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ORIGINAL ARTICLE

Association between age and inflammatory disease activity on magnetic resonance imaging in relapse onset multiple sclerosis during long-term follow-up

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Abstract

Background and purpose: Inflammatory disease activity in multiple sclerosis (MS) decreases with advancing age. Previous work found a decrease in contrast-enhancing lesions (CELs) with age. Here, we describe the relation of age and magnetic resonance imaging (MRI) measures of inflammatory disease activity during long-term follow-up in a large real-world cohort of people with relapse onset MS.

Methods: We investigated MRI data from the long-term observational Amsterdam MS cohort. We used logistic regression models and negative binomial generalized estimating equations to investigate the associations between age and radiological disease activity after a first clinical event.

Results: We included 1063 participants and 10,651 cranial MRIs. Median follow-up time was 6.1 years (interquartile range = 2.4–10.9 years). Older participants had a significantly lower risk of CELs on baseline MRI (40–50 years vs. <40 years: odds ratio [OR] = 0.640, 95% confidence interval [CI] = 0.45–0.90; >50 years vs. <40 years: OR = 0.601, 95% CI = 0.33–1.08) and a lower risk of new T2 lesions or CELs during follow-up (40–50 years vs. <40 years: OR = 0.563, 95% CI = 0.47–0.67; >50 years vs. <40 years: OR = 0.486, 95% CI = 0.35–0.68).

Conclusions: Greater age is associated with a lower risk of inflammatory MRI activity at baseline and during long-term follow-up. In patients aged >50 years, a less aggressive treatment strategy might be appropriate compared to younger patients.

KEYWORDS
demyelinating disease, MRI, multiple sclerosis

INTRODUCTION

The disease course of multiple sclerosis (MS) is largely age-dependent. Young people with MS experience a more aggressive inflammatory disease course with frequent relapses, which can most prominently be observed in pediatric onset MS [1]. Over time and at greater age, focal inflammation decreases, and the risk of developing a progressive disease course increases [2]. This relation between

age and inflammatory disease activity is also present in contrast-enhancing lesions (CELs) on magnetic resonance imaging (MRI) and clinical relapses, which both decline with advancing age in all clinical subtypes of MS [3–6].

Because the risk of inflammatory disease activity decreases over the duration of the disease, the question arises whether age also changes the risk of the development and severity of subsequent disease activity after a first clinically isolated syndrome (CIS), or after the initial diagnosis of MS. Two previously published studies including CIS patients reported a higher risk of a new clinical relapse in younger people [7, 8]. Such age-related change in inflammation potentially impacts the relative efficacy and thereby risk–benefit ratio of disease-modifying therapies (DMTs) that mainly target the peripheral immune system [9]. Perhaps older patients with a new diagnosis of MS benefit less from (aggressive) treatment simply because the risk of the next focal inflammatory event is lower [10–12]. It is also important to note in this context that the average age in phase 3 relapsing–remitting MS (RRMS) trials is approximately 36 years, substantially lower than the oldest decade in these CIS cohorts.

Most of the previous studies on the association between age and inflammation on MRI had a cross-sectional study design or a limited follow-up time [3], and they were often conducted in clinical trial populations, which are not representative of the real-world patient population due to the limited age range included in these trials [6]. In addition to the cross-sectional association between age and inflammation on MRI, and the risk of a subsequent clinical relapse after an initial diagnosis of CIS or RRMS, it would be of interest to gain more information on the predictive value of age on the development and severity of MRI activity during the disease course in a real-world cohort of people with MS. In this study, we investigated the association of age and the development of new T2 lesions and/or CELs during long-term follow-up in a large real-world cohort of people with relapse onset MS.

