 points), EDSS = 0 before relapse (OR 1.75 ± 0.29), age > 40 years (OR 1.29 ± 1.65), and proprioceptive ataxia (OR 1.05 ± 0.95). Other factors were related to a more favorable disease outcome: presence of subjective sensory disorders (OR 0.51 ± 0.17), and a longer disease duration (OR 0.73 ± 0.12). Other variables, including DMT at relapse time were considered when we constructed the model but their values were not significant enough to be retained in our final score.A free web application was developed to compute the probability of disability at 6 months post-relapse: https://shiny.idbc.fr/SMILE/, see Fig. 2.

Validation of prognostic capacities

Internal validation by bootstrapping the COPOUSEP data for cross-validation reported overoptimistic-corrected discriminative accuracy with an AUC of 0.82 (95% CI [0.73, 0.91]). This represented the probability that a randomly selected patient with disability worsening at 6 months post-relapse would have a higher predicted probability of disability worsening than a randomly selected patient without worsening.

Additionally, we externally validated the model with a different population (BUH cohort). The AUC was 0.71 (95% CI [0.62, 0.80], Fig. 3a). As illustrated in Fig. 3b, the calibration comparing the observed and expected probabilities of disability worsening in the BUH cohort, was acceptable, except for a possible underestimation of the probability of 6-month worsening in high-risk patients (Hosmer–Lemeshow statistic; $p=0.016$).

Medical decision-making

To illustrate the usefulness of the SMILE model in neurologists' daily practice, we looked at two clinical cases. The first was that of a 25-year-old woman who had had RRMS for

