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ORIGINAL COMMUNICATION

Kappa free light chain index as a diagnostic and prognostic biomarker in multiple sclerosis

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Abstract

Background The proposed 2024 McDonald criteria incorporate the kappa free light chain (KFLC) index as an additional biomarker in multiple sclerosis (MS) diagnosis. Emerging evidence suggests that a high KFLC index may relate to worse outcomes in people with MS (pwMS). This study had two main objectives: to evaluate the diagnostic performance of the KFLC index against the 2017 and proposed 2024 clinico-radiological McDonald criteria, and to explore its prognostic significance.

Methods We performed a retrospective cohort study of adults with a first episode suggestive of MS (2019–2024). All underwent lumbar puncture with simultaneous determination of the KFLC index and oligoclonal bands (OCB).

Results Among 150 participants, OCB showed sensitivities of 85.9% (2017) and 86.6% (2024) with specificities of 79.7% and 81.9%. A KFLC index cut-off of 12.0 yielded sensitivities of 87.5% (2017) and 88.1% (2024) with specificities of 79.2% and 81.4%, comparable to OCB. In pwMS, KFLC index ≥ 100 was associated with younger age (OR 1.53, p = 0.048), women (OR 1.53, p = 0.037), relapses (OR 2.30, p = 0.029) and new infratentorial or spinal cord (SC) lesions (OR 6.90, p = 0.003). In multivariable analysis, KFLC index ≥ 100 remained associated with new infratentorial or SC lesions (aOR 8.07, p = 0.019).

Conclusion The KFLC index shows diagnostic utility comparable to OCB; however, it is an adjunctive biomarker that complements clinical and MRI findings and should not be used as a standalone diagnostic test. An elevated KFLC index was associated with short-term accrual of infratentorial or SC lesions; these exploratory findings require validation in larger, longer-term cohorts.

Keywords Diagnosis · Kappa free light chain · Multiple sclerosis · Oligoclonal bands · Prognosis

Abbreviations

ADEM	Acute disseminated encephalomyelitis
AUC	Area under the curve
CDW	Confirmed disability worsening
CI	Confidence interval
CIS	Clinically isolated syndrome
CNS	Central nervous system
CRION	Chronic relapsing inflammatory optic neuropathy
CSF	Cerebrospinal fluid
DIT	Dissemination in time
DMT	Disease modifying therapy
Dx	Diagnosis
EDSS	Expanded Disability Status Scale
HE	High-efficacy
Ig	Immunoglobulin
IQR	Interquartile range
KFLC	Kappa free light chain
K-W	Kruskal–Wallis test
LP	Lumbar puncture
MRI	Magnetic resonance imaging
MOGAD	MOG antibody-associated disease
MS	Multiple sclerosis
M-W	Mann–Whitney U test
NMOSD	Neuromyelitis optica spectrum disorder
NPV	Negative predictive value
OCB	Oligoclonal bands
OR	Odds ratio
PIRA	Progression independent of relapse activity

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PPV	Positive predictive value
pwMS	People with multiple sclerosis
ROC	Receiver operating characteristic
SC	Spinal cord
SD	Standard deviation
sNfL	Serum neurofilament light chain

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, and neurodegenerative disease of the central nervous system (CNS) and the leading non-traumatic cause of neurological disability in young adults [1]. In MS, activated B-cells infiltrate the CNS, differentiate into plasma cells, and secrete immunoglobulins (Ig). In clinical practice, intrathecal Ig synthesis is traditionally assessed by detecting cerebrospinal fluid (CSF)-restricted IgG oligoclonal bands (OCB). The 2017 revision of the McDonald criteria recognised the presence of OCB as evidence of dissemination in time (DIT), especially in patients with clinically isolated syndrome (CIS) [2]. Its incorporation into the 2017 McDonald criteria improved diagnostic sensitivity, enabling earlier diagnosis, and potentially influencing long-term outcomes [3].

At the 2024 ECTRIMS meeting, the International Panel on MS Diagnosis proposed revisions to the McDonald criteria that include recognising a positive kappa free light chain (KFLC) index, alongside OCB, as evidence of intrathecal Ig synthesis [4]. The KFLC index achieves high diagnostic sensitivity and specificity comparable to OCB in MS [5], while presenting notable advantages: KFLC measurement is less technically demanding, highly reproducible due to its automated nature, and more cost-effective than traditional OCB detection methods [6, 7]. These attributes make KFLC index a compelling alternative, particularly in resource-constrained settings or when rapid diagnostic results are required [8, 9]. However, a major challenge to the implementation of the KFLC index in clinical practice has been the lack of a clear cut-off. Most of the reported KFLC index cut-offs ranged from 3 to 12, with an increased cut-off when patients with other inflammatory neurological disorders were used as controls [10]. A recent meta-analysis suggested an optimal cut-off of 6.1 for KFLC index to discriminate CIS/MS patients from control subjects [11].

Beyond diagnostic utility, the KFLC index is gaining attention as potential prognostic biomarker in MS. Elevated KFLC index values have been associated with higher relapse risk [12], progression independent of relapse activity (PIRA) [13], and a higher likelihood of treatment escalation [14]. Because data on the prognostic value of the KFLC index remain limited, further studies are needed.

Therefore, this study had two main objectives. First, to compare the diagnostic performance of the KFLC index with that of OCB according to both the 2017 and the proposed 2024 McDonald criteria, using only clinical and radiological evidence to minimise incorporation bias. Second, to investigate the prognostic value of the KFLC index, as an exploratory objective focused on early disease activity, by assessing its association with clinical and radiological worsening —including clinical relapses, Expanded Disability Status Scale (EDSS) progression, magnetic resonance imaging (MRI) activity and lesion topography, and treatment escalation— and by examining its association with known baseline predictors of poor prognosis in MS [15], such as ethnicity, baseline EDSS, MRI lesion burden, and serum neurofilament light chain (sNfL) levels.

Materials and methods

Setting

This retrospective cohort study was conducted at Dr. Balmis General University Hospital (HGUDB), a tertiary centre serving the Alicante Health Area in southeastern Spain. We reviewed all adults (≥ 18 years) who presented to the Neurology Department between January 1, 2019, and December 31, 2024, with a first clinical episode suggestive of MS, defined as a monophasic clinical event characterized by patient-reported symptoms and objective findings consistent with a focal or multifocal inflammatory demyelinating process in the CNS (developing acutely or subacutely, lasting ≥ 24 h, and occurring in the absence of fever or infection, with or without recovery) [2]. Our aim was to evaluate the diagnostic and prognostic utility of the KFLC index measured at the time of the initial work-up.

