



HAL
open science

Active and nonactive progression independent of relapse activity within the first 20 years of relapsing multiple sclerosis

Adil Maarouf, Jan Patrick Stellmann, Audrey Rico, Clemence Boutiere, Sarah Demortiere, Pierre Durozard, Wafaa Zaaraoui, Jean-Philippe Ranjeva, Jean Pelletier, Bertrand Audoin

► To cite this version:

Adil Maarouf, Jan Patrick Stellmann, Audrey Rico, Clemence Boutiere, Sarah Demortiere, et al.. Active and nonactive progression independent of relapse activity within the first 20 years of relapsing multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, 2024, jnnp-2024-333597. 10.1136/jnnp-2024-333597 . hal-04783734

HAL Id: hal-04783734

<https://amu.hal.science/hal-04783734v1>

Submitted on 14 Nov 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

**Active and nonactive progression independent of relapse activity within the first 20
years of relapsing multiple sclerosis**

Adil Maarouf^{1,2}, Jan-Patrick Stellmann^{2,3,4}, Audrey Rico^{1,2}, Clémence Boutiere¹, Sarah Demortiere¹, Pierre Durozard^{1,5}, Wafaa Zaaraoui^{2,3}, Jean-Philippe Ranjeva^{2,3}, Jean Pelletier^{1,2}, Bertrand Audoin^{1,2}

1 Aix Marseille Univ, APHM, Hôpital de la Timone, Department of Neurology, Marseille, France

2. Aix Marseille Univ, CNRS, CRMBM, Marseille France

3. APHM, Aix Marseille Univ, Hôpital de la Timone, Pôle d'Imagerie, CEMEREM, Marseille, France

4. APHM, Aix Marseille Univ, Hôpital de la Timone, Department of Neuroradiology, Marseille, France

5. Centre Hospitalier d'Ajaccio, France

Corresponding author: Bertrand Audoin, Aix Marseille Univ, APHM, Hôpital de la Timone, Pôle de Neurosciences Cliniques, Service de Neurologie, 13005 Marseille, France;
bertrand.audoin@ap-hm.fr

Funding/Support:

This study was supported by Fondation pour l'Aide à la Recherche sur la Sclérose En Plaques (ARSEP Fondation).

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Competing interests All authors certify that there is no any financial interest related to this study.

Word count:

Abstract: 250

Manuscript text: 1240

Number of references: 14

Number of tables: 3

Number of figure: 1

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd (“BMJ”) its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in Journal of Neurology, Neurosurgery, and Psychiatry and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge (“APC”) for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Contributions for the study:

Adil Maarouf played a major role in the acquisition of the data and the gathering of data.

Jan-Patrick Stellmann played a major role in the acquisition of the data and the gathering of data.

Audrey Rico played a major role in the acquisition of the data.

Clémence Boutière played a major role in the acquisition of the data.

Sarah Demortiere played a major role in the acquisition of the data.

Wafaa Zaaraoui played a major role in the acquisition of the data.

Jean-Philippe Ranjeva planned the study and played a major role in the acquisition of the data

Jean Pelletier planned the study and played a major role in the acquisition of the data

Bertrand Audoin planned and conducted the study, conducted statistical analysis and wrote the manuscript.

Abstract

Background

Progression independent of relapse activity (PIRA) has been described since the early stage of relapsing MS (RMS). However, little is known about the relation between PIRA and inflammatory activity that is particularly important at this stage of the disease.

Method

We included 110 patients in a prospective study within 18 months of RMS onset. MRI examinations and clinical visits were scheduled on the same day for months 0, 6, 12, 24, 36, 60, 84, 120, 180 and 240.

