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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.

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

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

14
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26

1 **Running Title:** Radiologically isolated syndrome diagnosis

2

3 **Keywords:** radiologically isolated syndrome; MRI; multiple sclerosis; diagnostic criteria;
4 prognosis

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

10

11 **Introduction**

12 The radiologically isolated syndrome (RIS) is identified by the incidental discovery of central
13 nervous system (CNS) white matter T2-weighted hyperintense foci on magnetic resonance
14 imaging (MRI) that demonstrate morphological and spatial characteristics highly typical of MS
15 but without clinical symptomatology related to inflammatory demyelination.¹⁻³ Clinical and
16 radiological features are known as RIS without a better explanation. Current RIS Criteria use
17 the dissemination in space (DIS) requirement from the 2005 McDonald criteria⁴, requiring 3 or
18 4 of four imaging criteria to be met.⁵

19 The 2009 RIS criteria¹, when accurately applied, have been validated and shown to predict
20 evolution to a first clinical attack at a rate of 34% at five years, increasing to 51% at ten years.^{6,7}

21 A direct transition to primary progressive multiple sclerosis (PPMS) has also been observed.⁸

22 Inspired by the proposed 2017 revisions to the McDonald criteria for multiple sclerosis⁹, other

23 suggested diagnostic criteria for RIS have been recently introduced without supportive clinical
24 evidence and value as experts' recommendations.¹⁰ Using the 2009 RIS Criteria within a

25 prospective cohort, we recently confirmed the influence of age, the presence of spinal cord lesions,
26 and gadolinium-enhancing lesions on the index scan as risk factors for evolution to symptomatic

27 multiple sclerosis.¹¹ Previously, the study of an international cohort had established the validity of

28 fulfilling DIS 2005 by 3 or 4 of 4 imaging criteria in RIS⁶⁻⁸, defined by 3 or 4 of 1) more than 9

29 T2 lesions or one gadolinium-enhancing lesion, 2) At least one juxtacortical lesion, 3) At least 3

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

8 In this study, we present the natural history of asymptomatic individuals with MRI anomalies
9 highly typical of multiple sclerosis but that fall short of fulfilling 2009 RIS/2005 DIS criteria on
10 MRI^{1,4,5} and evaluate the temporal course of their clinical evolution when previously identified
11 prognostic factors in RIS are applied. We confirm that the addition of the risk factors identified in
12 our multiple studies^{1,2,3,6,7,11} increases the risk of symptomatic evolution in these individuals to
13 rates similar to 2009 RIS, validating the need to include these individuals in the diagnostic
14 spectrum of RIS. Finally, we present validated revisions to the original criteria described in 2009.¹
15 These data should allow for earlier identification of presymptomatic subjects, which impacts
16 clinical care and subject enrollment in therapeutic trials in RIS.

17

18 **Materials and methods**

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

25

26 **Study criteria**

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

1 neurological anomalies or history suggestive of multiple sclerosis according to the 2009 RIS
2 criteria¹, an international expert group (CLF, MC, CLC, FDD, LM, DTO, OHK, CJA, NM, DP,
3 AS, JC) validated constitutive elements of the RIS criteria, including double-centralized MRI
4 reading. Brain and spinal cord MRIs collected from 37 multiple sclerosis expert sites
5 (*Supplementary Table 1*) were coded for DIS lesion location criteria from four regions: (1)
6 periventricular; (2) juxtacortical; (3) infratentorial; (4) spinal cord, lesion number for each
7 location, and the presence of contrast-enhancing lesions. Longitudinal clinical follow-up and
8 imaging data were collected using standardized protocols within participating centres to
9 accommodate different medical and insurance practices across multiple countries and healthcare
10 systems.