Subjects were included if they met all the following additional criteria:

- Lumbar puncture (LP) performed within six months of referral and before initiation of corticosteroids or disease-modifying therapies (DMTs).
- Simultaneous determination of the KFLC index and OCB.
- Baseline brain MRI showing at least one demyelinating lesion.
- Minimum follow-up of one year after LP.

Sample size

To estimate the minimum cohort needed to assess the diagnostic performance of the KFLC index, we assumed that approximately half of the patients undergoing LP would ultimately receive a diagnosis of MS and that

the KFLC index would have a sensitivity of about 85%. Using Epidat v4.2, with a 95% confidence level and an absolute precision of 10%, we calculated that at least 98 participants (49 with MS and 49 with non-MS) would be required. In practice, we included all eligible patients who met the study criteria, resulting in a final sample of 150 individuals.

Case ascertainment and data collection

The Immunology Department at HGUDB maintains a prospective registry of all paired serum and CSF samples analysed for KFLC index and OCB since January 2019. Electronic medical records linked to these samples were reviewed to identify individuals meeting the inclusion criteria.

Two neurologists (LREM and APS) reviewed each subject's clinical presentation and MRI scans and, without knowledge of CSF biomarker results, applied both the 2017 and the proposed 2024 clinico-radiological McDonald criteria to classify cases as MS or non-MS. This approach avoided incorporation bias because the KFLC index is only recognised in the proposed 2024 criteria, whereas OCB is included in both. For prognostic analyses, we used the full 2017 McDonald criteria, which remain the diagnostic standard.

From each eligible patient´s medical record, the following data were extracted: demographic and clinical characteristics, CSF and laboratory results, MRI findings, EDSS, DMTs and treatment changes due to lack of efficacy or side effects. EDSS assessments were performed by trained and certified examiners (www.neurostatus.net). EDSS progression (confirmed disability worsening, CDW) was defined using baseline-dependent thresholds and subsequent confirmation at 6 months: an EDSS increase of ≥ 1.5 points when baseline EDSS = 0; ≥ 1.0 point when baseline EDSS = 1.0–5.5; or ≥ 0.5 points when baseline EDSS > 5.5 [16]. Routine follow-up visits were scheduled every six months, with brain MRI performed annually and spinal cord MRI biennially on 3-T scanners.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee for Medical Research of the Health Department of Alicante General Hospital, Spain (PI2024-014).

Serum and CSF testing

Albumin concentrations in serum and CSF were measured on a BN II analyser (Siemens Healthineers) using N Antiserum to Human Albumin kits. All measurements were performed according to the manufacturer's instructions. OCB were analysed in paired serum and CSF samples through isoelectric focusing, followed by immunofixation. This process was carried out using the Hydragel 3 CSF isofocusing kit on the Hydrasys 2 scan focusing analyser (SEBIA), following the manufacturer's guidelines. OCB were considered positive when at least two distinct IgG bands were present in the CSF but absent in the paired serum sample.

KFLC concentrations in serum and CSF were quantified using an immunonephelometric assay (Freelite Mx, Optilite analyser, The Binding Site). To assess their intrathecal synthesis, the KFLC index was calculated using the formula: (CSF KFLC/serum KFLC)/(CSF albumin/serum albumin). Samples with KFLC concentrations below the lower limit of detection (0.30 mg/L) were assigned that value for analysis.

Statistical analysis

Data were analysed using SPSS version 27.0 (Chicago, USA). Frequency and association measures were applied according to the type and distribution of the variables.

Descriptive statistics for continuous variables, except for age, were presented as median (Me) and interquartile range (IQR). Age was reported as the mean ($\bar{x}$) with standard deviation (SD). Categorical variables were reported as frequency (n) or percentage (%). The Shapiro–Wilk test and the Kolmogorov–Smirnov test were used to assess the normality of the distribution for continuous variables.

Continuous variables —including the KFLC index, age, EDSS, and sNfL— were analysed both as continuous measures and after conversion to dichotomised categorical variables. For the KFLC index, the cut-off was determined using the optimal threshold identified by the Youden index from our receiver operating characteristic (ROC) curves, which maximizes the combined sensitivity and specificity. To address the potential influence of age, age-stratified analyses were performed using 50 years as the cut-off, consistent with definitions of late-onset MS [17]. By contrast, the number of T2 lesions was exclusively expressed as a dichotomised categorical variable, classified as either ≤ 9 or > 9 lesions.

To evaluate diagnostic performance, sensitivity was calculated as the ratio of true positives (TP) to the sum of TP and false negatives (FN), expressed as "$[TP/(TP + FN)] \times 100$". Specificity was calculated as the ratio of true negatives (TN) to the sum of TN and false positives (FP), using the formula "$[TN/(TN + FP)] \times 100$". Positive predictive value (PPV) was calculated as "$[TP/(TP + FP)] \times 100$", while negative predictive value (NPV) was computed using the formula "$[TN/(TN + FN)] \times 100$".

The 95% confidence intervals (CIs) were calculated for sensitivity, specificity, area under the curve (AUC) of ROC

curve, PPV, and NPV for each diagnostic variable studied (KFLC index and OCB). To assess agreement between the KFLC index and OCB for MS diagnosis, Cohen's kappa coefficient was calculated.

To assess the prognostic value of the KFLC index in people with MS (pwMS), Spearman's ρ coefficient was used to evaluate its correlation with independent continuous variables, including age, EDSS, and sNfL. For independent categorical variables —such as sex, ethnicity, clinical presentation, > 9 T2 lesions, enhancing lesions, infratentorial lesions, spinal cord (SC) lesions, corticosteroids for relapses, initiation of high-efficacy disease-modifying therapy (HE-DMT), DMT switch, new clinical relapses, new MRI lesions, and new infratentorial or SC lesions— the KFLC index was analysed as the dependent variable using the Mann–Whitney U test or the Kruskal–Wallis test, as appropriate. HE-DMT was defined as treatment with monoclonal antibodies, including alemtuzumab, natalizumab, ocrelizumab, ofatumumab, rituximab, and ublituximab [18].