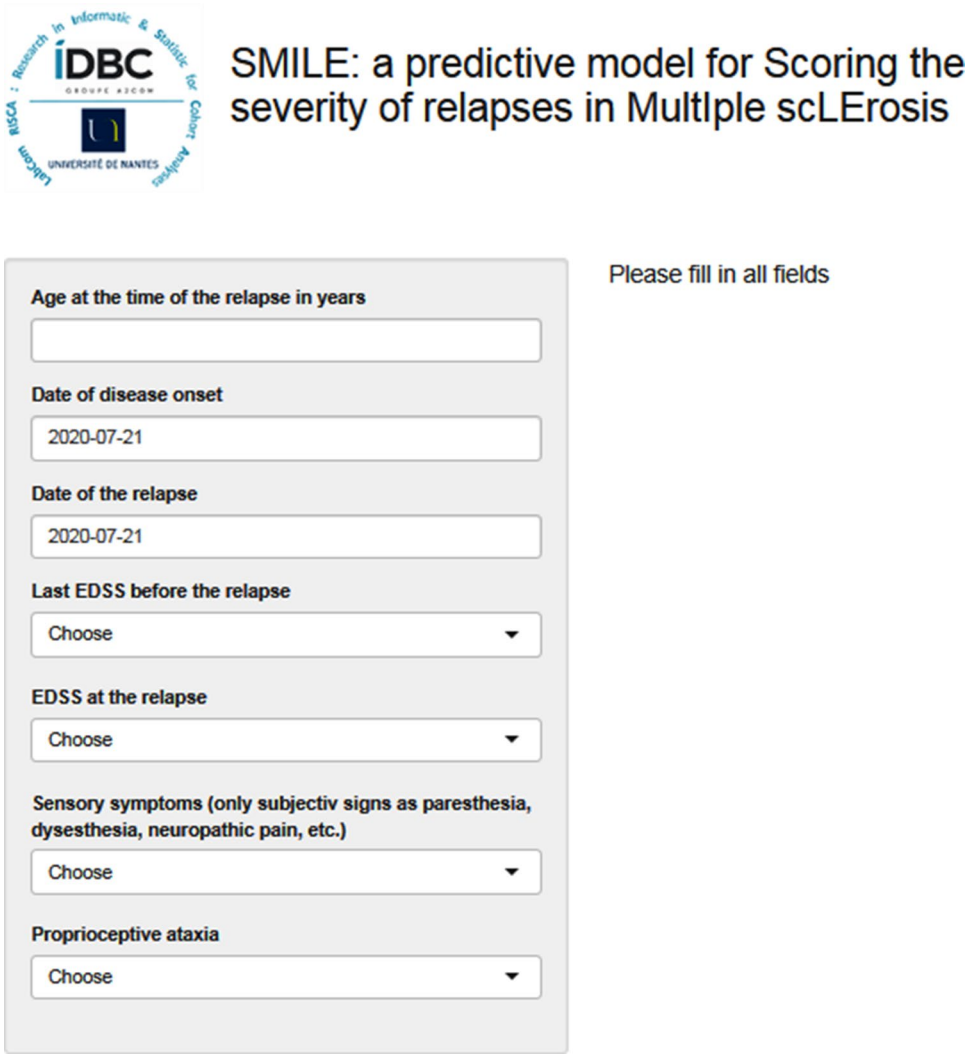

Fig. 2 Illustration of free web application

2 years (EDSS = 0), and who presented with a relapse involving objective sensory disorders and proprioceptive ataxia, causing a 3-point increase in her EDSS score. Her expected probability of 6-month worsening was estimated at 70%, meaning that closer medical follow-up (clinical/MRI) and more intensive relapse treatment could be considered (Fig. 4a). The second was that of a 34-year-old woman who had had RRMS for 7 years (EDSS = 1). She presented with a relapse involving both subjective and objective sensory disorders, causing a 3-point increase in her EDSS score. The probability of 6-month worsening was estimated at 10%. An increase in disability may be temporary for most patients with these symptoms, and intensive monitoring of relapse recovery will not be necessary in this patient (Fig. 4b).

Discussion

Patients with MS worry about their chances of recovery after relapse, but neurologists usually have no answer to give them. Even if there are often some clues at the time of relapse (e.g., relapse phenotype or EDSS score), a clinical tool for predicting residual disability would be helpful for ensuring personalized patient management.

In the present study, we constructed and validated a simple model (SMILE) that uses demographic, disease, and relapse phenotype criteria to predict post-relapse disability at 6 months. Importantly, we did not consider MRI data in this study, as we aimed to develop a clinical-based