11

12 **Brain and spinal cord MRI protocols**

13 The strategy was to collect all subjects with an initial brain MRI that revealed incidental
14 anomalies suggestive of demyelinating disease. Imaging studies were conducted on 1.5 Tesla
15 (T) or 3T MRI units from different manufacturers. The multicenter nature of the research and
16 the various MRI motives did not allow the standardization of sequences for the index scan. The
17 most frequent sequences performed were 3D T1-weighted with and without contrast-enhanced
18 imaging, diffusion-weighted imaging, gradient-echo T2 or susceptibility-weighted imaging, and
19 2D or 3D fluid-attenuated inversion recovery (FLAIR). If available, spinal cord imaging
20 protocols were also collected, including T1- and T2-weighted sequences in axial and sagittal
21 planes, with or without gadolinium. Follow-up MRIs were obtained at intervals according to
22 local practice, clinician judgement, and clinical MRI protocols.

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

1 requirements for RIS by 2009 Criteria¹).

2

3 **Statistical analysis**

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

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

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

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

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

10

11 **Standard protocol approvals, registrations, and patient consent**

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

17

18 **Data availability**

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

21

22 **Results**

23 **Demographic and clinical characteristics at index scan**

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

1 *Supplementary Table 2* summarize primary baseline demographic, clinical, and MRI features.
2 The study cohort was primarily women [n=539 (72.2%)] with a slight underrepresentation in
3 Group 1 (p=0.015). The mean (\pm SD) clinical follow-up time was 46.8 (\pm 45.4) months. Seventy-
4 one subjects (12.7%) had a family history of multiple sclerosis, with a similar distribution in the
5 three groups (p=0.865). The mean age of the whole cohort at the index scan was 37.7 years (\pm 12.3);
6 Group 1 and 2 subjects were, on average, three years younger than 2009-RIS subjects (p<0.001).
7 Of the 42 subjects (5.6%) who were identified before age 18, 22 were in Group 2 (8.8%), and 20
8 were in the 2009-RIS group (4.0%). Reasons for the index scan were available for 682 subjects
9 (91.3%) and were similar between the three groups (p=0.101) (*Table 1*). However, of the 65 (8.7%)
10 individuals in whom the reason for index MRI was not available, they were more likely to be in
11 Group 1 (p<0.001).

12 CSF analysis was performed in 408 of 747 (54.6%) subjects. It was consistent with intrathecal
13 inflammation (presence of at least two unique oligoclonal bands and/or an IgG index > 0.7) in
14 71.8% overall (78.2% in Group 1, 61.9% in Group 2, and 76.6% in 2009-RIS, p=0.013). OCBs
15 were more likely to be present in the 2009-RIS Group (n=197/257, 76.6%) compared to Groups
16 1-2 (n=101/151, 66.9%), [OR: 1.63 (CI:1.04-2.54), p=0.042].

17 Some subjects (62/747, 8.3%) were treated with immunoactive drugs during the RIS follow-up.
18 The log-rank parametric test to estimate different survival probabilities were not statistically
19 different without treated subjects (p=0.0178) and with DMT (p=0.082). In multivariate analysis,
20 the probability of presenting a clinical event of Groups 1 and 2 compared to the 2009-RIS Group
21 with or without including treated subjects was respectively: Group 1: HR 0.78 (0.50; 1.21) p=0.257
22 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
23 2: HR 0.59 (0.40; 0.86) p=0.006.

24

25 **Imaging characteristics**

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

1 1.33 (+ 0.92) for Group 2, and 1.08 (+0.73) for 2009-RIS.

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

6 Data on the presence or absence of gadolinium-enhancing lesions at baseline were available
7 for 623 (83.4%). Contrast enhancement on the index MRI was observed in 106 subjects
8 (17.0%), mainly in 2009-RIS: $n=85$ (18.1%). Gadolinium-enhancing lesions were not
9 different between Group 2 and the 2009-RIS Group at baseline ($p=0.190$) but were
10 undetectable in Group 1 ($p=0.003$). Data on gadolinium-enhancing lesions on follow-up scans
11 were available for 331 subjects, with 130 (39.3%) having enhancing lesions at one point after
12 the index scan (*Supplementary Table 2*).

13

14 **Evolution to Clinical Events**

15 **Whole Cohort**

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

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

22 After two years, a higher proportion of subjects in the 2009-RIS Group (52/276; 18.8%) developed
23 multiple sclerosis compared to those in Group 1 (8/58, 13.8%) or Group 2 (18/106, 17.0%). After
24 five years, this difference was accentuated while the risk of a clinical event was 33.8% (95% CI:
25 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)
26 for 2009-RIS.