METHODS

Data collection

We used data from the ongoing observational Amsterdam MS cohort study, which included patients seen at the MS Center Amsterdam at the Amsterdam University Medical Center (UMC) between 1987 and 2020 who gave written informed consent for participation. This cohort study was approved by the medical ethics committee of the Amsterdam UMC (location VUmc). We included all patients with relapse onset MS with a baseline MRI and at least one available follow-up MRI scan of the brain. Next, we included all available follow-up scans until the last time of follow-up for each participant. We collected data on presence, location, and number of T2 lesions; presence and number of CELs at baseline; and number of new/enlarging T2 lesions and/or CELs during follow-up, all based on the radiological reports. All MRI scans were rated during routine clinical care by neuroradiologists with experience in MS. We defined any new or enlarging T2 lesions during follow-up as an increase in T2 lesions. We defined MRI activity as any new CELs or increase in T2 lesions during follow-up. Data on the date of disease onset, date of diagnosis, age, sex, disease course, disability as measured by the Expanded Disability Status Scale [13], and DMT use were obtained from the patients' electronic health record as recorded by the treating neurologist.

Statistical analysis

We investigated differences between patients with and without CELs at baseline with independent samples *t*-tests. We investigated the association of age and the presence of CELs at baseline (dependent variable) with a binary logistic regression model, including sex and DMT use at baseline as independent variables. For the analyses, we separated DMT use into first-line and second-line DMT. First-line DMT included any of the interferons, glatiramer acetate, teriflunomide, and dimethyl fumarate. Second-line DMT included fingolimod, natalizumab, ocrelizumab, rituximab, siponimod, and cladribine.

We investigated the association of age at baseline scan and new inflammatory disease activity during follow-up with generalized estimated equations (GEEs) with an exchangeable correlation structure, corrected for follow-up duration, sex, and DMT use at the time of the scan. In addition, we did a similar analysis to investigate the association between age at the time of MRI scan and inflammatory disease activity at that specific MRI scan, corrected for sex and DMT use at the time of the scan. We investigated the association of age and number of new T2 lesions with a negative binomial GEE analysis. Statistical significance was taken to be at the two-tailed 0.05 level. The statistical analyses were performed with SPSS Statistics for Windows version 26.0 (IBM) and the R statistical software package for Windows version 4.0.3 [14].

RESULTS

Baseline

Baseline characteristics

We included 1063 participants in the analyses. Mean age at the baseline MRI was 34.9 years (SD = 10.2). Of this cohort, 69.7% were female, and 83.4% did not use DMT at baseline. CELs were present on 48.6% of the 741 baseline scans that used gadolinium contrast (Table 1).

Participants with CELs at baseline were significantly younger than those without CELs (mean age of patients with CELs = 32.8 years [SD = 9.9], mean age of patients without CELs = 35.8 years [SD = 10.1], $p < 0.001$). We found no significant differences in sex and DMT use between participants with and without CELs on baseline MRI (Table 1).

TABLE 1 Baseline characteristics.

Characteristic	All patients, *n* = 1063	CELs, *n* = 360	No CELs, *n* = 381	*p*
Sex, *n* (%) female	741 (69.7)	254 (70.6)	263 (69.0)	0.651
Age at baseline MRI, years, mean (SD)	34.9 (10.2)	32.8 (9.9)	35.8 (10.1)	<0.001*
Age at baseline MRI, *n* (%)				
<40 years	737 (69.3)	257 (74.2)	245 (64.3)	0.015*
40–50 years	235 (22.1)	73 (20.3)	105 (27.6)	
>50 years	91 (8.6)	20 (5.6)	31 (8.1)	
DMT use, *n* (%)				
Yes	171 (16.1)	60 (16.7)	58 (15.2)	0.579
No	887 (83.4)	298 (82.8)	332 (84.5)	
Unknown	*5 (0.5)*	*2 (0.6)*	1 (0.3)	

NOte: Italic values indicates the p-value presented is the value for the difference for all subgroups of one variable.

Abbreviations: CEL, contrast-enhancing lesion; DMT, disease-modifying therapy; MRI, magnetic resonance imaging. *p<0.05

*$p < 0.05$.