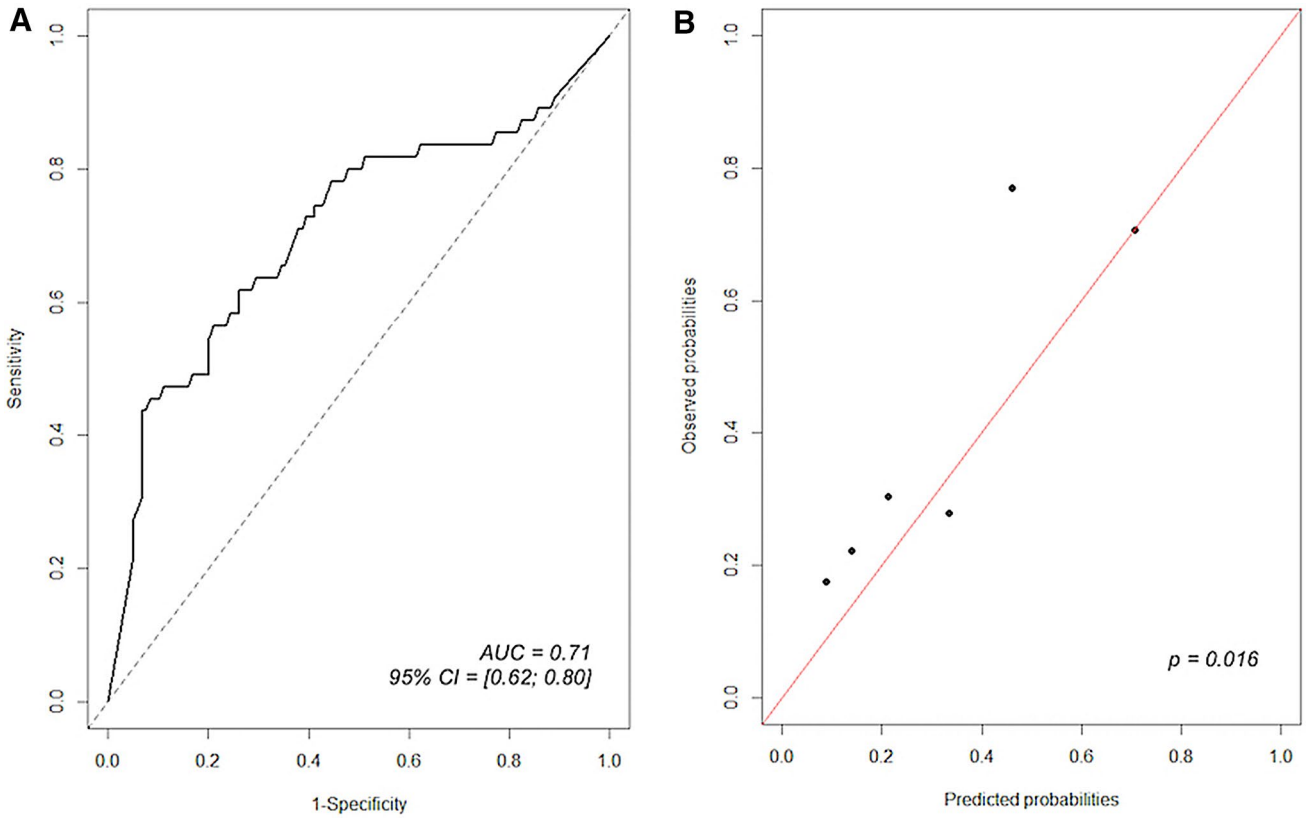

Fig. 3 Prognostic accuracy of SMILE model, externally validated with the Bordeaux University Hospital cohort. **a** Discriminative accuracy, AUC = 0.71, 95% CI [0.61, 0.79]. **b** Calibration accuracy, $p = 0.016$, Hosmer–Lemeshow statistic

model adapted to daily clinical practice and focused on the relapse phenotype. Even if MRI parameters are among the best prognostic factors for disease course, rapid access to imaging is rarely possible when patients consult for a relapse. We believe that the SMILE score can guide neurologists' therapeutic management of relapses and indicate whether the treatment and follow-up of severe relapses with a poor prognosis should be reinforced. Although a short course of IV methylprednisolone (IVMP) is currently the treatment of choice [20, 21] for the relapses that occur during MS (1000 mg × 3 days or 500 mg during 5 days), one randomized trial published in 1998 [22], has demonstrated that very high doses (10 g on 5 days) of IVMP are more effective than lower doses (2.5 g on 5 days) in reducing the number of MRI contrast-enhanced lesions at 30 and 60 days. Whether or not the early administration of a high dose (5 g or 10 g) of corticosteroids improves the chances of recovery has yet to be confirmed, but IVMP treatment escalation could be an option to discuss for patients at risk of significant disability. Other studies have yielded interesting results regarding plasma exchange as a rescue therapy for aggressive MS relapses [23, 24]. In fact, two small randomized trials [25, 26] suggest good response rates to plasma exchange in relapses unresponsive to steroids. Several case studies also report their utility in steroid refractory relapses [24, 27, 28] and some guidelines recommend plasma exchange as an adjunctive treatment for increasing the chances of recovery for steroid refractory relapses [29, 30]. Access to plasma exchange can be difficult in some centers and detecting patients at risk of bad recovery is particularly important to anticipate their management.

This score could be especially important for neurologists without MS expertise to evaluate a potential severe relapse and ask for help in specialized MS centers. The SMILE score can also be used to inform patients about their post-relapse prognosis, which is important information when it comes to shared medical decisions.

In the present study, we undertook a precise description of the neurological symptoms presented during each relapse. This fine-grained analysis was made possible by the COPOUSEP trial, where each relapse was characterized by the Kurtzke Functional Systems Scores, and clinically described by the treating neurologist. This was of particular importance, as it allowed us to clearly distinguish new symptoms from preexisting ones.

Relapse characteristics differed slightly between the two cohorts, with more severe relapse at baseline in the

