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The radiologically isolated syndrome: revised diagnostic criteria

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Abstract

The radiologically isolated syndrome (RIS) was defined in 2009 as the presence of asymptomatic, incidentally identified demyelinating-appearing white matter lesions in the central nervous system within individuals lacking symptoms typical of multiple sclerosis. The RIS criteria have been validated and predict the transition to symptomatic MS reliably. The performance of RIS criteria that require fewer MRI lesions is unknown.

2009-RIS subjects, by definition, fulfill 3-4 of 4 criteria for 2005 dissemination in space [DIS] and subjects fulfilling only 1 or 2 lesions in at least one 2017 DIS location were identified within 37 prospective databases. Univariate and multivariate Cox regression models were used to identify predictors of a first clinical event. Performances of different groups were calculated.

747 subjects (72.2% female, mean age 37.7 ±12.3 years at the index MRI) were included. The mean clinical follow-up time was 46.8 ±45.4 months. All subjects had focal T2 hyperintensities suggestive of inflammatory demyelination on MRI; 251 (33.6%) fulfilled 1 or 2 2017 DIS criteria (designated as Group 1 and Group 2, respectively), and 496 (66.4%) fulfilled 3 or 4 2005 DIS criteria representing 2009-RIS subjects. Group 1 and 2 subjects were younger than the 2009-RIS Group and were more likely to develop new T2 lesions over time ($p<0.001$). Groups 1 and 2 were similar regarding survival distribution and risk factors for transition to multiple sclerosis.

At five years, the cumulative probability for a clinical event was 29.0% for Groups 1-2 compared to 38.7% for 2009-RIS (p=0.0241). The presence of spinal cord lesions on the index scan and CSF-restricted oligoclonal bands in Groups 1-2 increased the risk of symptomatic MS evolution at five years to 38%, comparable to the risk of development in the 2009-RIS group. The presence of new T2 or gadolinium-enhancing lesions on follow-up scans independently increased the risk of presenting with a clinical event (p<0.001). The 2009-RIS subjects or Group 1-2 with at least 2 of the risk factors for a clinical event demonstrated better sensitivity (86.0%), negative predictive value (73.1%), accuracy (59.8%) and area under the curve (60.7%) compared to other criteria studied.

This large prospective cohort brings Class I evidence that subjects with fewer lesions than required in the 2009 RIS criteria evolve directly to a first clinical event at a similar rate when additional risk factors are present. Our results provide a rationale for revisions to existing RIS diagnostic criteria.

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Abbreviations: CIS = Clinically Isolated Syndrome; DMT = Disease-modifying treatment; OCB = Oligoclonal bands; PP = Primary Progressive; RIS = Radiologically isolated syndrome; RR = Relapsing-remitting; HR = hazard ratio; DIS = dissemination in space; DIT = dissemination in time; RISC = Radiologically Isolated Syndrome Consortium; SFSEP = Société Francophone de la Sclérose En Plaques; OFSEP = Observatoire Français de la Sclérose En Plaques

Introduction

The radiologically isolated syndrome (RIS) is identified by the incidental discovery of central nervous system (CNS) white matter T2-weighted hyperintense foci on magnetic resonance imaging (MRI) that demonstrate morphological and spatial characteristics highly typical of MS but without clinical symptomatology related to inflammatory demyelination.[1-3] Clinical and radiological features are known as RIS without a better explanation. Current RIS Criteria use the dissemination in space (DIS) requirement from the 2005 McDonald criteria[4], requiring 3 or 4 of four imaging criteria to be met.[5]

The 2009 RIS criteria[1], when accurately applied, have been validated and shown to predict evolution to a first clinical attack at a rate of 34% at five years, increasing to 51% at ten years.[6,7] A direct transition to primary progressive multiple sclerosis (PPMS) has also been observed.[8] Inspired by the proposed 2017 revisions to the McDonald criteria for multiple sclerosis[9], other suggested diagnostic criteria for RIS have been recently introduced without supportive clinical evidence and value as experts' recommendations.[10] Using the 2009 RIS Criteria within a prospective cohort, we recently confirmed the influence of age, the presence of spinal cord lesions, and gadolinium-enhancing lesions on the index scan as risk factors for evolution to symptomatic multiple sclerosis.[11] Previously, the study of an international cohort had established the validity of fulfilling DIS 2005 by 3 or 4 of 4 imaging criteria in RIS[6-8], defined by 3 or 4 of 1) more than 9 T2 lesions or one gadolinium-enhancing lesion, 2) At least one juxtacortical lesion, 3) At least 3

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periventricular lesions and 4) At least one infratentorial or spinal cord lesion. Nevertheless, a common occurrence in clinical practice involves the evaluation of subjects with MRI anomalies highly suggestive of multiple sclerosis that fulfil only 1 or 2 of 4 spatial dissemination location criteria, as defined in the 2017 McDonald criteria (2 distinct lesions in at least 2 different locations including periventricular, juxtacortical, infratentorial or spinal cord).[9,12] As shown in the RIS cohort flowchart (*Fig. 1*), these individuals either remain with this minimal lesion load, evolve to RIS, or directly transition to symptomatic multiple sclerosis.

In this study, we present the natural history of asymptomatic individuals with MRI anomalies highly typical of multiple sclerosis but that fall short of fulfilling 2009 RIS/2005 DIS criteria on MRI[1,4,5] and evaluate the temporal course of their clinical evolution when previously identified prognostic factors in RIS are applied. We confirm that the addition of the risk factors identified in our multiple studies[1,2,3,6,7,11] increases the risk of symptomatic evolution in these individuals to rates similar to 2009 RIS, validating the need to include these individuals in the diagnostic spectrum of RIS. Finally, we present validated revisions to the original criteria described in 2009.[1] These data should allow for earlier identification of presymptomatic subjects, which impacts clinical care and subject enrollment in therapeutic trials in RIS.

Materials and methods

This observational, multicenter study of prospectively acquired data was initiated by *Société Francophone de la Sclérose En Plaques* (SFSEP), *Observatoire Français de la Sclérose En Plaques* (OFSEP) Scientific Committees, The University of Texas Southwestern Medical Center at Dallas (Texas, USA), Mayo Clinic Rochester (Minnesota, USA), and Istanbul University Cerrahpasa (Turkey), on behalf of the RISC (*Radiologically Isolated Syndrome Consortium).*

Study criteria

Since 2010, all subjects with T2-weighted hyperintense foci suggestive of CNS demyelinating disease referred to 37 multiple sclerosis centres were prospectively followed. In the absence of

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neurological anomalies or history suggestive of multiple sclerosis according to the 2009 RIS criteria[1], an international expert group (CLF, MC, CLC, FDD, LM, DTO, OHK, CJA, NM, DP, AS, JC) validated constitutive elements of the RIS criteria, including double-centralized MRI reading. Brain and spinal cord MRIs collected from 37 multiple sclerosis expert sites (*Supplementary Table 1*) were coded for DIS lesion location criteria from four regions: (1) periventricular; (2) juxtacortical; (3) infratentorial; (4) spinal cord, lesion number for each location, and the presence of contrast-enhancing lesions. Longitudinal clinical follow-up and imaging data were collected using standardized protocols within participating centres to accommodate different medical and insurance practices across multiple countries and healthcare systems.

Brain and spinal cord MRI protocols

The strategy was to collect all subjects with an initial brain MRI that revealed incidental anomalies suggestive of demyelinating disease. Imaging studies were conducted on 1.5 Tesla (T) or 3T MRI units from different manufacturers. The multicenter nature of the research and the various MRI motives did not allow the standardization of sequences for the index scan. The most frequent sequences performed were 3D T1-weighted with and without contrast-enhanced imaging, diffusion-weighted imaging, gradient-echo T2 or susceptibility-weighted imaging, and 2D or 3D fluid-attenuated inversion recovery (FLAIR). If available, spinal cord imaging protocols were also collected, including T1- and T2-weighted sequences in axial and sagittal planes, with or without gadolinium. Follow-up MRIs were obtained at intervals according to local practice, clinician judgement, and clinical MRI protocols.