A dichotomised KFLC index with a cut-off of 100 — based on previously reported thresholds in the literature [12, 13]— was also examined for its association with the categorical variables listed above using the Chi-square test. For this analysis, odds ratio (OR) and its 95% CIs were calculated. Variables with $p < 0.05$ in bivariate analyses (Spearman's ρ, Mann–Whitney U, Kruskal–Wallis, or Chi-square, as appropriate) were considered for multivariable logistic regression, including adjusted OR (95% CI). In all the analyses, $p < 0.05$ was considered statistically significant.

Results

Out of 454 paired serum/CSF samples tested for the KFLC index and OCB, 150 patients met all inclusion criteria for analysis (Fig. 1). Reasons for exclusion were: evaluation outside the Neurology Department ($n = 183$), absence of a first demyelinating event ($n = 19$), delayed LP ($n = 35$), insufficient CSF volume ($n = 32$), MRI lacking demyelinating lesions ($n = 12$) and follow-up < 1 year ($n = 23$).

The mean age was 43 years, 50% were women, and 90% were of Caucasian ethnicity. On clinico-radiological assessment (i.e. ignoring CSF biomarkers), 64 patients met the 2017 McDonald criteria and 67 met the proposed

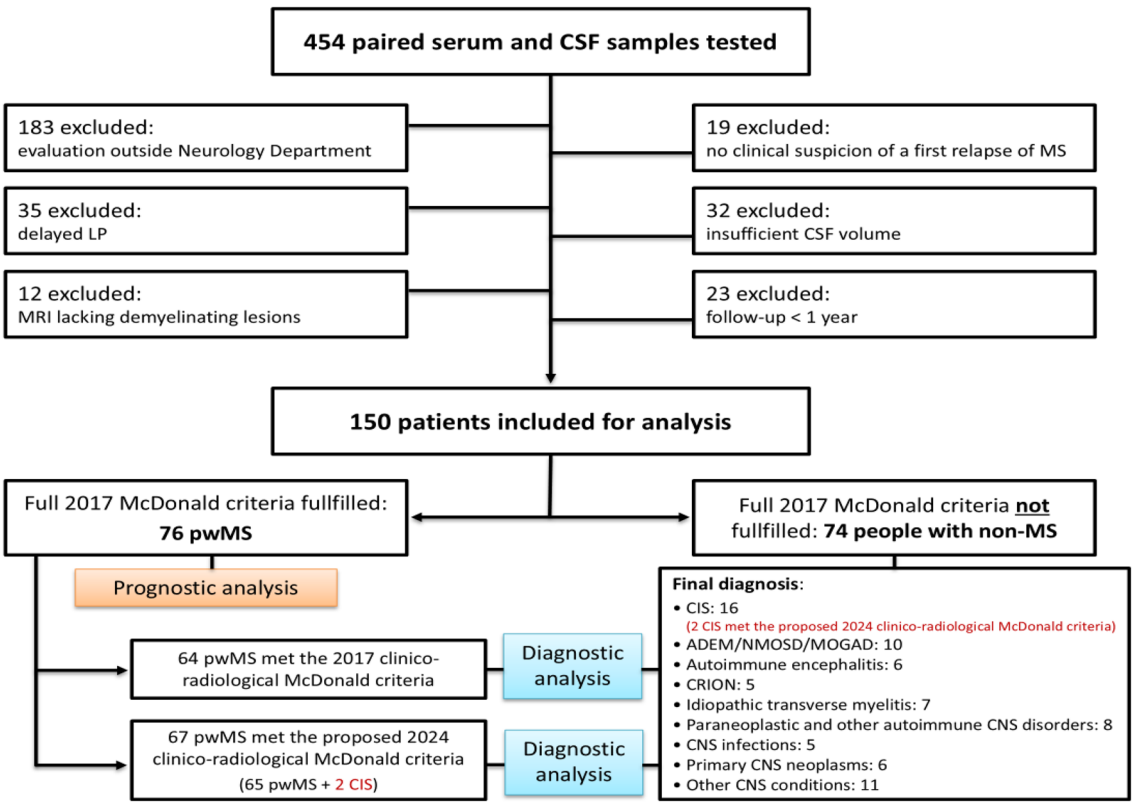

Fig. 1 Flowchart of participants. ADEM, acute disseminated encephalomyelitis; CIS, clinically isolated syndrome; CNS, central nervous system; CRION, chronic relapsing inflammatory optic neuropathy; CSF, cerebrospinal fluid; LP, lumbar puncture; MOGAD, MOG antibody-associated disease; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; pwMS, people with multiple sclerosis

2024 McDonald criteria. Seventy-six individuals satisfied the full 2017 McDonald criteria and were classified as pwMS. The remaining 74 participants who did not meet the full 2017 McDonald criteria (people with non-MS) were diagnosed with other disorders including: acute disseminated encephalomyelitis, neuromyelitis optica spectrum disorder, or MOG antibody-associated disease (ADEM/NMOSD/MOGAD) ($n = 10$); autoimmune encephalitis ($n = 6$); CIS ($n = 16$); CNS infections ($n = 5$); chronic relapsing inflammatory optic neuropathy (CRION) ($n = 5$); primary CNS neoplasms (gliomas or lymphomas) ($n = 6$); idiopathic transverse myelitis ($n = 7$); paraneoplastic and other autoimmune CNS disorders ($n = 8$); and other miscellaneous CNS conditions ($n = 11$). Detailed demographic characteristics and statistically significant differences between pwMS and people with non-MS are presented in Tables 1, 2, 3.

ROC analysis demonstrated that the KFLC index had good diagnostic accuracy under both the 2017 and the proposed 2024 clinico-radiological McDonald criteria (Figs. 2, 3), a result that was also observed in the age-stratified analyses (Table 4). Using the Youden index, the optimal cut-off was 12.0 for the overall cohort analysis. At this threshold, sensitivities and specificities were as follows (the 2017 vs the proposed 2024 clinico-radiological McDonald criteria):

- OCB: sensitivity 85.9% and 86.6%, specificity 79.7% and 81.9%.
- KFLC index 12.0: sensitivity 87.5% and 88.1%, specificity 79.2% and 81.4%.