Results

The mean (SD) age of patients was 30 (6.7) years at inclusion and median (range) follow-up 15 (9-20) years. Analysis of 1118 between-visit intervals revealed 93 confirmed disability accumulation events in 68 (62%) patients: 50 (54%) events related to relapse activity worsening and 43 (46%) PIRA events, including 17 (18%) with MRI activity. The risk of PIRA between two visits (stable event as the reference category) was associated with EDSS score (hazard ratio [HR]: 1.41; 95%CI, 1.18–1.69; $P<.001$), disease duration (HR: 0.75; 95% CI, 0.62–0.90; $P<.005$) and new lesions between the visits (HR: 1.09 per lesion; 95% CI, 1.01–1.17; $P<.05$). As compared with PIRA events with MRI activity, PIRA events without such activity occurred in patients with more disability (mean EDSS score 3, $p<.05$), longer disease duration (mean 11 years, $p<.001$) and greater number of T2-weighted lesions ($p<.05$).

Conclusion

This study evidenced that inflammatory activity increases the risk of PIRA in early RMS, arguing that a significant part of PIRA is accessible to treatment targeting inflammation in these patients.

Data availability statement

All data analyzed during this study will be shared anonymized by reasonable request of a qualified investigator to the corresponding author.

What is already known on this topic?

Progression independent of relapse activity (PIRA) has been described since the first stage of relapsing multiple sclerosis (RMS). However, little is known about the potential impact of inflammatory activity on the risk of PIRA.

What this study adds

Inflammatory activity increased the risk of PIRA in RMS. As compared with PIRA associated with inflammatory activity, non-active PIRA occurred later in patients who had acquired more lesions and had greater disability.

How this study might affect research, practice or policy

Full control of inflammatory activity could significantly reduce the risk of PIRA in early RMS.

Introduction

Disease progression independent of relapse activity (PIRA) was described in patients with relapsing multiple sclerosis (RMS) treated with high-efficacy therapy, which suggested that PIRA could occur independent of disease activity [1]. Hence, PIRA was interpreted as the clinical counterpart of the neurodegenerative component of MS. However, in patients without full control of disease activity, lesion accumulation could also contribute to PIRA [2–5]. In these patients, nonactive PIRA (naPIRA), defining patients free of relapse but also free of MRI activity, could better reflect the neurodegenerative component of MS as compared with those with active PIRA (aPIRA). Nevertheless, to what extent aPIRA contributes to PIRA in early RMS remains largely unknown because in previous studies MRI explorations were missing or not performed at the same time as clinical visits [2,3].

In the present study, we analyzed data from a prospective MRI study of 129 patients with RMS enrolled after their first clinical event and followed up to 20 years (median 15 years). Importantly, all clinical visits and MRI examinations (> 1100) were scheduled on the same day, which allowed for qualifying each confirmed disability accumulation (CDA) event as aPIRA, naPIRA or relapse-associated worsening (RAW).

Methods

Participants

From 2001 to 2011, 129 patients were included in a prospective MRI study based on the following criteria: 1) age 18 to 45 years; 2) occurrence of a first inflammatory demyelinating event in the central nervous system in the last 18 months; 3) presence of oligoclonal bands in cerebral spinal fluid; and 4) presence of at least 2 demyelinating lesions in the brain or spinal cord detected at the initial MRI performed before inclusion. This study involves human participants and was approved by local ethics committee (Timone Hospital, Marseille and Comité de Protection des Personnes Sud-Méditerranée), number CCPPRB Marseille 2: 99-47 for patients explored with 1.5T MR system and CPP Sud Méditerranée 1: 08-45 for patients explored with 3T MR system. All participants gave informed consent to participate in the study before taking part [6,7].

Study design

Brain MRI examinations and clinical visits were scheduled on the same day for months 0, 6, 12, 24, 36, 60, 84, 120, 180 and 240. Disability level was rated with the Expanded Disability Status Scale (EDSS)[8]. All relapses since the last visit were recorded.