Standardized analyses were performed on the index MRI and follow-up MRIs evaluating dissemination in time (DIT), defined as the presence of gadolinium-enhancing lesions on the index scan and/or at least one new T2-weighted hyperintense lesion on a follow-up scan. Hyperintense T2-weighted foci were required to be ≥ 3 mm^2 and have an appearance typical of multiple sclerosis to be included. Subjects were classified based on the following three groups: i) Group 1 (only 1 of 4 2017 DIS location criteria), ii) Group 2 (2 of 4 2017 DIS location criteria), and iii) 2009-RIS Group (3 or 4 of 4 2005 DIS location criteria meeting spatial dissemination

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requirements for RIS by 2009 Criteria[1]).

Statistical analysis

Variables of interest included demographic characteristics (*e.g.*, sex, age at the time of index scan), clinical data (*i.e.*, MS family history, the reason for MRI), cerebrospinal fluid (CSF) profile, and imaging data (1 or at least 3 periventricular lesions to differentiate 2017 and 2005 DIS criteria, location of lesions, and presence of contrast). Numeric variables were expressed as mean ± standard deviation or median and interquartile range. Normality and heteroskedasticity of continuous data were assessed with Shapiro-Wilk and Levene's tests, respectively. According to data distribution, continuous outcomes were compared with unpaired Student t-test or Mann-Whitney U test. Discrete outcomes were compared with chi-square or Fischer's exact test accordingly. The alpha risk was set to 0.05, and two-tailed tests were used.

To identify variables predictive of a clinical event, a logistic regression analysis was made, including all variables found to be statistically associated with the outcome in the univariate analysis, i.e., the presence of CSF oligoclonal bands, spinal cord T2-weighted lesion, T1-weighted gadolinium-enhancing lesion at index scan, and presence of new T2-weighted or T1-weighted gadolinium-enhanced lesion in follow-up MRI scans. It allowed us to calculate odd ratios (OR) and their 95% confidence intervals (CI). The association of each predictive variable of interest with the time to the first event were evaluated according to Kaplan-Meier survival analysis, and comparisons of survival distributions were made with the non-parametric log-rank test. Sub-analyses were performed with and without patients treated with immunoactive drugs during the follow-up period as RIS. DM-treated RIS were removed from the primary analysis. Hazard Ratios were quantified using univariate and multivariate Cox regression analyses that allowed us to calculate hazard ratios (HR) along with their 95% CI. Data were checked for multicollinearity with the Belsley-Kuh-Welsch technique. The Breusch-Pagan test and the Shapiro-Wilk test assessed the heteroskedasticity and normality of residuals. The alpha risk was set to 5.0%.

After identifying predictive variables of interest, the diagnostic performance, i.e., sensitivity, specificity, positive and negative predictive values, accuracy and area under the curve of different

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criteria, were calculated. To do so, the time to first event distribution was evaluated for MS converters and allowed to identify that 75% of the patients (third quartile) experienced a clinical event during the first 55 months of follow-up. Therefore, we assumed that all the patients with enough follow-up data during five years (60 months) and that did not experience a clinical event during such period were classified as controls.

The statistical analyses were performed using Easymedstat software (version 3.18; www.easymedstat.com), SAS v9.4 (SAS Inst., Cary, NC, US) software, as well as R software version 3.5.0 (R Core Team [online]; Accessed at: http://www.R-project.org/). A p-value <0.05 was considered significant.

Standard protocol approvals, registrations, and patient consent

This study was approved by the French regulatory authorities and ethics committee (*Comité de Protection des Personnes*) for the French MS Observatory (OFSEP) or local authorities for other countries. It was by the 1964 Declaration of Helsinki and its later amendments. Written informed consent was acquired from all study subjects. The RIS international database is registered as 2022–BS-002 and its specific analysis for the revised criteria was 2022–EI-031.

Data availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Demographic and clinical characteristics at index scan

A total of 747 individuals fulfilled the inclusion criteria for the study, with 85 (11.4%) subjects classified in Group 1, 166 (22.2%) in Group 2, and 496 (66.4%) in the 2009-RIS Group. The flowchart (Fig. 1) shows the sequence of activities within this study, and *Table 1 and*

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Supplementary Table 2 summarize primary baseline demographic, clinical, and MRI features.

The study cohort was primarily women [n=539 (72.2%)] with a slight underrepresentation in Group 1 (p=0.015). The mean (± SD) clinical follow-up time was 46.8 (± 45.4) months. Seventy-one subjects (12.7%) had a family history of multiple sclerosis, with a similar distribution in the three groups (p=0.865). The mean age of the whole cohort at the index scan was 37.7 years (±12.3); Group 1 and 2 subjects were, on average, three years younger than 2009-RIS subjects (p<0.001). Of the 42 subjects (5.6%) who were identified before age 18, 22 were in Group 2 (8.8%), and 20 were in the 2009-RIS group (4.0%). Reasons for the index scan were available for 682 subjects (91.3%) and were similar between the three groups (p=0.101) (*Table 1*). However, of the 65 (8.7%) individuals in whom the reason for index MRI was not available, they were more likely to be in Group 1 (p<0.001).

CSF analysis was performed in 408 of 747 (54.6%) subjects. It was consistent with intrathecal inflammation (presence of at least two unique oligoclonal bands and/or an IgG index > 0.7) in 71.8% overall (78.2% in Group 1, 61.9% in Group 2, and 76.6% in 2009-RIS, p=0.013). OCBs were more likely to be present in the 2009-RIS Group (n=197/257, 76.6%) compared to Groups 1-2 (n=101/151, 66.9%), [OR: 1.63 (CI:1.04-2.54), p=0.042].

Some subjects (62/747, 8.3%) were treated with immunoactive drugs during the RIS follow-up. The log-rank parametric test to estimate different survival probabilities were not statistically different without treated subjects (p=0.0178) and with DMT (p=0.082). In multivariate analysis, the probability of presenting a clinical event of Groups 1 and 2 compared to the 2009-RIS Group with or without including treated subjects was respectively: Group 1: HR 0.78 (0.50; 1.21) p=0.257 and Group 2: HR 0.60 (0.42; 0.87) p=0.006, and Group 1: HR 0.76 (0.47; 1.23) p=0.261 and Group 2: HR 0.59 (0.40; 0.86) p=0.006.

Imaging characteristics

On the index brain MRI scan, differences between the three groups were identified as expected regarding the number of T2-weighted hyperintense lesions (≥9T2, p<0.001) and periventricular lesions (≥3PV, p<0.001), but also on the presence of juxtacortical (≥1, p<0.001), and infratentorial lesions ((≥1, p<0.001). The mean time for follow-up scans was 1.06 years (+-0.56) for Group 1,

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1.33 (+- 0.92) for Group 2, and 1.08 (+-0.73) for 2009-RIS.

Baseline spinal cord imaging was performed at the treating physician's discretion at each study site, and 349 subjects (46.7%) had an available spinal cord MRI at the index brain MRI scan date. At least one spinal cord lesion was observed in 159/349 subjects (45.6%). The presence of spinal cord lesions at baseline was not different between groups (p=0.241).

Data on the presence or absence of gadolinium-enhancing lesions at baseline were available for 623 (83.4%). Contrast enhancement on the index MRI was observed in 106 subjects (17.0%), mainly in 2009-RIS: n=85 (18.1%). Gadolinium-enhancing lesions were not different between Group 2 and the 2009-RIS Group at baseline (p=0.190) but were undetectable in Group 1 (p=0.003). Data on gadolinium-enhancing lesions on follow-up scans were available for 331 subjects, with 130 (39.3%) having enhancing lesions at one point after the index scan (*Supplementary Table 2*).