TABLE 2 MRI activity during follow-up in different age groups.

	<40 years, *n* = 737	40–50 years, *n* = 253	>50 years, *n* = 73
Follow-up duration, years, median (IQR)	6.41 (31.0–138.0)	5.33 (26.0–112.0)	4.08 (22.5–90.5)
Patients with MRI activity during follow-up, *n* (%)	648 (87.9)	199 (78.7)	47 (64.4)
Patients with CELs during follow-up, *n* (%)	451 (61.2)	119 (47.0)	27 (37.0)
Patients with new T2 lesions during follow-up, *n* (%)	649 (88.0)	195 (77.1)	46 (63.0)
New lesions per follow-up scan, *n* (%)	7261	1960	363
0	4348 (59.5)	1257 (64.1)	210 (57.9)
1	615 (8.5)	162 (8.2)	31 (8.5)
2	298 (4.1)	88 (4.5)	25 (6.9)
3–5	410 (5.6)	74 (3.8)	13 (3.6)
>5	312 (4.3)	40 (2.0)	6 (1.7)
Volume enlarged	74 (1.0)	24 (1.2)	3 (0.8)
Unknown	1204 (16.5)	315 (16.1)	75 (20.7)

Abbreviations: CEL, contrast-enhancing lesion; IQR, interquartile range; MRI, magnetic resonance imaging.

*$p < 0.05$.

Predictors of inflammatory disease activity on MRI

Older age was associated with a lower risk of CELs on baseline MRI (40–50 years vs. <40 years: odds ratio [OR] = 0.640, 95% confidence interval [CI] = 0.45–0.90; >50 years vs. <40 years: OR = 0.601, 95% CI = 0.33–1.08). Sex and DMT use were not significant predictors of the presence of CELs on baseline MRI. Similar results were found when repeating the analysis with only patients without DMT use at baseline included (risk of CELs on baseline MRI = 40–50 years vs. <40 years: OR = 0.621, 95% CI = 0.43–0.91; >50 years vs. <40 years: OR = 0.644, 95% CI = 0.35–1.12).

Follow-up

Follow-up characteristics

The median follow-up duration from baseline to last MRI was 6.1 years (interquartile range = 2.4–10.9 years). During follow-up, 894 of the 1063 included participants (84.1%) had MRI activity; 890 (83.7%) had one or more new T2 lesions, and 597 (56.2%) had one or more CELs during follow-up.

When comparing age groups, the percentage of patients with any MRI activity during follow-up was highest in patients younger