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

1 Groups 1 and 2 to look at the survival rates and compare them against the 2009-RIS Group.
2 At five years, 29.0% of Group 1-2 and 38.7% of the 2009-RIS Group presented with a clinical
3 event, respectively ($p=0.002$).

4 5 **Additional Risk Factors**

6 *Table 2 summarizes* the covariates analyzed for the risk of a clinical event in Group 1-2
7 compared with the 2009-RIS Group. Clinical factors at the index MRI scan associated with an
8 increased risk of a first clinical event in the 2009-RIS Group were age <37 years [HR: 2.13 (CI:
9 1.46-3.09), $p<0.001$], male gender [HR: 1.75 (CI: 1.18-2.59), $p=0.005$], the presence of baseline
10 T1-gadolinium-enhancing lesions [HR: 1.90 (CI: 1.26-2.87), $p=0.002$], and the presence of
11 baseline spinal cord lesions [HR: 1.70 (CI: 1.05-2.74), $p=0.032$].

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

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

21 There was a difference between the survival distribution of patients presenting CSF-restricted
22 OCBs compared to those without OCBs in the whole cohort [HR: 1.60 (CI: 1.05-2.42),
23 $p=0.0276$], with a higher risk for Group 1-2 subjects [HR: 2.39 (CI: 1.14-5.01), $p=0.0205$],
24 whereas it did not impact clinical occurrence in the 2009-RIS Group [HR: 1.23 (CI: 0.73-2.06),
25 $p=0.443$].

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

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

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

10 The demonstration of dissemination in time (DIT) on follow-up scans, with new T2 lesions [HR:
11 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
12 Group 1-2], was significantly associated with the risk of evolution to a clinical event (*Table 2*).

13 There was no difference between Group 1-2 subjects who presented DIT on a follow-up scan
14 regarding the risk of a clinical event compared with 2009-RIS (p=0.920) (*Supplementary Fig.*
15 *5*).

16

17 **Performance Analysis**

18 The sensitivity, specificity, positive and negative predictive values, accuracy, and AUCs for
19 various iterations of RIS diagnostic criteria (calculated within subjects that had at least five years
20 of follow-up) are given in *Table 3*. A more robust specificity was demonstrated for any RIS
21 criteria with at least two risk factors [68.5% (62.3%-74.2%) and 74.6% (66.7%-81.6%)].

22 According to our findings, 2009-RIS subjects or those who do not fulfil 2009-RIS criteria
23 (Group 1-2) on the index scan but meet at least 2 of the risk factors for a clinical event (OCBs,
24 spinal cord lesion or DIT on MRI in follow-up), demonstrate a sensitivity of 86.0% (79.4%-
25 91.1%). The positive predictive value was higher for the 2009-RIS criteria with risk factors
26 [58.9% (48.4%-68.9%)], as well as the negative predictive value [59.4% (48.4%-68.9%)] *versus*
27 [50.7% (47.1%-54.3. The area under the curve was higher for the 2009 RIS-Group with risk
28 factors [58.8% (52.3%-65.2%)] than for Group 1-2 without risk factors [53.0% (47.1%-58.8%)].

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

1 predictive value [73.1% (63.4%-80.9%)], accuracy [59.8% (54.1%-65.3%)], and AUC [60.7%
2 (55.0%-66.2%)]. Positive predictive value [55.4% (52.1; 58.6)] and specificity [35.4% (28.0;
3 43.3)] were lower since the number of group 1-2 patients who did not convert during the follow-
4 up was smaller than all the converted subjects.