Evolution to Clinical Events

Whole Cohort

At the time of analysis, Feb 1st, 2022, 207 (27.7%) subjects experienced a clinical event. Clinical symptoms were progressive from the onset for 12 (5.8%) or acute for 195 (94.2%), consisting of myelitis in 93/195 (47.7%), optic neuritis in 31 (15.9%), brainstem syndrome in 28 (14.4%) and long sensory or motor tracts other than myelitis in 23 (11.8%), and unspecified in 20 (10.2%)**.**

There was a difference between Groups in the probability of evolving to a first clinical event (p=0.0178) *(Fig. 2).*

After two years, a higher proportion of subjects in the 2009-RIS Group (52/276; 18.8%) developed multiple sclerosis compared to those in Group 1 (8/58, 13.8%) or Group 2 (18/106, 17.0%). After five years, this difference was accentuated while the risk of a clinical event was 33.8% (95% CI: 21.1-49.5) for Group 1, 25.2% (96% CI: 17.7-35.1) for Group 2, and 38.7% (95% CI: 32.7-46.0) for 2009-RIS.

There was no difference between the survival distributions of Group 1 and Group 2 at any time point during the follow-up period (p=0.351) *(Supplementary Fig. 1)*, allowing us to combine

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Groups 1 and 2 to look at the survival rates and compare them against the 2009-RIS Group.

At five years, 29.0% of Group 1-2 and 38.7% of the 2009-RIS Group presented with a clinical event, respectively (p=0.002).

Additional Risk Factors

Table 2 summarizes the covariates analyzed for the risk of a clinical event in Group 1-2 compared with the 2009-RIS Group. Clinical factors at the index MRI scan associated with an increased risk of a first clinical event in the 2009-RIS Group were age <37 years [HR: 2.13 (CI: 1.46-3.09), p<0.001], male gender [HR: 1.75 (CI: 1.18-2.59), p=0.005], the presence of baseline T1-gadolinium-enhancing lesions [HR: 1.90 (CI: 1.26-2.87), p=0.002], and the presence of baseline spinal cord lesions [HR: 1.70 (CI: 1.05-2.74), p=0.032].

In Group 1-2, two variables were associated with an increased risk of a clinical event at the index MRI scan: CSF-restricted OCBs [HR: 2.39 (CI: 1.14-5.01), p=0.021] and the presence of baseline spinal cord lesions [HR: 2.76 (CI: 1.30-5.87), p=0.008]. When the 2009-RIS Group was compared to Group 1-2 associated with the predictive variable at index scan (CSF-restricted OCBs, or spinal cord involvement), survival distribution according to the occurrence of a first clinical event was not statistically different (*Supplementary Fig. 2*).

In the cohort, the conversion rate was significantly enhanced by younger age. Patients younger than age 37 at the time of index MRI evolved to MS at a rate 1.5 times faster than those who were older than 37 (p<0.001) (*Supplementary Fig. 3*).

There was a difference between the survival distribution of patients presenting CSF-restricted OCBs compared to those without OCBs in the whole cohort [HR: 1.60 (CI: 1.05-2.42), p=0.0276], with a higher risk for Group 1-2 subjects [HR: 2.39 (CI: 1.14-5.01), p=0.0205], whereas it did not impact clinical occurrence in the 2009-RIS Group [HR: 1.23 (CI: 0.73-2.06), p=0.443].

There was no association with the risk of a clinical event and sex, family history of multiple sclerosis, the reason for MRI (*Supplementary Fig. 4*), or brain T2 lesion location, except for the spinal cord location.

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There was no correlation between any combination of the spatial distribution of brain lesions and the risk of a clinical event at two years. There was an association between the probability of experiencing a clinical event at two years and the presence of gadolinium enhancement on the index scan [OR=1.86; CI [1.16-2.99], p=0.013] (*Supplementary Table 3*).

At five years from index MRI, Group 1-2 subjects who had OCBs and spinal cord lesions exhibited a 38% (95% CI: 20-65) risk of a clinical event, which was not different from 2009-RIS subjects (38.7%, 95% CI: 32.7-46.0) (*Fig. 3*). Group 1-2 subjects with normal CSF and spinal cord MRI studies experienced significantly lower risk for a clinical event (11.4%, 95% CI: 5.5-21.3) when compared to 2009-RIS subjects ($p<0.001$).

The demonstration of dissemination in time (DIT) on follow-up scans, with new T2 lesions [HR: 3.91 (CI: 1.22-12.51), p=0.022 for 2009-RIS Group and HR:1.85 (CI: 1.14-3.01), p=0.014 for Group 1-2], was significantly associated with the risk of evolution to a clinical event (*Table 2*). There was no difference between Group 1-2 subjects who presented DIT on a follow-up scan regarding the risk of a clinical event compared with 2009-RIS (p=0.920) (*Supplementary Fig. 5*).

Performance Analysis

The sensitivity, specificity, positive and negative predictive values, accuracy, and AUCs for various iterations of RIS diagnostic criteria (calculated within subjects that had at least five years of follow-up) are given in *Table 3*. A more robust specificity was demonstrated for any RIS criteria with at least two risk factors [68.5% (62.3%-74.2%) and 74.6% (66.7%-81.6%)]. According to our findings, 2009-RIS subjects or those who do not fulfil 2009-RIS criteria (Group 1-2) on the index scan but meet at least 2 of the risk factors for a clinical event (OCBs, spinal cord lesion or DIT on MRI in follow-up), demonstrate a sensitivity of 86.0% (79.4%-91.1%). The positive predictive value was higher for the 2009-RIS criteria with risk factors [58.9% (48.4%-68.9%)], as well as the negative predictive value [59.4% (48.4%-68.9%)] *versus* [50.7% (47.1%-54.3. The area under the curve was higher for the 2009 RIS-Group with risk factors [58.8% (52.3%-65.2%)] than for Group 1-2 without risk factors [53.0% (47.1%-58.8%)].

The 2023 RIS criteria have better performances on sensitivity [86.0% (79.4%-91.1%)], negative

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predictive value [73.1% (63.4%-80.9%)], accuracy [59.8% (54.1%-65.3%)], and AUC [60.7% (55.0%-66.2%)]. Positive predictive value [55.4% (52.1; 58.6)] and specificity [35.4% (28.0; 43.3] were lower since the number of group 1-2 patients who did not convert during the follow-up was smaller than all the converted subjects.

Proposed revisions to the RIS diagnostic criteria

Current RIS criteria already require that at least 3 of 4 of the 2005 DIS criteria be fulfilled, which may still be used to diagnose RIS. We identified that if fewer than 3 2005 DIS location criteria are fulfilled, then the diagnosis of RIS can still be made with one or two unique lesions in 2 different locations and the additional presence of 2 of 3 of the following risk factors: CSF-restricted OCBs, spinal cord lesions, or evidence of dissemination in time on any follow-up scans (*Table 4*).

In clinical practice, if the patient does not fulfil 2009-RIS criteria on the index scan, our proposed updated RIS criteria could be fulfilled at the time of diagnosis with at least one brain T2 lesion in predefined locations, a positive CSF study and the presence of spinal cord lesions. If only one of these risk factors is present, then one should wait for the demonstration of DIT in any location on any follow-up scans to diagnose RIS (*Fig. 4*). At 5 years, the risk stratification for presenting a clinical event is less than 10% RIS Subjects with 1 or 2 lesions in two locations without risk factor, 16% with 1 risk factor, and nearly 50% with more than 2 risk factors, as for Group 3 2009-RIS (*Supplementary Fig. 5*).