Statistics

CDA was considered according to the used 3 strata definitions (increase in EDSS score by 1.5 points if the last EDSS score was 0, increase by 1 point if the EDSS score was 1 to 5.5, or increase by 0.5 points if the EDSS score was > 5.5), confirmed after at least 6 months. The existence of a PIRA event was defined at each visit considering the presence of CDA during the interval and the absence of any relapse during the same interval. With new T2-weighted lesions and PIRA during the same interval, we retained an aPIRA event. If PIRA occurred in an interval without new lesions, we retained an naPIRA event. PIRA events had to be present in all longitudinal follow-up data. With the presence of CDA and relapse during the same interval, we retained a RAW event. If no CDA occurred in an interval, we retained a STABLE event.

We compared patient characteristics at the beginning of each interval associated with an episode of PIRA (RAW, aPIRA and naPIRA), including age, disease duration, EDSS score, and number of brain T2 lesions, by using linear mixed-effects models accounting for recurrent measurements in patients. To explore factors associated with PIRA between two consecutive visits (with STABLE events as the reference category), we computed Cox proportional-hazards regression models for recurrent events with patient ID used as a cluster variable and first clinical event or the next visit as the end time, estimating hazard ratios (HRs) and 95% confidence intervals (CIs). The initial Cox proportional-hazards model included age, EDSS score, disease duration, total lesion number, type of treatment (no versus high/moderate/low efficacy therapy) at the last visit and number of new T2-weighted lesions before and since the last visit. The model was then reduced by backward selection of variables. We used the Akaike Information Criterion to select variables. All analyses were performed with Statistics in R v4.2.1.

Data availability

All data will be shared anonymized by reasonable request of a qualified investigator to the corresponding author.

Results

Characteristics of the cohort

At the time of the analysis, 110 of 129 (85%) patients were still being followed (88 females, mean [SD] age 30 [6.7] years at the first MRI/clinical visit); 14 patients dropped out after the

first MRI and 5 before 5 years. At the first MRI/clinical visit, the mean (SD) time since the first MS symptoms was 0.48 (0.35) years. At the last MRI/clinical visit, the median (range) follow-up of patients was 15 (9-20) years, corresponding to 1569 patient-years. The number of combined MRI/clinical visits was 1120, corresponding to a median (range) of 10 (4-19) visits per patient.

During the same period of inclusion (2001-2011), 571 patients visited the MS centre of Marseille for a first demyelinating MS event. These patients represented 87% of the estimated number of patients with a first demyelinating MS event during this period (n=657) according to the incidence of MS in the Provence region [9]. The 110 patients followed and the 571 who visited the center did not differ in demographic characteristics (sex ratio and age) (p=0.28 and p=0.11).

CDA during follow-up

Analysis of the 1118 between-visit intervals revealed 93 CDA events in 68 of 110 (62%) patients: 50 (54%) RAW and 43 PIRA (46%) (Table 1 and Figure). PIRA events included 26 naPIRA (60%) and 17 aPIRA (40%) events. As compared with aPIRA events, naPIRA events occurred in patients with more disability (mean EDSS score 3, p<.05), longer disease duration (mean 11 years, p<.001) and greater number of T2-weighted lesions (mean 55; p<.05) (Tables 1 and 2). The initial Cox proportional-hazards model included age, EDSS score, disease duration, total lesion number, type of treatment (no versus high/moderate/low efficacy therapy) at last visit and number of new T2-weighted lesions before and since the last visit; it was then reduced by backward selection of variables and then stepwise backward selection of variables. The final model included only EDSS score (HR: 1.41; 95%CI: 1.18–1.69, p<.005), disease duration (HR: 0.75; 95%CI: 0.62–0.90, p<.005) and number of new T2-weighted lesions between the two visits (HR: 1.09; 95%CI: 1.01–1.17, p<.05) (Table 3).

Discussion

Events related to disease activity (RAW and aPIRA) contribute to almost 75% of all CDA events occurring within the first 20 years of RMS. NaPIRA contributed to the remaining CDA events and occurred more frequently after several years of disease evolution (mean 11 years) in patients with significant disability (mean EDSS score 3) and a high number of lesions. In the present study, we selected patients younger than 45 years at inclusion to limit the risk of including patients not at the real first stage of MS and patients with progressive MS

erroneously classified as RMS. Therefore, the association found between lesion accumulation and risk of concomitant PIRA could not be generalized to late-onset RMS.