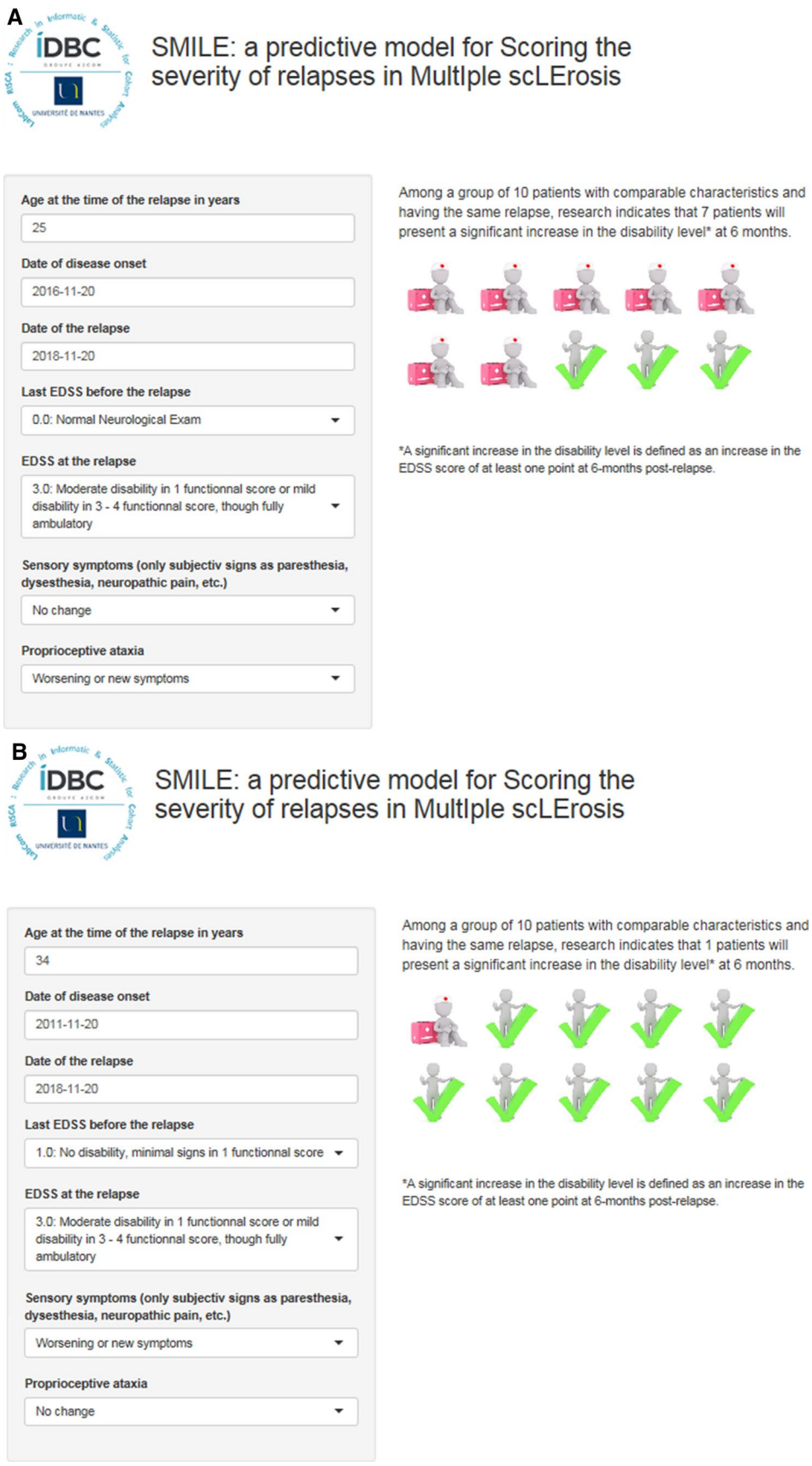

Fig. 4 Examples of clinical use of free web application. **a** Case 1. **b** Case 2

COPOUSEP trial. This can be explained by stricter relapse-defining criteria in the COPOUSEP trial. The heterogeneity between the training and validation datasets is one of the strengths of our study, in that it respected the definition of external validation. Together, these two cohorts constituted a more representative sample of MS patient diversity, reinforcing the importance of our score in daily practice.

Six variables were included in our final model, two related to relapse phenotype symptoms. Subjective sensory disorders appeared to be related to a more favorable relapse outcome, consistent with previous findings [31, 32]. By contrast, gait disorders related to proprioceptive ataxia appeared to be a risk factor for disability at 6 months. These symptoms are often related to the presence of spinal cord lesions that significantly contribute to short-term disability accrual [33]. Age ≥ 40 years at relapse appeared to be a risk factor in our study, reflecting the fact that the ability to recover from relapses declines with age [3, 6, 7]. Some studies have also shown that relapses are more severe at the beginning of the disease, which explains why a shorter disease duration was associated with poorer recovery in our study [5, 34]. An EDSS score of 0 before the relapse was associated with a higher risk of disability at 6 months. In a recent study, Stewart et al. found that a higher EDSS score before the relapse was linked to a smaller EDSS increase [10]. The nonlinearity of the EDSS score may explain this inverse relationship between the EDSS score before relapse and the risk of residual disability at 6 months post-relapse [35]. Severe relapses accompanied by a greater increase in the EDSS score appeared to be a major risk factor for mid-term disability in our study. These results are in line with the literature, with relapse severity being a major risk factor for incomplete recovery [6, 36].