Among people with non-MS ($n = 74$), 15 (20.3%) had a KFLC index ≥ 12.0 (diagnostic cut-off). By final diagnosis: CIS 9/16; ADEM/NMOSD/MOGAD 2/10 (ADEM 1, NMOSD 1); autoimmune encephalitis 1/6; idiopathic transverse myelitis 1/7; CNS infection 1/5; other miscellaneous CNS conditions 1/11 (Creutzfeldt-Jakob disease); CRION 0/5; paraneoplastic/other autoimmune CNS disorders 0/8; primary CNS neoplasms 0/6.

Combining KFLC index 12.0 with OCB increased sensitivity to 95.3% (2017 clinico-radiological McDonald criteria) and 95.5% (proposed 2024 clinico-radiological McDonald criteria), whereas a sequential strategy (KFLC index first, OCB second if KFLC index was negative) modestly decreased sensitivity but improved specificity (Table 5). Concordance analysis showed a good agreement between OCB and KFLC index 12.0 (Cohen's kappa ≈ 0.74) (Table 6).

Among the 76 participants who met the full 2017 McDonald criteria for MS, the KFLC index correlated inversely with age (Spearman's $\rho = -0.26$, $p = 0.013$) and was higher in women than in men ($p = 0.002$) (Table 7). Patients who developed new infratentorial or spinal cord lesions during follow-up had higher baseline KFLC index values ($p = 0.005$; Fig. 4). No significant associations were observed between the KFLC index and other variables such as ethnicity, clinical presentation, baseline EDSS, CDW, or initiation of HE-DMT.

When the KFLC index was dichotomised at 100 (Table 8), a KFLC index ≥ 100 was more common in patients younger than 40 years (OR = 1.53, $p = 0.048$), in women (OR = 1.53, $p = 0.037$), in those who experienced new clinical relapses (OR = 2.30, $p = 0.029$), and in those who developed new infratentorial or spinal cord lesions (OR = 6.90, $p = 0.003$). In multivariable logistic regression, only the association with new infratentorial or spinal cord lesions remained significant (adjusted OR = 8.07, $p = 0.019$) (Table 9).

Discussion

Our results confirm that the KFLC index is a robust diagnostic biomarker for MS. Using a cut-off of 12.0, the diagnostic accuracy of the KFLC index was comparable to that obtained with OCB under both the 2017 and the proposed 2024 clinico-radiological McDonald criteria. Combining the KFLC index with OCB increased sensitivity beyond 95%, replicating the synergistic effect reported in other cohorts [19–21]. Most of the reported KFLC index cut-offs ranged from 3 to 12 [10, 19–24]. This variability likely reflects differences in assay platforms, diagnostic frameworks, and control populations; values tend to be higher when the control group includes inflammatory neurological disorders [10]. Our optimal cut-off lies at the upper end of this range and reflects the composition of our cohort.

Most previous studies have assessed the diagnostic performance of the KFLC index within the full McDonald criteria, which already incorporate OCB and are therefore prone to incorporation bias. To address this, we evaluated the KFLC index against clinico-radiological McDonald criteria that exclude CSF biomarkers to classify patients as MS or non-MS. This approach allowed an independent assessment and confirmed that the KFLC index maintains high diagnostic accuracy even when CSF biomarkers are not part of the initial case definition. The high diagnostic performance of the KFLC index was also observed in the age-stratified analyses (≥ 50 years). These results support the adjunctive use of the KFLC index alongside clinical and MRI assessment in patients with late-onset MS. However, these data should be interpreted with caution due to the small sample size of this subgroup. To our knowledge, this is the first study to apply the proposed 2024 McDonald criteria, which formally recognise the KFLC index as a diagnostic biomarker, while simultaneously controlling for

Table 1 Baseline characteristics of sample using the 2017 clinico-radiological McDonald criteria

Variables//Diagnosis	pwMS ($n=64$)	people with non-MS ($n=74$)	p value*
Time to Dx, months, Me (IQR)			
From first symptom to MRI	1 (0–3)	1 (0–2)	0.532
From first symptom to LP	2 (0–5)	1 (0–4)	0.566
Age, years, $\bar{x} \pm SD$	39.4 ± 12.1	47.7 ± 15.6	**0.001**
Women, n (%)	33 (51.6)	40 (54.1)	0.770
Ethnicity, n (%)			0.774
Caucasian	57 (89.1)	67 (90.5)	
non-Caucasian	7 (10.9)	7 (9.5)	
Clinical presentation, n (%)			**0.002**
Unilateral optic neuritis	6 (9.4)	9 (12.2)	
Bilateral optic neuritis	1 (1.6)	7 (9.5)	
Focal supratentorial syndrome	7 (10.9)	17 (23.0)	
Brainstem syndrome	17 (26.6)	7 (9.5)	
Cerebellar syndrome	4 (6.3)	6 (8.1)	
Partial myelopathy	26 (40.6)	15 (20.3)	
Complete myelopathy	1 (1.6)	7 (9.5)	
EDSS at baseline, Me (IQR)	1.0 (0–3.0)	-	-
MRI at baseline, n (%)			
1–9 T2 lesions	33 (51.6)	59 (79.7)	
>9 T2 lesions	31 (48.4)	13 (17.6)	**<0.001**
Enhancing lesions	36 (56.3)	25 (33.8)	**<0.001**
Infratentorial lesions	43 (67.2)	19 (25.7)	**<0.001**
Spinal cord (SC) lesions	44 (68.8)	20 (27.0)	**<0.001**
CSF at baseline			
OCB, n (%)	55 (85.9)	15 (20.3)	**<0.001**
CSF KFLC, mg/L, Me (IQR)	4.44 (2.1–8.6)	0.35 (0.3–1.8)	**<0.001**
KFLC index, Me (IQR)	70.3 (25.3–163.7)	5.2 (2.8–10.4)	**<0.001**
sNfL at baseline, pg/mL, Me (IQR)	12 (10–18)	-	-
Therapy			
Corticosteroids for relapses, n (%)	27 (42.2)	22 (29.7)	0.557
Time to DMT initiation, months, Me (IQR)	6 (4–17)	-	-
Initiation of HE-DMT, n (%)	35 (54.7)	-	-
DMT switch, n (%)	10 (15.9)	-	-
Follow-up duration, months, Me (IQR)	41 (31–53)	34 (18–47)	**0.016**
Outcomes, n (%)			
New clinical relapses	20 (31.2)	6 (8.1)	**<0.001**
New MRI lesions	30 (46.9)	7 (9.5)	**<0.001**
New infratentorial or SC lesions	11 (17.1)	3 (4.1)	**0.037**
Deaths	0 (0)	8 (10.8)	**0.015**

CSF, cerebrospinal fluid; DMT, disease modifying therapy; Dx, diagnosis; EDSS, Expanded Disability Status Scale; HE, high-efficacy; IQR, interquartile range; KFLC, kappa free light chain; LP, lumbar puncture; Me, median; mg/L, milligrams per litre; MS, multiple sclerosis; MRI, magnetic resonance imaging; n, number; OCB, oligoclonal bands; pg/mL, picograms per millilitre; pwMS, people with multiple sclerosis; SC, spinal cord; SD, standard deviation; sNfL, serum neurofilament light chain; $\bar{x}$, mean

*Significant p values are indicated in bold and underlined

incorporation bias. Our findings therefore provide timely evidence for the inclusion of the KFLC index in routine diagnostic practice.