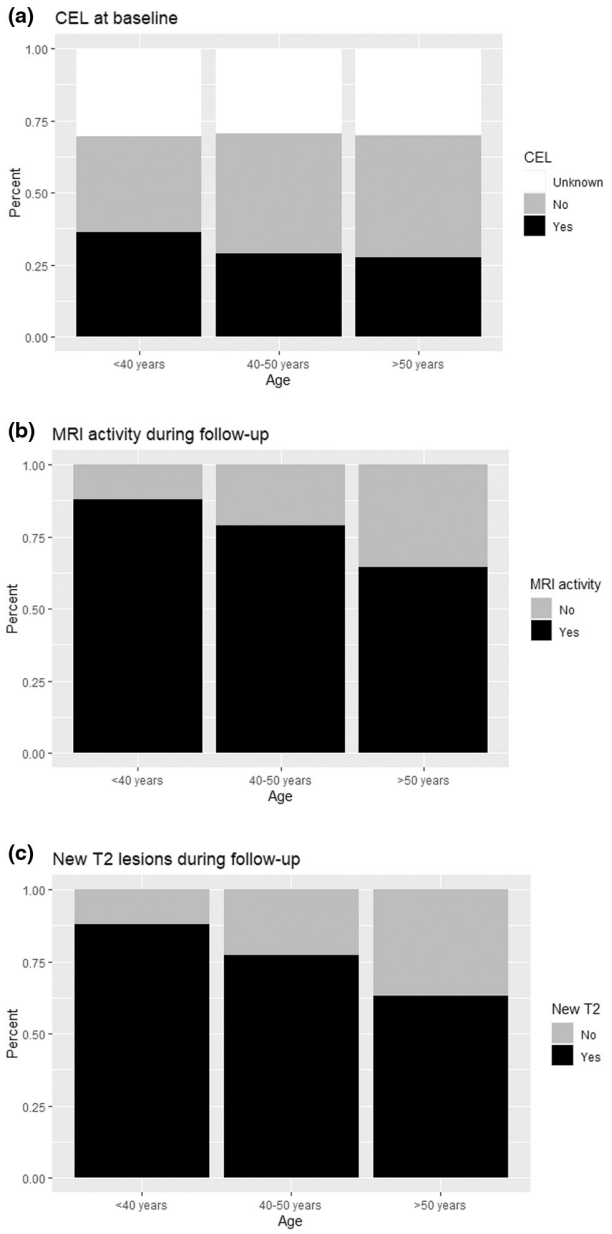

FIGURE 1 Age versus presence of contrast-enhancing lesions (CELs) and new T2 lesions. (a) Age versus presence of contrast-enhancing lesions (CELs) on baseline magnetic resonance imaging (MRI). Scans with no contrast administered or missing results are categorized as "Unknown." (b) Age at baseline versus presence of MRI activity on follow-up MRI. (c) Age at baseline versus presence of new T2 lesions on follow-up MRI.

than 40 years, and decreased in older age groups. For example, 87.9% of patients with a baseline age of <40 years showed any MRI activity during follow-up, whereas 64.4% of patients with a baseline age of >50 years showed any MRI activity during follow-up. The percentage of patients with CELs during follow-up was 61.2% in the patients with a baseline age <40 years, and 37.0% in patients with a baseline age >50 years. The percentage of patients with new T2 lesions similarly decreased in older age groups (Table 2, Figure 1). A similar decrease in MRI activity was seen in subgroup analyses based on type of DMT used (Table S1 and S2).

Predictors of inflammatory disease activity: Baseline age

Greater age at baseline was associated with lower odds of MRI activity during follow-up (40–50 years vs. <40 years: OR = 0.563, 95% CI = 0.47–0.67; >50 years vs. <40 years: OR = 0.486, 95% CI = 0.35–0.68). This association was also present between baseline age and the presence of CELs (40–50 years vs. <40 years: OR = 0.554, 95% CI = 0.43–0.70; >50 years vs. <40 years: OR = 0.639, 95% CI = 0.38–1.09), and for the association between baseline age and the presence of new T2 lesions (40–50 years vs. <40 years: OR = −0.589, 95% CI = 0.49–0.70; >50 years vs. <40 years: OR = 0.496, 95% CI = 0.36–0.69). Greater age at baseline was also associated with a lower total number of new T2 lesions on MRI during follow-up (40–50 years vs. <40 years: rate ratio [RR] = 0.583, 95% CI = 0.51–0.67; >50 years vs. <40 years: RR = 0.433, 95% CI = 0.35–0.54; Table 3). Age was also associated with lower odds of MRI activity during follow-up in subgroup analyses based on DMT type (Table S2).