The present study indicates that PIRA events in early RMS could not be exclusively related to diffuse inflammation and/or secondary degeneration and that the accumulation of asymptomatic demyelinating lesions in the brain were observed in 40% of all PIRA events. Crucially, the association found between lesion accumulation since the last visit and risk of PIRA at each visit suggests that the accumulation of demyelinating lesions not associated with relapse may be involved in the pathogenesis of PIRA. The risk of PIRA at each visit was increased to a mean of 9% for each new single brain T2 lesion that occurred since the last visit. This association between MRI activity and subsequent disability worsening can partly explain the elevation of neurofilament light chain observed more than one year before disability worsening independent of clinical relapses [10]. One may suppose that subclinical relapse activity could result in disability worsening as the central nervous system reserve is lost [5]. Moreover, the contribution of aPIRA events was probably under-estimated here because of lack of available spinal-cord MRI images. Indeed, previous studies found that lesion accumulation in the spinal cord contributed highly to disability [11,12]. Finally, we found that naPIRA events occurred generally after several years of disease in patients with a high number of lesions and more disability. All these findings suggest that many PIRA events occurring in RMS could be accessible to early treatment with high-efficacy therapy that fully controls disease activity and reduces early disability accumulation [13,14]. In the present study, we did not find an association between treatment and risk of PIRA. However, the interpretation of this result is difficult because the decision to treat and the choice of therapy were based on the physician's preference and highly depended on the level of disease activity. Thus, the design of the present study allowed for depicting an association between disease activity and risk of PIRA but not the potential effect of therapy on risk of PIRA.

The strengths of the study are its prospective design, the long-term follow-up, the high number of standardized clinical and MRI examinations performed concomitantly, the inclusion of patients right after RMS onset, and the low number of patients lost to follow-up. Limitations are lack of spinal-cord MRI images, the relatively small sample size and the monocentric design. Moreover, the effect of EDSS levels on the risk of progression needs to be interpreted with caution because the non-continuous character of the EDSS scale might bias our analyses, in which EDSS score was used as a continuous variable.

Conclusions

APIRA and naPIRA may have different pathophysiologies, and full control of disease activity from disease onset may significantly reduce the risk of PIRA in RMS.

References

- 1 Kappos L, Wolinsky JS, Giovannoni G, *et al.* Contribution of Relapse-Independent Progression vs Relapse-Associated Worsening to Overall Confirmed Disability Accumulation in Typical Relapsing Multiple Sclerosis in a Pooled Analysis of 2 Randomized Clinical Trials. *JAMA Neurol.* 2020;77:1132–40.
- 2 Tur C, Carbonell-Mirabent P, Cobo-Calvo Á, *et al.* Association of Early Progression Independent of Relapse Activity With Long-term Disability After a First Demyelinating Event in Multiple Sclerosis. *JAMA Neurol.* 2023;80:151–60.
- 3 Portaccio E, Bellinva A, Fonderico M, *et al.* Progression is independent of relapse activity in early multiple sclerosis: a real-life cohort study. *Brain.* 2022;145:2796–805.
- 4 Müller J, Cagol A, Lorscheider J, *et al.* Harmonizing Definitions for Progression Independent of Relapse Activity in Multiple Sclerosis: A Systematic Review. *JAMA Neurol.* 2023;80:1232–45.
- 5 Lublin FD. Worsening MS—A reappraisal of how we characterize the MS disease course. *Mult Scler.* 2023;29:1699–700.
- 6 Audoin B, Zaaraoui W, Reuter F, *et al.* Atrophy mainly affects the limbic system and the deep grey matter at the first stage of multiple sclerosis. *J Neurol Neurosurg Psychiatr.* 2010;81:690–5.
- 7 Wybrecht D, Reuter F, Pariollaud F, *et al.* New brain lesions with no impact on physical disability can impact cognition in early multiple sclerosis: A ten-year longitudinal study. *PLoS One.* 2017;12:e0184650.
- 8 Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology.* 1983;33:1444–52.
- 9 Fromont A, Binquet C, Sauleau EA, *et al.* Geographic variations of multiple sclerosis in France. *Brain.* 2010;133:1889–99.
- 10 Abdelhak A, Benkert P, Schaedelin S, *et al.* Neurofilament Light Chain Elevation and Disability Progression in Multiple Sclerosis. *JAMA Neurol.* 2023;80:1317–25.
- 11 Kerbrat A, Gros C, Badji A, *et al.* Multiple sclerosis lesions in motor tracts from brain to cervical cord: spatial distribution and correlation with disability. *Brain.* 2020;143:2089–105.
- 12 Brownlee WJ, Altmann DR, Prados F, *et al.* Early imaging predictors of long-term outcomes in relapse-onset multiple sclerosis. *Brain.* 2019;142:2276–87.
- 13 Harding K, Williams O, Willis M, *et al.* Clinical Outcomes of Escalation vs Early Intensive Disease-Modifying Therapy in Patients With Multiple Sclerosis. *JAMA Neurol.* 2019;76:536–41.
- 14 Spelman T, Magyari M, Piehl F, *et al.* Treatment Escalation vs Immediate Initiation of Highly Effective Treatment for Patients With Relapsing-Remitting Multiple Sclerosis: Data From 2 Different National Strategies. *JAMA Neurol.* 2021;78:1197–204.