Beyond diagnosis, we observed that an elevated KFLC index (≥ 100) was associated with the development of new infratentorial or spinal cord lesions in patients who fulfilled the full 2017 McDonald criteria. We selected this threshold

Table 2 Baseline characteristics of sample using the proposed 2024 clinico-radiological McDonald criteria

Variables//Diagnosis	pwMS ($n=67$)	people with non-MS ($n=72$)	p value*
Time to Dx, months, Me (IQR)			
From first symptom to MRI	1 (0–3)	1 (0–2)	0.506
From first symptom to LP	2 (0–5)	1 (0–4)	0.542
Age, years, $\bar{x} \pm SD$	39.4 ± 11.9	48.0 ± 15.6	**0.001**
Women, n (%)	36 (53.7)	38 (52.8)	0.910
Ethnicity, n (%)			0.887
Caucasian	60 (89.6)	65 (90.3)	
non-Caucasian	7 (10.4)	7 (9.7)	
Clinical presentation, n (%)			**0.003**
Unilateral optic neuritis	6 (9.0)	9 (12.5)	
Bilateral optic neuritis	1 (1.5)	7 (9.7)	
Focal supratentorial syndrome	7 (10.4)	17 (23.6)	
Brainstem syndrome	17 (25.4)	7 (9.7)	
Cerebellar syndrome	4 (6.0)	6 (8.3)	
Partial myelopathy	27 (40.3)	15 (20.8)	
Complete myelopathy	1 (1.5)	7 (9.7)	
EDSS at baseline, Me (IQR)	1.0 (0–3.0)	-	-
MRI at baseline, n (%)			
1–9 T2 lesions	34 (50.8)	58 (80.5)	
>9 T2 lesions	33 (49.3)	12 (16.7)	**<0.001**
Enhancing lesions	36 (53.7)	25 (34.7)	**<0.001**
Infratentorial lesions	44 (65.7)	19 (26.4)	**<0.001**
Spinal cord (SC) lesions	45 (67.2)	20 (27.8)	**<0.001**
CSF at baseline			
OCB, n (%)	58 (86.6)	13 (18.1)	**<0.001**
CSF KFLC, mg/L, Me (IQR)	4.45 (2.1–8.6)	0.33 (0.3–1.8)	**<0.001**
KFLC index, Me (IQR)	70.3 (25.2–167.8)	5.0 (2.7–9.6)	**<0.001**
sNfL at baseline, pg/mL, Me (IQR)	12 (10–18)	-	-
Therapy			
Corticosteroids for relapses, n (%)	27 (41.5)	22 (30.6)	0.511
Time to DMT initiation, months, Me (IQR)	6 (4–13)	-	-
Initiation of HE-DMT, n (%)	35 (52.2)	-	-
DMT switch, n (%)	11 (16.4)	-	-
Follow-up duration, months, Me (IQR)	41 (31–53)	34 (18–47)	**0.019**
Outcomes, n (%)			
New clinical relapses	20 (29.8)	6 (8.3)	**0.002**
New MRI lesions	32 (47.8)	5 (6.9)	**<0.001**
New infratentorial or SC lesions	11 (16.4)	3 (4.2)	**0.049**
Deaths	0 (0)	8 (11.1)	**0.012**

CSF, cerebrospinal fluid; DMT, disease modifying therapy; Dx, diagnosis; EDSS, Expanded Disability Status Scale; HE, high-efficacy; IQR, interquartile range; KFLC, kappa free light chain; LP, lumbar puncture; Me, median; mg/L, milligrams per litre; MS, multiple sclerosis; MRI, magnetic resonance imaging; n, number; OCB, oligoclonal bands; pg/mL, picograms per millilitre; pwMS, people with multiple sclerosis; SC, spinal cord; SD, standard deviation; sNfL, serum neurofilament light chain; $\bar{x}$, mean

*Significant p values are indicated in bold and underlined

based on previous studies: in an Austrian cohort of newly diagnosed patients, a KFLC index ≥ 100 predicted early clinical and MRI activity independently of sNfL levels [12]. This cut-off of KFLC index was also used in a Swedish study which indicated that a KFLC index ≥ 100 at baseline was an independent risk factor for PIRA in a cohort of 114 people with an early relapsing–remitting MS (RRMS) [13]. Other groups have reported similar associations between higher

Table 3 Final diagnosis and clinical presentation of people with non-MS (full 2017 McDonald criteria)

Final diagnosis of people with non-MS, n	Clinical presentation, n
CIS, 16	Unilateral optic neuritis, 2 Focal supratentorial syndrome, 3 Brainstem syndrome, 3 Partial myelopathy, 3 Other, 5
ADEM/NMOSD/MOGAD, 10	Bilateral optic neuritis, 3 Focal supratentorial syndrome, 1 Brainstem syndrome, 1 Cerebellar syndrome, 1 Partial myelopathy, 1 Complete myelopathy, 3
Autoimmune encephalitis, 6	Focal supratentorial syndrome, 5 Brainstem syndrome, 1
CRION, 5	Unilateral optic neuritis, 4 Bilateral optic neuritis, 1
Idiopathic transverse myelitis, 7	Partial myelopathy, 5 Complete myelopathy, 2
Paraneoplastic and other autoimmune CNS disorders, 8	Bilateral optic neuritis, 1 Focal supratentorial syndrome, 1 Brainstem syndrome, 1 Cerebellar syndrome, 3 Partial myelopathy, 2
CNS infections, 5	Unilateral optic neuritis, 2 Focal supratentorial syndrome, 1 Partial myelopathy, 2
Primary CNS neoplasms, 6	Focal supratentorial syndrome, 2 Brainstem syndrome, 1 Partial myelopathy, 1 Complete myelopathy, 2
Other miscellaneous CNS conditions, 11	Unilateral optic neuritis, 1 Bilateral optic neuritis, 2 Focal supratentorial syndrome, 4 Cerebellar syndrome, 2 Partial myelopathy, 1 Other, 1