Predictors of inflammatory disease activity: Age at MRI

In addition to the association between baseline age and MRI activity during follow-up, there was also a significant association between age at the time of the scan and MRI activity on that scan. Greater age at MRI was associated with a lower risk of MRI activity during follow-up (40–50 years vs. <40 years: OR = 0.535, 95% CI = 0.46–0.62; >50 years vs. <40 years: OR = 0.308, 95% CI = 0.26–0.37). Greater age at MRI was also specifically associated with lower odds of CELs during follow-up (40–50 years vs. <40 years: OR = 0.596, 95% CI = 0.49–0.73; >50 years vs. <40 years: OR = 0.359, 95% CI = 0.27–0.48). Regarding new T2 lesions during follow-up, greater age was associated with lower odds of an increase in T2 lesions during follow-up (40–50 years vs. <40 years: OR = 0.540, 95% CI = 0.46–0.63; >50 years vs. <40 years: OR = 0.327, 95% CI = 0.27–0.40), and with a lower total number of new T2 lesions during follow-up (40–50 years vs. <40 years: RR = 0.652, 95% CI = 0.58–0.73; >50 years vs. <40 years: RR = 0.436, 95% CI = 0.37–0.52). As expected, DMT use at the time of the MRI scan was associated with lower odds of MRI activity during follow-up (first-line DMT vs. no DMT: OR = 0.818, 95% CI = 0.72–0.94; second-line DMT vs. no DMT: OR = 0.142, 95% CI = 0.12–0.17; Table 4).

DISCUSSION

Our investigation shows that greater age at baseline is strongly associated with a lower risk of CELs on baseline MRI, and a lower risk of radiological inflammatory disease activity during long-term follow-up. In addition, we found that if inflammatory disease activity is present during follow-up, the number of lesions is lower in older patients.

TABLE 3 Age at baseline versus MRI activity during follow-up.

	Any MRI activity		Presence of CELs	
Characteristic	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Sex				
Male	1.0 (reference)	0.029*	1.0 (reference)	0.057
Female	0.825 (0.69–0.98)		0.812 (0.66–1.01)	
Age at baseline				
<40 years	1.0 (reference)		1.0 (reference)	
40–50 years	0.563 (0.47–0.67)	<0.001*	0.554 (0.43–0.70)	<0.001*
>50 years	0.486 (0.35–0.68)	<0.001*	0.639 (0.38–1.09)	0.098
DMT use				
No DMT	1.0 (reference)		1.0 (reference)	
First-line DMT	0.887 (0.77–1.03)	0.112	0.686 (0.57–0.82)	<0.001*
Second-line DMT	0.173 (0.14–0.21)	<0.001*	0.259 (0.20–0.34)	<0.001*
Other DMT	0.872 (0.39–1.97)	0.741	1.916 (0.88–4.17)	0.101
	Presence of new T2 lesions		**Number of new T2 lesions**	
	OR (95% CI)	***p***	**RR (95% CI)**	***p***
Sex				
Male	1.0 (reference)	0.088	1.0 (reference)	0.217
Female	0.867 (0.74–1.02)		0.923 (0.81–1.05)	
Age at baseline				
<40 years	1.0 (reference)		1.0 (reference)	
40–50 years	0.589 (0.49–0.70)	<0.001*	0.583 (0.51–0.67)	<0.001*
>50 years	0.496 (0.36–0.69)	<0.001*	0.433 (0.35–0.54)	<0.001*
DMT use				
No DMT	1.0 (reference)		1.0 (reference)	
First-line DMT	0.907 (0.78–1.06)	0.214	0.937 (0.85–1.04)	0.209
Second-line DMT	0.151 (0.12–0.18)	<0.001*	0.250 (0.21–0.30)	<0.001*
Other DMT	0.772 (0.33–1.82)	0.553	0.687 (0.39–1.23)	0.204

Abbreviations: CEL, contrast-enhancing lesion; CI, confidence interval; DMT, disease-modifying therapy; MRI, magnetic resonance imaging; OR, odds ratio; RR, rate ratio.

*$p < 0.05$.

Several previous studies have reported on the association between age and presence of clinical and radiological inflammatory disease activity [3–6, 15]. In a British Colombia cohort study of 2477 RRMS patients, there was a decrease of relapses with greater age and over time [4]. Another observational study included 200 RRMS and secondary progressive MS patients, and found a lower risk of CELs on MRI with greater age [5]. A cohort study including 1543 people with all MS subtypes also found an association between age and the presence of CELs in a cross-sectional setting [3].