Table 1: Patient characteristics by type of event

	RAW n=36	Active PIRA n=15	Nonactive PIRA n=17	STABLE n=110
Episodes	50 (4.5%, 95%CI: 3.3%–5.9%)	17 (1.5%, 95%CI: 0.9%–2.4%)	26 (2.3%, 95%CI: 1.5%–3.4%)	1025 (91.5%, 95%CI: 86.0%–97.3%)
Sex, F/M	43/7 (86%/14%)	16/1 (94.1%/5.9%)	22/4 (84.6%/15.4%)	808/217 (79%/21%)
Age at disease onset, mean (SD); median [range]; years	30.9 (7.9); 31.0 [18.6–44.8]	30.2 (6.3); 32.2 [22.0–43.1]	29.0 (5.1); 28.8 [23.0–44.0]	29.5 (6.7); 29.3 [16.3–45.6]
Age at last visit, mean (SD); median [range]; years	37.8 (7.3); 37.6 [24.1–50.3]	39.1 (5.7); 38.9 [29.1–53.8]	40.4 (13.9); 37.2 [21.9–49.8]	34.6 (8.1); 34.1 [16.3–60.9]
Disease duration at last visit, mean (SD); median [range]; years	8.7 (4.5); 9.2 [2.3–18.8]	8.1 (3.9); 7.6 [2.2–15.5]	10.7 (4.3); 10.4 [3.2–19.0]	5.5 (4.9); 3.8 [0–21.4]
Number of T2-weighted lesions at last visit, mean (SD); median [range]; number	47.2 (51.6); 34 [3–335]	49.8 (36.3); 53 [6–129]	54.5 (40); 46 [6–151]	37.0 (45.9); 24 [0–335]
EDSS score at last visit, mean (SD); median [range]	2.2 (1.6); 2 [0–7]	1.7 (1.8); 1 [0–6]	3 (1.8); 2.8 [1–6]	1.2 (1.4); 1 [0–8]
EDSS score at the visit, mean (SD); median [range]	3.9 (1.8); 4 [1.5–8]	3.1 (1.7); 2.5 [1.5–7]	4.2 (1.6); 4 [1.5–6.5]	1.2 (1.4); 1 [0–8]

RAW = relapse-associated worsening, PIRA = progression independent of relapse activity, STABLE = no confirmed disability accumulation between 2 visits, EDSS = Expanded Disability Status Scale

Table 2: Disease characteristics at the beginning of episodes with confirmed EDSS score progression labelled as RAW (the reference category), active PIRA or nonactive PIRA.