Concerning other relapse phenotypes, motor symptoms, cognitive symptoms and sphincter disorders are typically known to be predictive of bad recovery [6, 7, 37]. In our cohort, there were very low representation of cognitive symptoms (1 in Copousep and 7 in the validation cohort). Sphincter disorders were better represented but remain rarer thus explaining why it has not been retained in the final model.

Last, for motor symptoms, our results are not in accordance with previous studies [7, 10]]. In contrast to bowel/bladder and cognitive disorders, motor dysfunctions were common in the two cohorts, but their severity was difficult to evaluate. It may be that the patients in our study presented a mild-to-moderate motor relapse that did not constitute a real risk factor for poor recovery.

Our study had several limitations. First, the limited size of our datasets resulted in small numbers of some relapse phenotypes (e.g., bowel/bladder or cognitive relapses). Second, our model was built using prospective data collected during a clinical trial among patients who presented with moderate-to-severe relapses (treated with corticosteroids). Therefore, mild relapses from which patients usually recover well were not taken into account in our model. Finally, we did not have access to clinical data to confirm EDSS worsening at 3/6 months. This may imply an overestimation of the percentage of patients with residual disability after their relapse. In practice, it does not constitute a loss of chance for patients but maybe a less precise selection of severe relapses.

In conclusion, SMILE is the first clinical-based model for predicting the risk of residual disability after relapse. We are confident that the SMILE score will prove useful in daily practice, allowing patients with MS to receive more detailed and personalized counselling, and guiding neurologists in their management of relapse in these patients. As it is based solely on clinical data, all available when patients consult for a relapse, it is a simple model that can be used in both hospital and ambulatory practice.

Data availability statement

Data are available upon reasonable request. Please contact the corresponding author.

Compliance with ethical standards

Conflicts of interest F. Lejeune reports no disclosures. A. Chatton reports no disclosures. D.-A. Laplaud reports personal fees and non-financial support from Biogen, Merck, Novartis, Genzyme, Teva, Roche and MedDay, all outside the submitted work. S. Wiertlewski received consultancy fees, speaker fees, honoraria and clinical research grants from Biogen-Idec, Merck, Novartis, Genzyme, Roche, Sanofi-Aventis and Teva, all outside the submitted work. G. Edan reports no disclosures. E. Le Page has received grants, personal fees and non-financial support from Biogen Idec, Genzyme, Merck-Serono, Novartis, Roche, Sanofi and Teva, all outside the submitted work. A. Kerbrat reports no disclosures. D. Veillard reports no disclosures. S. Hamonic reports no disclosures. N. Jousset reports no disclosures. F. Le Frère reports no disclosures. J.-C. Ouallet reports personal fees from Biogen, Roche and Genzyme, and grants, personal fees and non-financial support from Novartis and Merck, all outside the submitted work. B. Brochet reports grants from the French Ministry of Health, personal fees and non-financial support from Biogen-Idec, grants from Merck-Serono, personal fees and non-financial support from Novartis, personal fees and non-financial support from Genzyme, grants, personal fees and non-financial support from Teva, and grants and non-financial support from Bayer, all outside the submitted work. A. Ruet has received consultancy fees, speaker fees, research grants (non-personal) or honoraria from Medday, Novartis, Biogen Idec, Genzyme, Roche, Teva, and Merck, all outside the submitted work. Y. Foucher has received speaking honoraria from Biogen and Sanofi-Genzyme. L. Michel has received grants and fees from Biogen Idec, Merck Serono, Roche, Sanofi Genzyme, Teva and Novartis, all outside the submitted work.

Ethics approval Data confidentiality and safety were ensured in accordance with the recommendations of the French National Ethics Committee (CNIL-Commission Nationale Informatique et Libertés), which provided approval for the EDMUS database. All data identifying patients were anonymised. All human studies were performed in

accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Specific national laws were also observed.

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