Discussion

This analysis of our prospective cohort compares the association between demographic, clinical, biological, and MRI characteristics and the risk of a first clinical event in a large cohort of individuals diagnosed with 2009 RIS criteria to two other asymptomatic groups who fall short of meeting the number of lesions needed based on the DIS 2005 criteria. Although individuals in these latter groups do not fulfil the current requirements for RIS, some have been observed anecdotally to evolve either to 2009 RIS or directly to a first CNS demyelinating clinical event, as suggested by previous experts' recommendations.[10] Our study supports that individuals with less

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white matter MRI lesions characteristic of CNS demyelination may represent earlier cases at risk of clinical MS in medical parlance described as pre-RIS.[15,16] However, our study confirms that in the presence of specific clinical and MRI characteristics, some are likely to directly evolve into clinical multiple sclerosis, like individuals diagnosed with RIS by 2009 Criteria. Therefore, we propose an evidence-based modification of the RIS diagnostic criteria while expanding the inclusion of additional RIS individuals at high risk of a first clinical event. The evidence we present is not all-inclusive, and some individuals may still not be effectively classified until longer-term follow-up establishes a diagnosis. However, as demonstrated in our study, some individuals can still convert to RIS rather than multiple sclerosis.

RIS was defined more than ten years ago, with the 2009 diagnostic criteria validated worldwide.[1,6] Since then, the search for optimal clinical, biological, and radiological markers that predict the risk of disease activity and, more precisely, the occurrence of clinical symptoms has been ongoing. The longest published observational study extends to 10 years of follow-up, with 51% of individuals predicted to experience clinical signs consistent with acute or progressive disease.[7,8] Across several prospective, observational studies, risk factors for symptomatic conversion include younger age, presence of CSF-restricted OCBs, and infratentorial or spinal cord lesions on index MRI[6,7,17], and the presence of gadolinium-enhancing lesions at the index scan.[11] Throughout the past decade of studying RIS, we have periodically encountered patients with typical CNS demyelinating lesions on MRI who fell short of the original RIS criteria. Here, we find that RIS can also be reliably diagnosed in subjects who only meet one or two 2005 DIS criteria or fulfilling the currently used DIS criteria for multiple sclerosis[9] but also have CSF-unique OCBs, gadolinium-enhancing and spinal cord lesions on baseline imaging, and new T2 or gadolinium-enhancing lesions on follow-up imaging. This highlights the importance of regular, thorough MRI follow-up and longitudinal changes. The subsequent occurrence of a clinical event with a history of prior radiological advancement underscores the significance of this finding.

The risk of evolution to multiple sclerosis in subjects with at least one or two lesions is like in 2009 RIS subjects when there is the presence of CSF-restricted OCBs, spinal cord lesions or gadolinium-enhancing lesions at baseline or at least one new T2-hyperintense or gadolinium-enhancing lesion on any follow-up imaging scan. These findings support appropriate modifications to the current diagnostic criteria for RIS. The proposed changes allow for the diagnosis of RIS with fewer MRI

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lesions while emphasizing the importance of other paraclinical data. Our proposed modifications are also mindful of having a better AUC to avoid misdiagnosis while maintaining sensitivity to allow for more precise early disease identification and recommended management.

In this study, younger patients with fewer T2-weighted hyperintense lesions suggestive of inflammatory demyelination might experience new lesion development that mirrors disease activity on MRI seen in multiple sclerosis.[18] More contemporary criteria allow an earlier diagnosis for RIS and may be more relevant in younger individuals. At the same time, the upper age limits are not impacted. The subsequent occurrence of a clinical event with a history of prior radiological advancement highlights the clinical importance of this finding. Our findings also demonstrate that an asymptomatic subject with few lesions but additional risk factors for clinical evolution may have the same prognosis as traditionally defined RIS.

Around the time of the index scan, adding OCBs and spinal cord lesions increases specificity and accuracy while reducing sensitivity, as already demonstrated in pediatric RIS.[19] These observations are aligned to preserve diagnostic specificity, particularly in the context of RIS, where clinical symptomology is lacking.[20-22] This issue is mainly present in subjects fulfilling less than 3 of 4 Criteria for DIS. For example, suppose CSF analysis is not available at the time of the index scan. In that case, identification of risk factors will rely on spinal cord lesions at diagnosis and DIT on follow-up scans only. We, therefore, strongly recommend the supportive evidence of CSF studies at the time of diagnosis to improve specificity. In these individuals, the low particularity of brain MRI alone without additional risk factors should prompt clinicians to exercise even more caution regarding the possibility of RIS overdiagnosis.[20-22] Although not available in our dataset, we expect that future imaging diagnostic criteria for RIS and multiple sclerosis may include additional imaging modalities such as central vein imaging, paramagnetic rims, and 3-dimensional conformational characteristics to increase the specificity for CNS demyelinating lesions[23-25] or biological markers such as neurofilament light chain.[26] Since our data reflect measures from real-world clinical practice, the uniform and systematic collection of these and other promising biomarkers was impossible. Including such measures in the future should be aligned with future embodiments of the multiple sclerosis diagnostic criteria.

Evolving from Group 1 to Group 2 to RIS, included subjects were older, predominantly women, with CSF-restricted OCBs and gadolinium-enhancing lesions on the index scan. This could have

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impacted our results as younger females, not surprisingly, have a much higher likelihood of radiological activity and clinical activity, reflected in our DIS grouping results and conversion rates. However, as this is the natural history of the disease with the expected sex differences along the ageing continuum in multiple sclerosis[18,19], our data likely represents a typical RIS population encountered in the clinical practice making our results more applicable to such a setting, as opposed to just applying to a more stringent clinical trial setting.

Many individuals in this cohort and prior RIS cohorts have been exposed to multiple sclerosis disease-modifying therapies, despite the earlier lack of randomized clinical trials evidence to support treatment at this phase.[13,14] The ARISE study, evaluating the time to a first clinical event comparing dimethyl fumarate to placebo, demonstrated the superiority of using a disease-modifying treatment over a placebo in subjects with 2009 RIS.[13] Results from other ongoing randomized, controlled clinical trials evaluating the impact of multiple sclerosis DMTs in RIS are expected soon.[14] These trials further emphasize the immediate need for an early and accurate contemporary RIS diagnosis to avoid potential clinical impairment.

Our study has limitations. There was sufficient follow-up to draw meaningful conclusions (mean follow-up time, 3.8 years). However, the total sample size did not allow for sub-analyses of minimum follow-up times. Not all subjects underwent a baseline spinal cord MRI scan and lumbar puncture evaluation, as is often the case in real-world clinical studies. Whether to include spinal cord MRI and CSF analysis in the routine diagnostic RIS workup varies among clinicians. We did not exclude the subjects without CSF or spinal cord MRI data to avoid selection bias. As such, while our findings reflect more on the reality of the current clinical practice and not standardized MRI protocols, they are open to some biases. Therefore, we did perform sub-analyses accounting for this variability in clinical practice, and specificity and sensitivity did not differ from the whole cohort. We also initially included subjects exposed to DMT at the RIS stage for the same reasons. Our proposed revised RIS criteria have low specificity as they combine the 2009 RIS Group and Group 1-2 with risk factors. The specificity increases in scenarios where at least two risk factors, either from 2009-RIS criteria or Group 1-2 subjects, are added, resulting in a higher AUC. This is explained by the low number of patients with enough follow-up data and no risk factors and the inclusion of fewer than 20 individuals classified as negative within the revised RIS criteria.

With the widespread use of MRI technology, an increase in the incidental observation of T2-

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weighted hyperintense lesions and the risk of RIS misdiagnosis is expected.[20, 22] Our data suggest that any subject with imaging features suggestive of CNS demyelination with less than three spatial DIS criteria, when accurately classified, may evolve to clinical MS, following a similar clinical course as those with RIS. It also corresponds better to the DIS criteria used in clinical practice.[9] While novel biomarkers to use in RIS remain highly interesting, our results underscore the value of readily available conventional imaging and paraclinical data along with longitudinal medical follow-up for characterizing and predicting clinical outcomes at the earliest phase of CNS demyelinating disease.[23-26] These revisions to the previous 2009 RIS criteria provide an opportunity for earlier classification of subjects while minimizing the risk of misdiagnosis, enhancing the quality of the negative predictive value with a similar positive predictive value. Additional novel radiological or biological markers may improve specificity further.[23-27] The natural history data in RIS that we have published over the years is reassuring and demonstrates that the prognostic and predictive factors operational for symptomatic MS also operate in the asymptomatic phase of RIS.[1-3,6-28] One could therefore predict with relative certainty that the same characteristics at the imaging or biomarker level have the potential to improve our specificity for RIS as well.[25-27]

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Competing interests

CLF has participated in international meetings. Expert in academic boards and Speaker honoraria were either declined or donated to the URRIS research unit, University Cote d'Azur, Nice, France.