ADEM, acute disseminated encephalomyelitis; CIS, clinically isolated syndrome; CNS, central nervous system; CRION, chronic relapsing inflammatory optic neuropathy; MOGAD, MOG antibody-associated disease; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; n, number

KFLC index values and disease severity. A Spanish study reported that a KFLC index ≥ 130 at baseline identified patients who later experienced DMT failure [14]; the same group previously showed that a KFLC index ≥ 58 predicted reaching an EDSS of 3 [25]. Other studies, that did not differentiate between CIS and early MS, have reported similar associations. In a Portuguese cohort study of 28 CIS/MS patients, higher KFLC index values predicted EDSS progression [26], whereas an Italian cohort study of 59 CIS/MS people showed that only 10% of patients with a KFLC index ≥ 106 were free from new clinical relapses [27].

Our study adds to this evidence by showing that the KFLC index may also convey information about lesion topography. Patients with higher KFLC index values were more likely to develop new lesions in the brainstem and spinal cord, regions associated with greater functional impact [15]. This association remained significant in multivariable analysis, suggesting that the KFLC index can help identify patients at risk of accruing lesions in eloquent regions at a time when therapeutic decisions about HE-DMT rely heavily on prognostic biomarkers. In support of the clinical relevance of lesion distribution, a recent Dutch cohort showed that early spinal cord lesions strongly predict disability progression and that new infratentorial lesions are linked to a trend toward worse long-term outcomes, although their combined presence did not worsen prognosis beyond the effect of either lesion type alone [28].

Not all studies agree on the prognostic utility of the KFLC index. A small case–control study with two decades of follow-up found no difference in KFLC index between benign and aggressive forms of MS. However, that analysis included only 20 benign and 15 aggressive cases and was

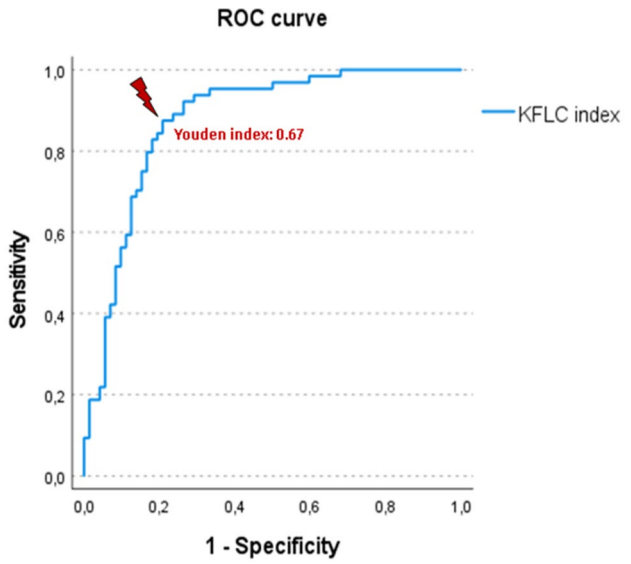

Fig. 2 ROC curve of KFLC index using the 2017 clinico-radiological McDonald criteria. KFLC, kappa free light chain; ROC, receiver operating characteristic

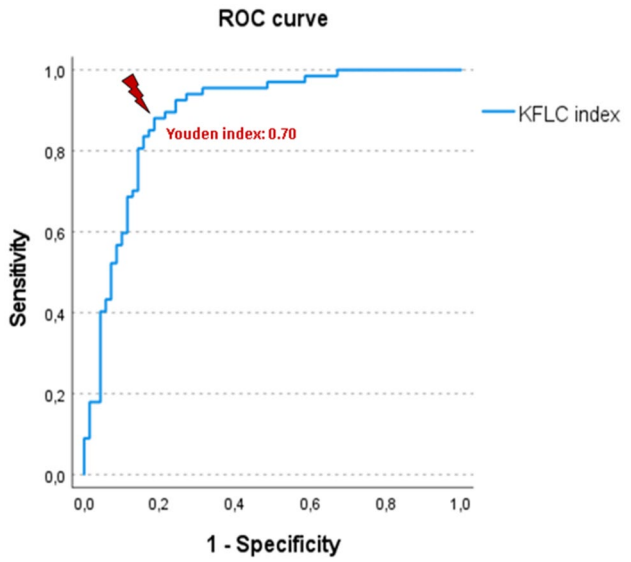

Fig. 3 ROC curve of KFLC index using the proposed 2024 clinico-radiological McDonald criteria. KFLC, kappa free light chain; ROC, receiver operating characteristic

subject to survivor bias; thus, the negative result should be interpreted cautiously [29].

Strengths of our study include the application of both the 2017 and the proposed 2024 McDonald criteria and the avoidance of incorporation bias through initial classification based solely on clinical and MRI findings. Limitations include the relatively small number of patients with MS (leading to wide confidence intervals in some analyses), the retrospective design and the follow-up duration (median 3–4 years) which limits inferences about long-term disability or progression. Prognostic estimates should be considered preliminary and require validation in adequately powered, prospective studies with extended follow-up.

Conclusion

Our data support KFLC index as an adjunctive biomarker that enhances diagnostic assessment when integrated with clinical evaluation and MRI. In exploratory analyses, an elevated KFLC index was associated with short-term infratentorial or spinal cord lesion accrual; confirmation in larger, longer-term cohorts is required to determine its role in prognosis.