Our study confirms these cross-sectional associations between age and presence of CELs on MRI. In addition, we show that age at baseline is predictive of the presence and severity of MRI activity during follow-up. In accordance with this, a previous study conducted in 330 patients with a first demyelinating event found that younger age was associated with an increased risk of having a second demyelinating event within 1 year of follow-up (hazard ratio for each 10-year decrease in age = 1.51, 95% CI = 1.28–1.80, $p < 0.0001$) [7]. Another study including 1058 CIS patients reported a higher risk of a subsequent clinical relapse in younger patients compared to the oldest included patient group (40–49 years) [8].

The finding that age is strongly associated with inflammatory disease activity may have important consequences for clinical practice. Currently, age is often not taken into account when monitoring people with MS [16]. However, as MRI activity decreases with age, it could be argued that age of the patient should be seen as an important factor in deciding how often MRI monitoring should take place. As we see the lowest percentage of MRI activity in patients aged >50 years, perhaps a monitoring strategy with less frequent MRI scans is appropriate for this population compared to younger patients.

Another aspect in which age should be considered an important factor is when making treatment decisions [17]. Treatment

TABLE 4 Age at MRI versus MRI activity on that specific scan during follow-up.

	Any MRI activity		Presence of CELs	
Characteristic	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Sex				
Male	1.0 (reference)	0.011*	1.0 (reference)	0.036*
Female	0.817 (0.70–0.96)		0.799 (0.65–0.99)	
Age at MRI				
<40 years	1.0 (reference)		1.0 (reference)	
40–50 years	0.535 (0.46–0.62)	<0.001*	0.596 (0.49–0.73)	<0.001*
>50 years	0.308 (0.26–0.37)	<0.001*	0.359 (0.27–0.48)	<0.001*
DMT use				
No DMT	1.0 (reference)		1.0 (reference)	
First-line DMT	0.818 (0.72–0.94)	0.003*	0.611 (0.52–0.72)	<0.001*
Second-line DMT	0.142 (0.12–0.17)	<0.001*	0.140 (0.10–0.20)	<0.001*
Other DMT	0.636 (0.30–1.36)	0.241	0.823 (0.41–1.66)	0.586
	Presence of new T2 lesions		**Number of new T2 lesions**	
	OR (95% CI)	***p***	**RR (95% CI)**	***p***
Sex				
Male	1.0 (reference)	0.085	1.0 (reference)	0.216
Female	0.872 (0.75–1.02)		0.924 (0.82–1.05)	
Age at MRI				
<40 years	1.0 (reference)		1.0 (reference)	
40–50 years	0.540 (0.46–0.63)	<0.001*	0.652 (0.58–0.73)	<0.001*
>50 years	0.327 (0.27–0.40)	<0.001*	0.436 (0.37–0.52)	<0.001*
DMT use				
No DMT	1.0 (reference)		1.0 (reference)	
First-line DMT	0.857 (0.74–0.99)	0.036*	0.931 (0.84–1.03)	0.168
Second-line DMT	0.130 (0.11–0.16)	<0.001*	0.250 (0.21–0.30)	<0.001*
Other DMT	0.607 (0.29–1.29)	0.194	0.689 (0.40–1.20)	0.188

Abbreviations: CEL, contrast-enhancing lesion; CI, confidence interval; DMT, disease-modifying therapy; MRI, magnetic resonance imaging; OR, odds ratio; RR, rate ratio.

*$p < 0.05$.

with DMTs is mostly aimed at preventing or minimizing focal inflammatory disease activity and is often started early after the patient is diagnosed with MS [18–21]. When choosing the most appropriate treatment for an individual patient, age at the time of diagnosis is not always considered as an important decision factor. However, because most clinical trials in MS only include patients aged between 18 and 55 years, it is unclear whether older patients equally benefit from the investigated DMT. We recently showed that the association between age and presence of CELs is present across the spectrum of MS disease courses in four large randomized controlled trial datasets [6]. Moreover, post hoc analyses of previously published trial data suggest that treatment efficacy is highest in younger patients [22, 23]. A meta-analysis of 38 clinical trials estimated no predicted benefit of DMT treatment for the prevention of disability worsening in average MS patients after the age of 53 years [10].