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She did not receive any financial compensation for her participation in the scientific committee of the French MS Society, the Revue Neurologique, OFSEP, ARSEP and ECTRIMS apart from travel expenses.

DTO received personal compensation for consulting and advisory services from Alexion, Biogen, Celgene/Bristol Myers Squibb, EMD Serono, Genentech, Genzyme, Janssen Pharmaceuticals, Novartis, Osmotica Pharmaceuticals, RVL Pharmaceuticals, Inc., TG Therapeutics, Viela Bio, Inc., and research support from Biogen and EMD Serono/Merck. Dr Okuda has issued national and international patents and pending patents related to developed technologies. Dr Okuda also received royalties for intellectual property licensed by The Board of Regents of The University of Texas System.

AS received research grants from The Turkish Multiple Sclerosis Society, The Scientific and Technological Research Council of Turkey & Istanbul University-Cerraphasa Research Support Funds. Received honoraria or consultancy fees for participating in advisory boards, giving educational lectures and/or travel and registration coverage for attending scientific congresses or symposia from F. Hoffmann-La Roche Ltd, Sanofi-Genzyme, Alexion, Merck-Serono, Novartis, Biogen Idec/Gen Pharma of Turkey and Abdi Ibrahim Ilaç, Turkey.

CLC reports no competing interest.

CJA has received grant support from the National Multiple Sclerosis Society and the National Institutes of Health (NIH). In the last three years, she has received honoraria or consulting fees from Biogen, Sanofi-Genzyme, Novartis, Genentech, Alexion Pharmaceuticals, Serono, and Horizon Therapeutics for participation on advisory boards and data safety monitoring committees.

LM reports no competing interest.

CCD has received honoraria or consulting fees from Novartis, Sanofi and Merck in the last three years for participation on advisory boards and giving educational lectures.

HZ has no competing interest regarding this study. Unrelated to this study, HZ received personal compensation for consulting, travel and registration coverage for attending scientific congresses from Alexion, BMS, Novartis, Biogen Idec, and Merck, and research grants from Roche.

CL has received a research grant from the ARSEP foundation, Neuratris, and Biogen. In the last three years, she has received honoraria or consulting fees from Biogen, Sanofi-Genzyme, Novartis,

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Roche and Merck.

FDD reports no competing interest.

ELP reports no competing interest.

CB has received consulting honoraria from Alexion, Sanofi, Merck, Biogen, BMS, Novartis, Roche and Teva.

AR personal fees, non-financial support and research grants from Biogen; personal fees and non-financial support from Novartis; personal fees, non-financial support and research grants from Roche; personal fees from Merck; personal fees from Alexion; personal fees from Horizon therapeutics; research grants from Genzyme; outside the submitted work

JC has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Biogen, Novartis, Merck, Sanofi-Genzyme, Roche, BMS, Alexion, Horizon Therapeutics, none related to this study.

DAL has participated in advisory boards for Alexion, Merck, Novartis and Roche in the last three years. Apart from travel expenses, he did not receive any financial compensation for his participation in the scientific committee of OFSEP and ARSEP.

OC reports no competing interest.

GM reports no competing interest.

JDS reports no competing interest.

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NM has no financial conflicts related to this work and has received research funding from the NIH (award number K23NS101099), the National Multiple Sclerosis Society and the Charles H. Hood Foundation.

MT reports no competing interest.

ML reports no competing interest.

MC reports no competing interest.

ET has received honoraria, travel grants, or research grants from the following pharmaceutical

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DP has received consulting honoraria from F. Hoffmann-La Roche, Sanofi-Genzyme, and Novartis.

OHK reports no competing interest.

Supplementary material

Supplementary material is available at *Brain* online.

Appendix 1

Consortium collaborators

Full details are provided in the Supplementary material.

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Figure legends

Figure 1 Flow chart of the cohort.

Figure 2 Kaplan-Meier survival analysis with the endpoint of time to the first acute or progressive event. The graph compares the group with the current definition of 2009-RIS fulfilling 3 or 4 of 4 DIS criteria[5] (green line) with Group 1 fulfilling 1 of 4 DIS criteria[9] (blue line); Group 2 fulfilling 2 of 4 DIS criteria[9] (orange line). There was a difference overall between the survival distributions of Group 1 (DIS 1), Group 2 (DIS 2) and 2009-RIS (DIS 3/4) (p=0.0255). At 2 years, the risk of a clinical event was 13% (event-free survival 87% (95% CI: 43-73) for Group 1 (DIS 1), 14% for group 2 (event-free survival 86% (95% CI: 61-80) for Group 2 (DIS 2) and 16% (event-free survival 84% (95% CI: 79-87) for 2009-RIS. There was no difference between the survival distributions of Group 1 (DIS 1) and Group 2 (DIS 2) (p=0.351). At 2 years, the clinical event-free survival was 87% (95% CI: 76-93) for Group 1 (DIS 1) and 86% (95% CI: 78-91) for Group 2 (DIS 2). At 5 years, the risk of a clinical event was 29% (event-free survival 71% (95% CI: 76-93) for Group 1 (DIS 1), 28% for group 2 (event-free survival 72% (95% CI: 78-91) for Group 2 (DIS 2) and 45% (event-free survival 55% (95% CI: 48-62) for 2009-RIS. There was no difference between the survival distributions of Group 1 (DIS 1) and Group 2 (DIS 2) (p=0.479). At 2 years, the clinical event-free survival was 87% (95% CI: 76-93) for Group 1 (DIS 1) and 86% (95% CI: 79-91) for Group 2 (DIS 2).

Figure 3 Kaplan-Meier survival analysis with the endpoint of time to the first acute or progressive event comparing the current definition of 2009-RIS fulfilling 3 or 4 of 4 DIS criteria[5] (red line) with risk factors at the index scan. Group 1 and 2 subjects fulfilling 1 or 2 of 4 DIS criteria[9] *AND* (presence of oligoclonal bands *AND* presence of spinal cord lesions) (blue line); Group 1 and 2 subjects fulfilling 1 or 2 of 4 DIS criteria WITHOUT (oligoclonal bands *OR* spinal cord lesions) (green line); Group 1 and 2 subjects fulfilling 1 or 2 of 4 DIS criteria AND (presence of oligoclonal bands *OR* spinal cord lesions) (orange line). There was a difference between survival distributions of group 1/2 WITH OCB AND spinal cord lesion, group 1/2 WITH OCB OR SC lesion, group 1/2 WITHOUT OCB AND SC lesion and RIS (p=0.0319). At 2 years,

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the risk of the clinical event was 24% (event-free survival was 76% (95% CI: 51-89) for group 1/2 WITH OCB AND SC lesion, 18%(event-free survival was 82% (95% CI: 71-89) for group 1/2 WITH OCB OR SC lesion, 10% (event-free survival was 90% (95% CI: 78-95) for group 1/2 WITHOUT OCB AND SC lesion and 16% (event-free survival was 84% (95% CI: 79-87) for 2009-RIS. At 5 years, the risk of the clinical event was 34% (event-free survival was 62% (95% CI: 35-80) for group 1/2 WITH OCB AND SC lesion, 24% (event-free survival was 76% (95% CI: 51-89) for group 1/2 WITH OCB OR SC lesion, 13% (event-free survival was 87% (95% CI: 74-94) for group 1/2 WITHOUT OCB AND SC lesion and 42% (event-free survival was 58% (95% CI: 50-64) for 2009-RIS.

Figure 4 Kaplan-Meier survival analysis with the endpoint of time to the first acute or progressive event comparing the current definition of subjects fulfilling 2023 Radiologically Isolated Syndrome Criteria. The orange line represents subjects who fulfilled 2023 RIS criteria or not (blue line); HR 2.24 (1.44-3.46), Log-rank test $p<0.001$.