Table 4 AUC value and optimal cut-off of the KFLC index using both the 2017 and the proposed 2024 clinico-radiological McDonald criteria

2017 criteria		AUC (CI 95%)	Youden index	Optimal cut-off
Overall cohort analysis				
KFLC index		0.876 (0.814–0.935)	0.67	12.0
Age-stratified analysis				
< 50 years ($n = 93$)	KFLC index	0.828 (0.740–0.915)	0.61	9.5
≥ 50 years ($n = 45$)	KFLC index	0.967 (0.921–1.000)	0.83	12.5
2024 criteria		AUC (CI 95%)	Youden index	Optimal cut-off
Overall cohort analysis				
KFLC index		0.889 (0.830–0.945)	0.70	12.0
Age-stratified analysis				
< 50 years ($n = 94$)	KFLC index	0.845 (0.760–0.930)	0.65	9.5
≥ 50 years ($n = 45$)	KFLC index	0.967 (0.921–1.000)	0.83	12.5

AUC, area under the curve; CI, confidence interval; KFLC, kappa free light chain; n, number

Table 5 Diagnostic properties of OCB and KFLC index 12.0 using both the 2017 and the proposed 2024 clinico-radiological McDonald criteria

2017 criteria	Sensitivity (CI 95%)	Specificity (CI 95%)	PPV (CI 95%)	NPV (CI 95%)
OCB	85.9 (75.0–93.4)	79.7 (68.8–88.2)	78.6 (67.1–87.5)	86.8 (76.4–93.8)
KFLC index 12.0	87.5 (76.8–94.4)	79.2 (68.0–87.8)	78.9 (67.6–87.7)	87.7 (77.2–94.5)
OCB and KFLC index 12.0	95.3 (86.9–99.0)	75.0 (63.4–84.5)	77.2 (66.4–85.9)	94.7 (85.4–98.9)
OCB (if KFLC index ≥ 12.0)	89.3 (78.1–96.0)	26.7 (7.8–55.1)	82.0 (70.0–90.6)	40.0 (12.2–73.8)
OCB (if KFLC index < 12.0)	62.5 (24.5–91.5)	94.7 (85.4–98.9)	62.5 (24.5–91.5)	94.7 (85.4–98.9)
2024 criteria	Sensitivity (CI 95%)	Specificity (CI 95%)	PPV (CI 95%)	NPV (CI 95%)
OCB	86.6 (76.0–93.7)	81.9 (71.1–90.0)	81.7 (70.7–89.9)	86.8 (76.4–93.8)
KFLC index 12.0	88.1 (77.8–94.7)	81.4 (70.3–89.7)	81.9 (71.1–90.0)	87.7 (77.2–94.5)
OCB and KFLC index 12.0	95.5 (87.5–99.1)	77.1 (65.6–86.3)	80.0 (69.6–88.1)	94.7 (85.4–98.9)
OCB (if KFLC index ≥ 12.0)	89.8 (79.2–96.2)	30.8 (9.1–61.4)	85.5 (74.2–93.1)	40.0 (12.2–73.8)
OCB (if KFLC index < 12.0)	62.5 (24.5–91.5)	94.7 (85.4–98.9)	62.5 (24.5–91.5)	94.7 (85.4–98.9)

CI, confidence interval; KFLC, kappa free light chain; NPV, negative predictive value; OCB, oligoclonal bands; PPV, positive predictive value

Table 6 Concordance between OCB and KFLC index 12.0 using both the 2017 and the proposed 2024 clinico-radiological McDonald criteria

2017 criteria	Cohen´s Kappa (CI 95%)	2024 criteria	Cohen´s Kappa (CI 95%)
OCB–KFLC index 12.0	0.74 (0.62–0.85)	OCB–KFLC index 12.0	0.74 (0.62–0.85)

CI, confidence interval; KFLC, kappa free light chain; OCB, oligoclonal bands

Table 7 Bivariate associations between the KFLC index and baseline predictors of poor prognosis and early disease activity outcomes in pwMS (full 2017 McDonald criteria)

Variables of pwMS (n = 76)	Non-parametric tests: M-W or K-W (p value*) KFLC index Ω	Spearman's ρ: Coefficient (p value*) KFLC index Ω
Age Ω	–	**−0.26 (0.013)**
Sex Δ	**M-W (0.002)**	–
Ethnicity Δ	M-W (0.196)	–
Clinical presentation Δ	K-W (0.156)	–
EDSS at baseline Ω	–	−0.09 (0.253)
MRI at baseline Δ		–
> 9 T2 lesions	M-W (0.171)	
Enhancing lesions	M-W (0.708)	
Infratentorial lesions	M-W (0.567)	
Spinal cord (SC) lesions	M-W (0.959)	
sNfL at baseline Ω	–	+0.23 (0.122)
Therapy		
Corticosteroids for relapses Δ	M-W (0.663)	-
Time to DMT initiation Ω	–	−0.03 (0.404)
Initiation of HE-DMT Δ	M-W (0.343)	–
DMT switch Δ	M-W (0.777)	–
Follow-up duration Ω	–	−0.06 (0.314)
Outcomes Δ		
New clinical relapses	M-W (0.248)	–
New MRI lesions	M-W (0.581)	–
New infratentorial or SC lesions (Fig. 4)	**M-W (0.005)**	–
EDSS progression (CDW)	M-W (0.961)	–

CDW, confirmed disability worsening; DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; HE, high-efficacy; KFLC, kappa free light chain; K-W, Kruskal–Wallis test; M-W, Mann–Whitney U test; MRI, magnetic resonance imaging; pwMS, people with multiple sclerosis; SC, spinal cord; sNfL, serum neurofilament light chain

Ω continuous variables; Δ categorical variables

*Significant p values are indicated in bold and underlined

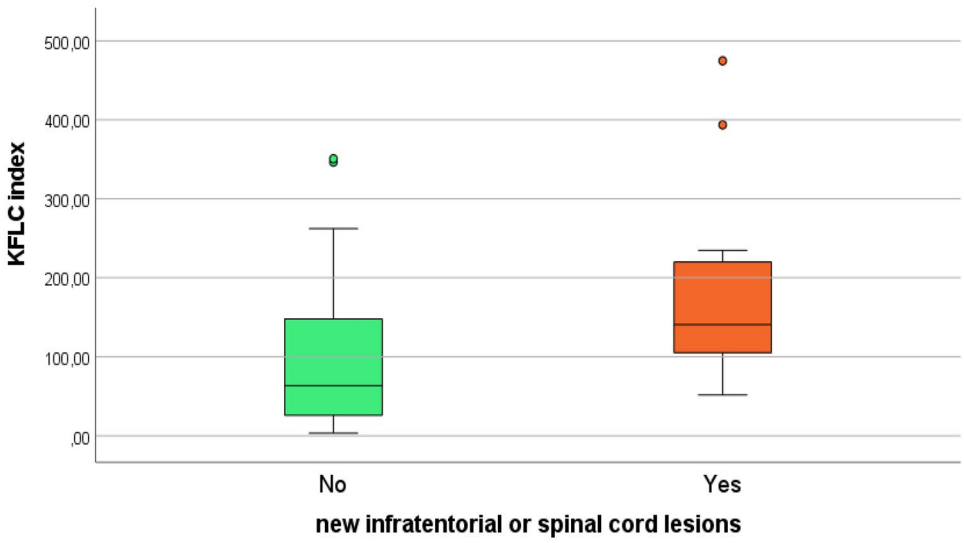

Fig. 4 Box plot of the distribution of the KFLC index in pwMS (full 2017 McDonald criteria). KFLC, kappa free light chain; pwMS, people with multiple sclerosis