	Intercept	Active PIRA	Nonactive PIRA
Age at last visit, <i>year</i>	39.6 (35.8–43.3) p < 0.001	-1.8 (-5.1–1.6) p = 0.300	2.5 (-0.6–5.6) p = 0.108
Disease duration at last visit, <i>year</i>	5.7 (4.6–6.9) p < 0.001	0 (-2.0–2.0) p = 0.989	3.3 (1.5–5.1) p < 0.001
EDSS score at last visit	2 (1.5–2.5) p < 0.001	-0.5 (-1.4–0.4) p = 0.288	0.9 (0.1–1.7) p = 0.033
Number of T2-weighted lesions at last visit	44.4 (29.5–59.3) p < 0.001	-0.8 (-7.8–6.2) p = 0.828	6.9 (0.5–13.4) p = 0.034

Data are estimates and 95% confidence intervals from linear mixed effects models adjusting for recurrent events. PIRA = progression independent of relapse activity, EDSS = Expanded Disability Status Scale.

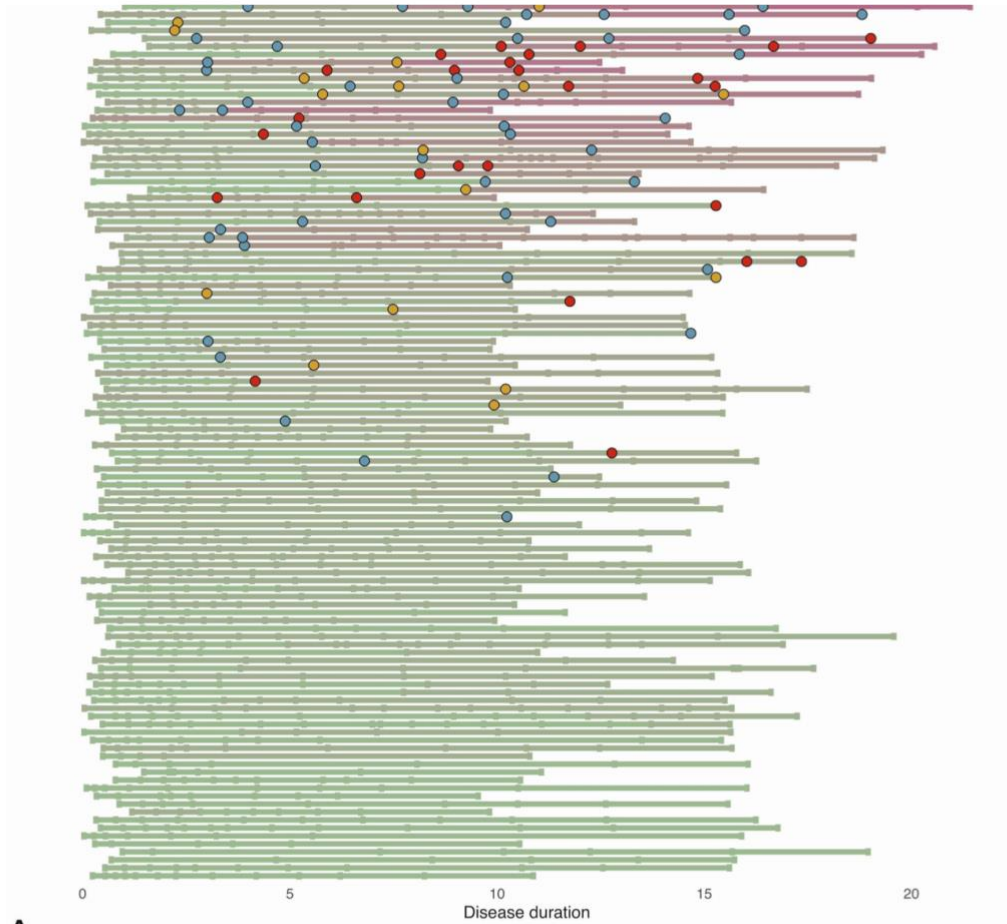
Table 3: Predictors for a PIRA event.