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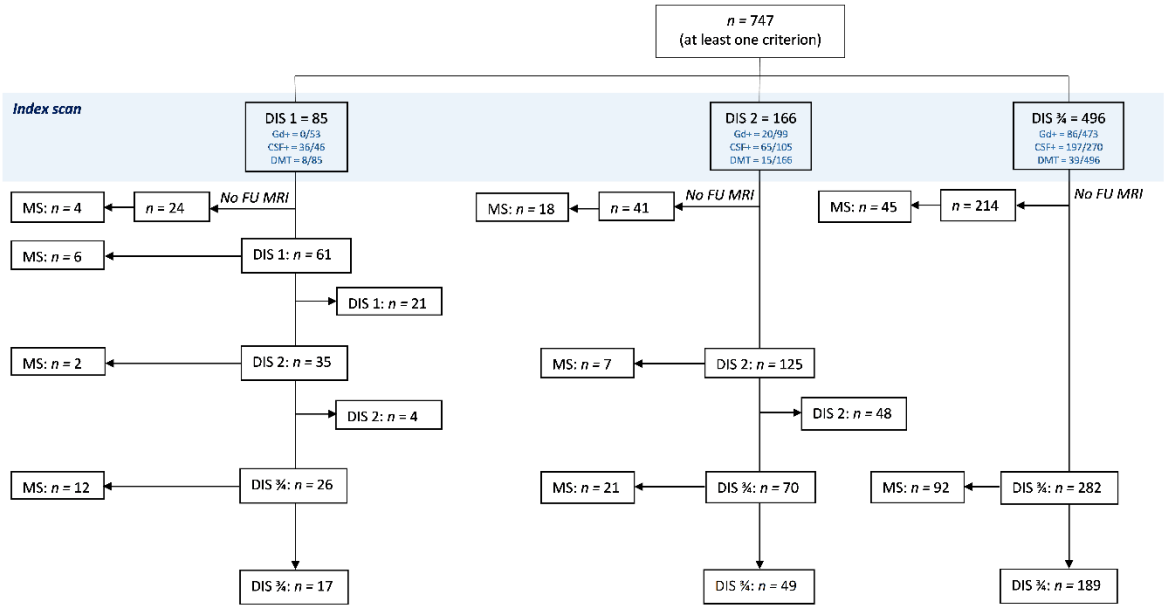
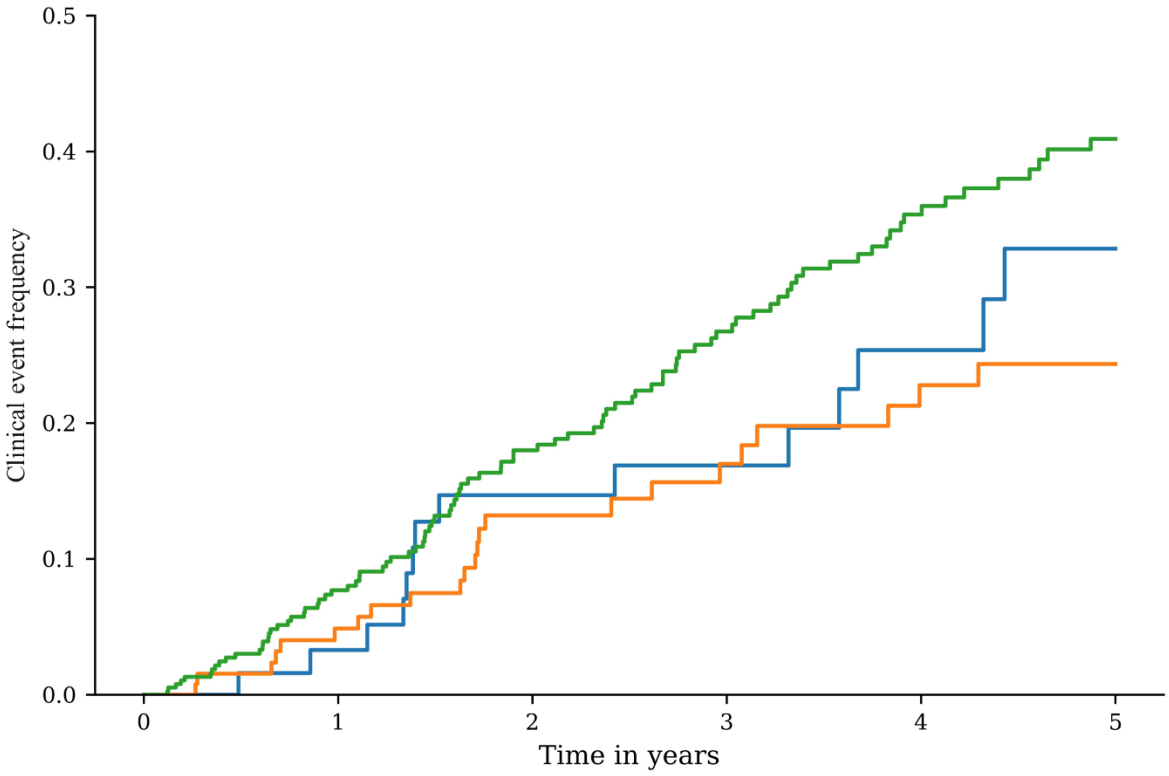
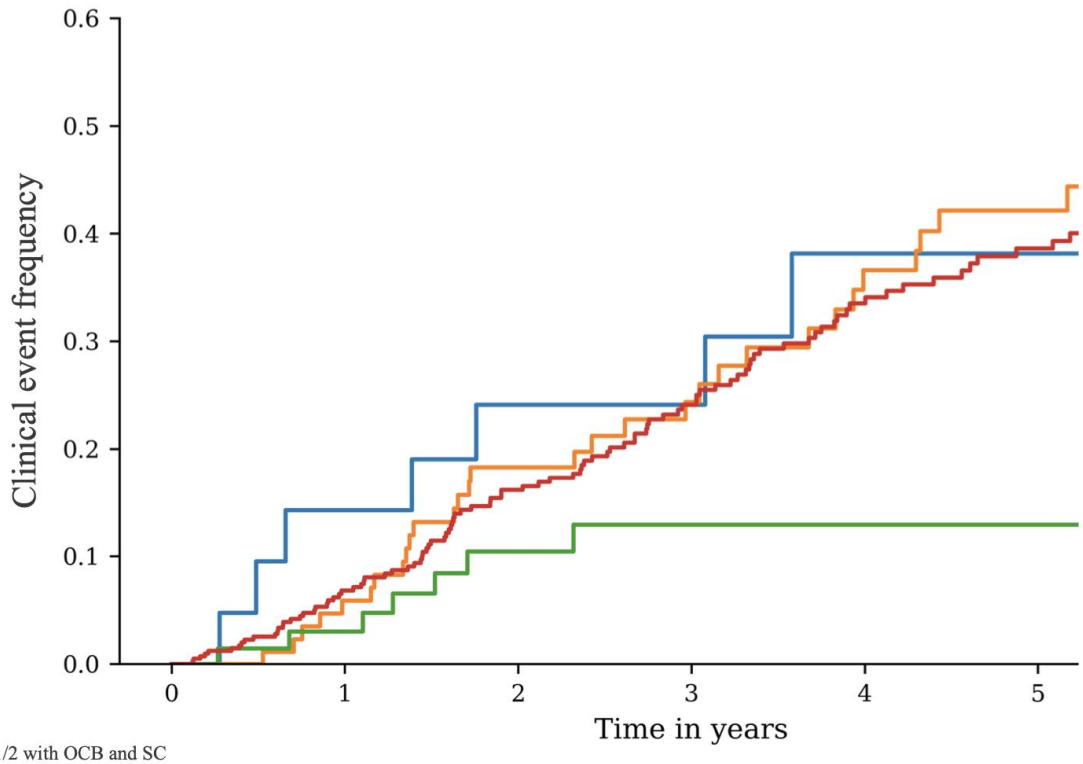