Table 8 Chi-square analysis of KFLC index (≥ 100) and baseline predictors of poor prognosis and early disease activity outcomes in pwMS (full 2017 McDonald criteria)

Variables of pwMS (n = 76)	KFLC index ≥ 100 (*n* = 30)	KFLC index < 100 (*n* = 46)	OR (CI 95%)	*p* value*
Age, n (%)				**0.048**
≥ 40 years	10 (33.3)	26 (56.5)	1.53	
< 40 years	20 (66.7)	20 (43.5)	(1.01–2.32)	
Sex, n (%)				**0.037**
Men	9 (30.0)	25 (54.3)	1.53	
Women	21 (70.0)	21 (45.7)	(1.04–2.27)	
Ethnicity, n (%)				0.243
Caucasian	25 (83.3)	42 (91.3)	1.92	
non-Caucasian	5 (16.7)	4 (8.7)	(0.56–6.57)	
Clinical presentation, n (%)				0.121
Unilateral optic neuritis	4 (13.3)	3 (6.5)		
Bilateral optic neuritis	1 (3.3)	0 (0)		
Focal supratentorial syndrome	4 (13.3)	5 (10.9)		
Brainstem syndrome	3 (10.0)	15 (32.6)	-	
Cerebellar syndrome	1 (3.3)	3 (6.5)		
Partial myelopathy	17 (56.7)	16 (34.8)		
Complete myelopathy	0 (0)	1 (2.2)		
EDSS at baseline, n (%)				0.311
< 3 points	15 (50.0)	20 (43.5)	0.65	
≥ 3 points	5 (16.7)	12 (26.1)	(0.27–1.56)	
MRI at baseline, n (%)				
> 9 T2 lesions	15 (50.0)	19 (41.3)	1.21 (0.74–1.99)	0.456
Enhancing lesions	15 (50.0)	21 (45.7)	1.10 (0.68–1.77)	0.711
Infratentorial lesions	18 (60.0)	29 (63.0)	0.95 (0.66–1.37)	0.789
Spinal cord (SC) lesions	22 (73.3)	31 (67.4)	1.09 (0.81–1.46)	0.582
sNfL at baseline, n (%)				0.400
< 15 pg/mL	4 (13.3)	12 (26.1)	1.41	
≥ 15 pg/mL	6 (20.0)	6 (13.0)	(0.53–3.77)	
Therapy, n (%)				
Corticosteroids for relapses	13 (43.3)	17 (37.0)	1.17 (0.67–2.05)	0.578
> 6 months to DMT initiation	14 (46.7)	20 (43.5)	1.03 (0.63–1.67)	0.558
Initiation of HE-DMT	18 (60.0)	22 (47.8)	1.33 (0.87–2.03)	0.195
DMT switch	7 (23.3)	6 (13.0)	1.65 (0.62–4.40)	0.314
Follow-up duration, n (%)				
> 24 months	22 (73.3)	36 (78.3)	0.95 (0.74–1.22)	0.443
> 48 months	8 (26.7)	12 (26.1)	1.03 (0.48–2.22)	0.568
Outcomes, n (%)				
New clinical relapses	12 (40.0)	8 (17.4)	2.30 (1.07–4.95)	**0.029**
New MRI lesions	14 (46.7)	16 (34.8)	1.34 (0.77–2.33)	0.300
New infratentorial or SC lesions	9 (30.0)	2 (4.3)	6.90 (1.6–29.76)	**0.003**
EDSS progression (CDW)	6 (20.0)	10 (21.7)	0.93 (0.39–2.21)	0.860
deaths	0 (0)	0 (0)	-	-

CDW, confirmed disability worsening; CI, confidence interval; DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; HE, high-efficacy; KFLC, kappa free light chain; K-W, Kruskal–Wallis test; M-W, Mann–Whitney U test; MRI, magnetic resonance imaging; n, number; OR, odds ratio; pg/mL, picograms per millilitre; pwMS, people with multiple sclerosis; SC, spinal cord; sNfL, serum neurofilament light chain

*Significant *p* values are indicated in bold and underlined

Table 9 Exploratory multivariable logistic regression of KFLC index (≥100) and early disease activity outcomes in pwMS (full 2017 McDonald criteria)

Variables of pwMS//KFLC index ≥ 100	Adjusted OR (CI 95%)	*p* value*
Age		0.352
≥40 years	1	
<40 years	1.67 (0.57–4.96)	
Sex		0.057
Men	1	
Women	3.13 (0.96–9.66)	
New clinical relapses		0.161
No	1	
Yes	2.36 (0.71–7.82)	
New infratentorial or SC lesions		**0.019**
No	1	
Yes	8.07 (1.42–45.96)	

CI, confidence interval; KFLC, kappa free light chain; OR, odds ratio; pwMS, people with multiple sclerosis; SC, spinal cord

*Significant *p* values are indicated in bold and underlined

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Declarations

Conflict of interests The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: LMN has received speaking honoraria or travel expenses for participation in scientific meetings from AbbVie, Esteve, Kern Pharma, Merck, Neuraxpharm, Novartis, Roche, Sandoz, and Sanofi. SMD has no conflicts of interest. LREM declares fees for lectures or assistance to congresses from Alter, Bristol Myers Squibb, Daiichi Sankyo, Merck, Novartis, and Roche. APS has received personal compensation from Merck Serono, Novartis, Roche, and Sandoz for serving on a scientific advisory board or speaking.

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Consent for publication Not applicable.

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