Another factor that should be considered in starting treatment in older patients is the increased risk of side effects in greater age. Due to immunosenescence, the risk of infections as a side effect of DMT might increase. In addition, older patients have increased age-related comorbidities, such as vascular and metabolic comorbidities, which might also contribute to a higher risk of side effects of DMT [9]. These changes result in a different risk–benefit ratio in older patients compared to younger patients, and should be considered when making treatment decisions in older MS patients.

A limitation of the real-world setting of our study might be that the treatment landscape has evolved in the past decades. We found a strong association between the use of DMT and the occurrence of inflammatory disease activity, with extremely low odds for inflammatory disease activity in patients using high-efficacy DMT. As our study followed patients for a long period of time, the change in treatment landscape might influence our

results. However, we corrected all of our analyses for DMT use, which should have minimized the influence of this confounding factor. Another limitation was the relatively low number of included patients older than 50 years at baseline. Furthermore, we did not correct for number of MRI scans done per patient, which could influence the probability of detecting MRI activity. It could also be that the older patient groups had a shorter follow-up duration than the youngest group, but we did correct for follow-up duration in our analyses. In addition, we did not have any relapse data available, or data on treatment with steroids in the case of any relapses, which could be a possible confounder in the analyses regarding CELs. Lastly, it is important to note that we did not have any data on disability progression. It is known that older patients are more prone to disability progression, which is likely not due to focal inflammatory disease activity, but it is not entirely clear what the effect of the different DMTs is on disability progression.

In conclusion, this study confirms age as a strong predictor of the occurrence and severity of radiological disease activity during long-term follow-up. Age should be used as a factor in clinical decision-making regarding the initiation and (dis)continuation of DMT, as the risk–benefit ratio of DMTs changes as patients age. As our study shows the lowest risk and severity of MRI activity in patients >50 years old, this patient group may be well managed with a less aggressive treatment strategy.

AUTHOR CONTRIBUTIONS

Eline Coerver: Conceptualization; Methodology; Investigation; Data curation; Writing – original draft. **Sophie Janssens:** Data curation; Investigation; Writing – review & editing. **Aroosa Ahmed:** Data curation; Investigation; Writing – review & editing. **Mark Wessels:** Data curation; Writing – review & editing. **ZoZoé Van Kempen:** Writing – review & editing. **Bas Jasperse:** Writing – review & editing; Data curation. **Frederik Barkhof:** Data curation; Writing – review & editing. **Marcus Koch:** Writing – review & editing. **Jop Mostert:** Writing – review & editing. **Bernard Uitdehaag:** Writing – review & editing. **Joep Killestein:** Writing – review & editing; Conceptualization; Supervision. **Eva Strijbis:** Conceptualization; Methodology; Writing – review & editing; Supervision.

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CONFLICT OF INTEREST STATEMENT

F.B. serves on the steering committee and is an independent data monitoring committee member for Biogen, Merck, Roche, and Eisai. He acts as a consultant for Roche, Biogen, Merck, IXICO, Jansen, and Combinostics. He has research agreements with Novartis, Merck, Biogen, GE, and Roche. He is cofounder and share-holder of Queen Square Analytics. M.W.K. has received consulting fees and travel support from Biogen Idec, Novartis, Roche, Sanofi Genzyme, and EMD Serono. B.M.J.U. reports research support and/or consultancy fees from Biogen Idec, Genzyme, Merck Serono, Novartis, Roche, Teva, and Immunic Therapeutics. J.K. reports grants from Biogen, Novartis, Teva, Bayer Schering Pharma, Glaxo Smith Kline, Merck, Genzyme, and Roche. The remaining authors have no disclosures.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. Anonymized data not published within this article will be made available by request from any qualified investigator.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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