Figure 1
159x86 mm (x DPI)



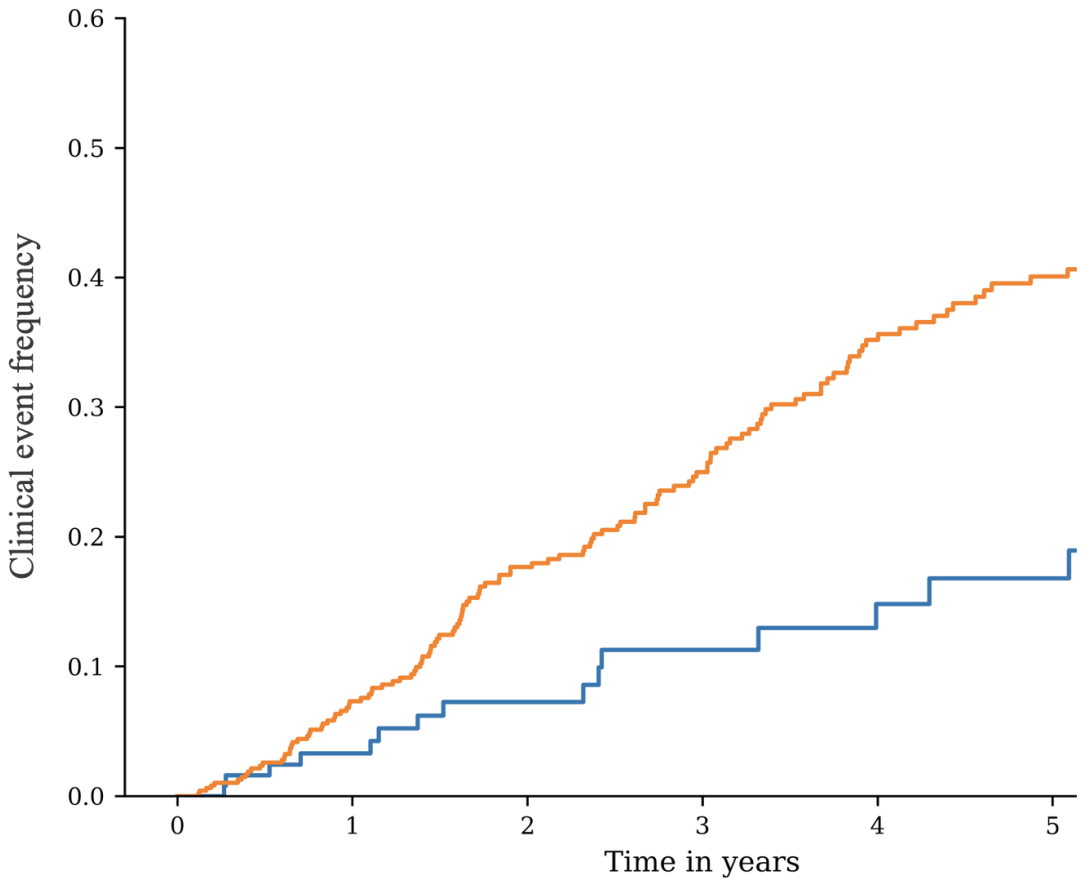
Group 1						
At risk	70	54	42	30	24	0
Censored	7	21	27	38	41	63
Events	0	2	8	9	12	14
Group 2						
At risk	136	112	79	60	51	0
Censored	12	30	54	70	75	125
Events	0	6	15	18	22	23
Group 3						
At risk	385	274	197	147	106	0
Censored	70	155	205	236	261	359
Events	0	26	53	72	88	96

Figure 2
159x144 mm (x DPI)



Group 1/2 with OCB and SC						
At risk	21	18	14	12	8	7
Censored	0	0	2	4	6	7
Events	0	3	5	5	7	7
Group 1/2 with BOC or SC						
At risk	98	79	59	45	35	27
Censored	3	17	27	37	40	45
Events	0	5	15	19	26	29
Group 1/2 without OCB and SC						
At risk	76	58	41	30	26	21
Censored	16	32	45	55	59	64
Events	0	2	6	7	7	7
Group 3						
At risk	416	305	224	167	119	87
Censored	69	155	209	247	276	300
Events	0	25	52	71	90	98

Figure 3
159x156 mm (x DPI)



Revised RIS criteria fulfilled						
At risk	135	105	76	55	46	39
Censored	19	45	70	88	95	101
Events	0	4	8	11	13	14
Revised RIS criteria not fulfilled						
At risk	490	369	272	207	149	111
Censored	69	158	218	261	293	321
Events	0	32	69	91	117	127

Figure 4
159x147 mm (x DPI)

Table 1 Main clinical and MRI characteristics of the whole cohort and subgroups defined according to fulfilling dissemination in space (DIS)[5] at index scan

Variables	Total Cohort	Group 1 (1/4 DIS location criterion)	Group 2 (2/4 DIS location criteria)	2009-RIS (3 or 4 /4 DIS criteria)	*P* [b]
n (%)[a]	*n* = 747	*n* = 85	*n* = 166	*n* = 496	
Age<37	365/747 (48.86%)	54/85 (63.5%)	95/166 (57.2%)	216/496 (43.6%)	<0.001
Female Sex	539/747 (72.2%)	51/85 (60.0%)	127/166 (76.5%)	354/496 (71.4%)	0.015
Positive Family History of MS	71/559 (12.7%)	7/63 (11.1%)	17 /141 (12.1%)	47 /355 (13.2%)	0.865
Reason for index MRI not available	65/747 (8.7%)	16/85 (18.8%)	6/166 (3.6%)	43/496 (8.7%)	<0.001
Documented Reason for index MRI					
Headache	239/682 (35.0%)	28 /69 (40.5%)	61/160 (38.1%)	150/453 (33.1%)	0.101
Ear-Nose-Throat	109/682 (16.0%)	10/69 (14.5%)	21/160 (13.1%)	78/453 (17.2%)	
Mood disorders	53/682 (7.8%)	6/69 (8.7%)	11/160 (6.9%)	36/453 (7.9%)	
Ophthalmological	45/682 (6.6%)	4/69 (5.8%)	8/160 (5.0%)	33/453 (7.3%)	
Endocrinopathy	35/682 (5.1%)	3/69 (4.3%)	5/160 (3.1%)	27/453 (6.0%)	
Trauma	35/682 (5.1%)	4/69 (5.8%)	8/160 (5.0%)	23/453 (5.1%)	
≥ 1 Contrast-enhancing lesion on an index scan	106/623 (17.0%)	0 /53 (0%)	21/100 (21%)	85/470 (18.1%)	0.002
CSF positive for oligoclonal bands	293/408 (71.8%)	36/46 (78.2%)	65/105 (61.9%)	197/257 (76.6%)	0.013
Follow-up duration, Months (Mean ± SD)	46.79 ± 45.44	52.74 ± 45.53	56.70 ± 53.81	42.05 ± 41.22	<0.001
Disease-modifying treatments initiated before clinical event	62/747 (8.3%)	8/85 (9.4%)	15/166 (9.0 %)	39/496 (7.9%)	<0.001
Number of clinical events (CIS or PPMS) during follow-up	207 / 747 (27.7%)	24 / 85 (28.2%)	46 / 166 (27.7%)	137 / 496 (27.6%)	0.099

DIS = Dissemination in space, CSF = cerebrospinal fluid, RIS = Radiologically isolated syndrome, CIS = Clinically isolated syndrome, PMS = Primary progressive MS onset.

[a] Percentages represent data availability as not all individuals had all data available.

[b] The following statistics are used as appropriate to compare Group 1, Group 2 and RIS: The association between Groups and variables was tested with the Chi-squared test. The alpha risk was set to 0.05. The Shapiro-Wilk test and Levene's test assessed the normality and heteroskedasticity of data. The difference between Follow-up (months) according to modalities of DIS at baseline was assessed with the Mann-Whitney. The alpha risk was set to 5% ($\alpha = 0.05$).