	Full model			Reduced model		
Variable	Beta (SE)	HR (95% CI)	P	Beta (SE)	HR (95% CI)	P
Age at last visit, <i>per year</i>	-0.02 (0.03)	0.98 (0.93, 1.03)	0.463			
Disease duration at last visit, <i>per year</i>	-0.33 (0.11)	0.72 (0.60, 0.87)	< 0.001	-0.29 (0.10)	0.75 (0.62, 0.90)	0.002
EDSS score at last visit	0.26 (0.11)	1.29 (0.97, 1.72)	0.079	0.35 (0.09)	1.41 (1.18, 1.69)	< 0.001
Number of T2-weighted lesions at last visit, <i>per lesion</i>	0.00 (0.00)	1.00 (0.99, 1.01)	0.678			
Number of new T2-weighted lesions before last visit, <i>per lesion</i>	-0.01 (0.03)	0.99 (0.95, 1.04)	0.745			
Number of new T2-weighted lesions since last visit, <i>per lesion</i>	0.08 (0.04)	1.09 (1.02, 1.16)	0.007	0.08 (0.04)	1.09 (1.02, 1.17)	0.024
Drug at last visit						
No (ref)	–	–	–			
H	0.99 (0.58)	2.70 (0.69, 10.67)	0.156			
L	0.36 (0.51)	1.43 (0.51, 4.02)	0.497			
M	0.49 (0.49)	1.63 (0.67, 3.94)	0.281			

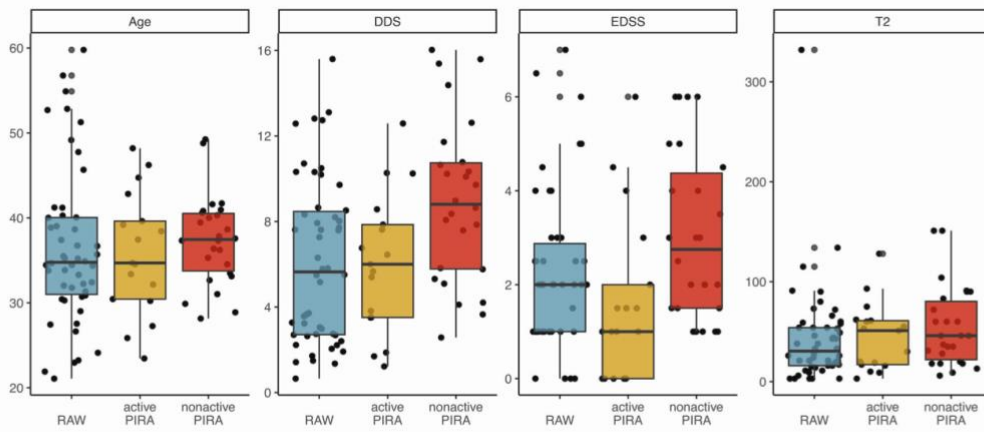
Results from a multivariate Cox proportional-hazards regression models for recurrent events with patient ID as a cluster variable estimating hazard ratios (HRs) and 95% confidence intervals (CIs). We report a full model with all included variables and a reduced model after backward stepwise selection of variables. EDSS = Expanded Disability Status Scale. DDS = Disease Duration since first Symptoms; H= high efficacy therapy; M = Moderate efficacy therapy; L = Low efficacy therapy.

Figure

(A) Individual disease course for 110 patients ordered from bottom to top by their last documented Expanded Disability Status Scale (EDSS) score. The colour of the bar represents the EDSS at the beginning of each episode. Filled dots represent the timepoint of confirmed progression events classified as relapse associated worsening (RAW), active progression independent of relapse activity (PIRA) or nonactive PIRA. (B) Boxplots illustrating the difference in selected characteristics at the beginning of each episode with a confirmed progression event. Horizontal line is median, box edges are interquartile range and whiskers are range.



A



B