Table 2 Predictors of a clinical event during follow-up between Groups 1-2 and 2009-RIS at index scan

Variables	Group 1-2		2009-RIS (3 or 4 /4 DIS criteria)		Survivals' comparison between 2009-RIS and Group 1-2 associated with variable of interest	
	HR (95% C.I)	p[a]	HR (95% C.I)	p[a]	HR (95% C.I)	p[a]
Age< 37	1.05 [0.63; 1.75]	0.856	2.13 [1.46; 3.09]	<0.001		
Female Sex	0.68 [0.41; 1.15]	0.150	0.57 [0.39; 0.85]	0.005		
Positive Family History of MS	0.99 [0.45; 2.20]	0.987	0.88 [0.50; 1.55]	0.665		
Headache as a reason for index MRI[b]	0.90 [0.54; 1.51]	0.697	1.16 [0.81; 1.68]	0.412		
CSF positive for oligoclonal bands	2.39 [1.14; 5.01]	0.021	1.23 [0.73; 2.06]	0.443	0.97 [0.67; 1.41]	0.886
Presence of Spinal cord lesion(s)	2.76 [1.30; 5.87]	0.008	1.70 [1.05; 2.74]	0.032	1.43 [0.92; 2.24]	0.116
Contrast-enhancing lesion(s) on index scan	0.83 [0.30; 2.28]	0.712	1.90 [1.26; 2.87]	0.002		
New T2 lesion(s) on follow-up scans obtained before clinical event (CIS or PPMS) confirming DIT	3.91 [1.22; 12.51]	0.022	1.85 [1.14; 3.01]	0.014	0.76 [0.54; 1.06]	0.100
Contrast enhancing lesion(s) on follow-up scans obtained before clinical event (CIS or PPMS)	1.46 [0.70; 3.05]	0.308	1.46 [0.94; 2.27]	0.090		

DIS = Dissemination in space, CSF = cerebrospinal fluid, RIS = Radiologically isolated syndrome, CIS = Clinically isolated syndrome, PMS = Primary Progressive MS onset, DIT = Dissemination in time.

[a]Following statistics are used as appropriate to compare Group 1-2 and RIS in the univariate analysis. The association between the occurrence of a clinical event and variables were tested with the univariate Cox regression analysis test. The alpha risk was set to 0.05.

[b]Headache is chosen as the most common reason for MRI to enter as a variable in the analyses

Table 3 Performances analysis of 2009 and 2023 RIS criteria

	2009 RIS criteria		2009 RIS criteria not fulfilled		2017 DIS criteria only		2023 RIS criteria
	At least three of the following: ≥9 T2 or ≥1 gadolinium-enhancing lesions ≥1 Juxtacortical lesion ≥1 Infratentorial lesion ≥3 periventricular lesions				At least two of the following: ≥1 Juxtacortical lesion ≥1 Infratentorial lesion ≥1 periventricular lesion ≥1 spinal cord lesion		Fulfillment of 2005 DIS criteria or At least one lesion in one typical location[a] associated with two of the three following risk factors: Spinal cord lesion Positive OCB status New asymptomatic T2 or gadolinium-enhancing lesion during follow-up (DIT)
	Without risk factors	With risk factors	Without risk factors	With risk factors	Without risk factors	With risk factors	
No of analyzed patients	*n* = 299	*n* = 238	*n* = 299	*n* = 292	*n* = 299	*n* = 292	*n* = 288
Sensitivity	66.9 [61.2;72.1]	49.1 [42.7; 55.6]	33.1 [25.7; 41.2]	31.3 [24.0; 39.4]	22.2 [16.8; 28.5]	21.8 [14.5; 30.7]	86.0 [79.4; 91.1]
Specificity	45.3 [39.8; 50.9]	68.5 [62.3; 74.2]	54.7 [46.3; 62.9]	74.6 [66.7; 81.6]	66.7 [56.6; 75.7]	78.8 [65.3; 88.9]	35.4 [28.0; 43.3]
Positive predictive value	55.5 [48.0; 62.8]	58.9 [48.4; 68.9]	42.7 [35.9; 49.9]	56.6 [47.5; 57.2]	57.5 [48.2; 66.3]	68.6 [53.7; 80.4]	55.4 [52.1; 58.6]
Negative predictive value	57.3 [47.8; 66.4]	59.4 [50.9; 67.6]	44.5 [40.0; 49.1]	50.7 [47.1; 54.3]	29.7 [26.6; 33.0]	32.3 [28.6; 36.2]	73.1 [63.4; 80.9]
Accuracy	56.2 [50.4; 61.9]	59.2 [52.7; 65.5]	43.8 [38.1; 49.6]	52.4 [46.5; 58.2]	36.9 [31.5; 42.5]	40.1 [32.5; 48.1]	59.8 [54.1; 65.3]
AUC	56.1 [50.2; 61.8]	58.8 [52.3; 65.2]	43.9 [38.2; 49.8]	53.0 [47.1; 58.8]	44.4 [38.8; 50.2]	50.3 [42.4; 58.3]	60.7 [55.0; 66.2]

[a]At least 1 juxtacortical lesion, or at least 1 periventricular lesion, or at least 1 infratentorial lesion, or at least 1 spinal cord lesion.

Table 4 Radiologically Isolated Syndrome Criteria[a]

2009 RADIOLOGICALY SYNDROME CRITERIA	2023 RADIOLOGICALY SYNDROME CRITERIA
A. The presence of incidentally identified CNS white matter anomalies meeting the following MRI criteria: 1. Ovoid, well-circumscribed, and homogeneous foci with or without involvement of the corpus callosum 2. T2-hyperintensities measuring > 3 mm and fulfilling Barkhof criteria (3 of 4) for dissemination in space CNS anomalies not consistent with a vascular pattern B. No historical accounts of remitting clinical symptoms C. MRI anomalies do not account for clinically apparent impairments D. MRI anomalies are not due to the direct physiological effects of substances E. Exclusion of MRI phenotypes suggestive of leukoaraiosis or extensive WM pathology lacking involvement of the corpus callosum F. MRI anomalies not better accounted for by another disease process	**I.** RADIOLOGICAL CRITERIA A. MRI with incidental CNS white matter anomalies demonstrating radiological characteristics highly suggestive of demyelinating disease and meeting the following criteria: 1. ovoid, well-circumscribed, and homogeneous foci > 3mm^2 with or without the involvement of the corpus callosum 2. involvement of periventricular, juxtacortical, infratentorial, and spinal cord regions 3. anomalies inconsistent with a microvascular or non-specific white matter disease pattern WITH B. Index MRI fulfilling 3 or 4 out of 4 dissemination in space criteria according to the 2005 multiple sclerosis diagnostic imaging criteria. OR C. Index MRI fulfilling at least one of 4 dissemination in space requirements, additionally fulfilling 2 of the following: 1. presence of abnormal cerebrospinal fluid-restricted oligoclonal bands 2. presence of at least one spinal cord lesion consistent with inflammatory demyelination 3. evidence of dissemination in time on any follow-up MRI defined by the presence of one or more new T2-weighted hyperintensities or gadolinium enhancement typical for MS[c] **II.** EXCLUSION CRITERIA A. No historical account of relapsing-remitting or progressive clinical symptoms consistent with neurological dysfunction B. MRI anomalies or neurological examination findings do not account for clinically apparent impairment(s) to the individual C. Another disease process has not been identified to better account for the CNS MRI anomalies.

[a]Complementary expert recommendation: Multiple Sclerosis specialty-trained Neurologists to apply these criteria.
[b]At least 1 juxtacortical lesion, or at least 1 periventricular lesion, or at least 1 infratentorial lesion, or at least 1 spinal cord lesion.
[c]Within the brain if a single spinal cord focus was the original incidental anomaly identified.