6 **Proposed revisions to the RIS diagnostic criteria**

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

12 In clinical practice, if the patient does not fulfil 2009-RIS criteria on the index scan, our proposed
13 updated RIS criteria could be fulfilled at the time of diagnosis with at least one brain T2 lesion in
14 predefined locations, a positive CSF study and the presence of spinal cord lesions. If only one of
15 these risk factors is present, then one should wait for the demonstration of DIT in any location on
16 any follow-up scans to diagnose RIS (*Fig. 4*). At 5 years, the risk stratification for presenting a
17 clinical event is less than 10% RIS Subjects with 1 or 2 lesions in two locations without risk factor,
18 16% with 1 risk factor, and nearly 50% with more than 2 risk factors, as for Group 3 2009-RIS
19 (*Supplementary Fig. 5*).

21 **Discussion**

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

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

10 RIS was defined more than ten years ago, with the 2009 diagnostic criteria validated
11 worldwide.^{1,6} Since then, the search for optimal clinical, biological, and radiological markers
12 that predict the risk of disease activity and, more precisely, the occurrence of clinical
13 symptoms has been ongoing. The longest published observational study extends to 10 years
14 of follow-up, with 51% of individuals predicted to experience clinical signs consistent with
15 acute or progressive disease.^{7,8} Across several prospective, observational studies, risk factors
16 for symptomatic conversion include younger age, presence of CSF-restricted OCBs, and
17 infratentorial or spinal cord lesions on index MRI^{6,7,17}, and the presence of gadolinium-
18 enhancing lesions at the index scan.¹¹ Throughout the past decade of studying RIS, we have
19 periodically encountered patients with typical CNS demyelinating lesions on MRI who fell
20 short of the original RIS criteria. Here, we find that RIS can also be reliably diagnosed in
21 subjects who only meet one or two 2005 DIS criteria or fulfilling the currently used DIS
22 criteria for multiple sclerosis⁹ but also have CSF-unique OCBs, gadolinium-enhancing and
23 spinal cord lesions on baseline imaging, and new T2 or gadolinium-enhancing lesions on
24 follow-up imaging. This highlights the importance of regular, thorough MRI follow-up and
25 longitudinal changes. The subsequent occurrence of a clinical event with a history of prior
26 radiological advancement underscores the significance of this finding.

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

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

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

12 Around the time of the index scan, adding OCBs and spinal cord lesions increases specificity and
13 accuracy while reducing sensitivity, as already demonstrated in pediatric RIS.¹⁹ These
14 observations are aligned to preserve diagnostic specificity, particularly in the context of RIS, where
15 clinical symptomology is lacking.²⁰⁻²² This issue is mainly present in subjects fulfilling less than 3
16 of 4 Criteria for DIS. For example, suppose CSF analysis is not available at the time of the index
17 scan. In that case, identification of risk factors will rely on spinal cord lesions at diagnosis and DIT
18 on follow-up scans only. We, therefore, strongly recommend the supportive evidence of CSF
19 studies at the time of diagnosis to improve specificity. In these individuals, the low particularity
20 of brain MRI alone without additional risk factors should prompt clinicians to exercise even more
21 caution regarding the possibility of RIS overdiagnosis.²⁰⁻²² Although not available in our dataset,
22 we expect that future imaging diagnostic criteria for RIS and multiple sclerosis may include
23 additional imaging modalities such as central vein imaging, paramagnetic rims, and 3-dimensional
24 conformational characteristics to increase the specificity for CNS demyelinating lesions²³⁻²⁵ or
25 biological markers such as neurofilament light chain.²⁶ Since our data reflect measures from real-
26 world clinical practice, the uniform and systematic collection of these and other promising
27 biomarkers was impossible. Including such measures in the future should be aligned with future
28 embodiments of the multiple sclerosis diagnostic criteria.

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

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

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

15 Our study has limitations. There was sufficient follow-up to draw meaningful conclusions (mean
16 follow-up time, 3.8 years). However, the total sample size did not allow for sub-analyses of
17 minimum follow-up times. Not all subjects underwent a baseline spinal cord MRI scan and lumbar
18 puncture evaluation, as is often the case in real-world clinical studies. Whether to include spinal
19 cord MRI and CSF analysis in the routine diagnostic RIS workup varies among clinicians. We did
20 not exclude the subjects without CSF or spinal cord MRI data to avoid selection bias. As such,
21 while our findings reflect more on the reality of the current clinical practice and not standardized
22 MRI protocols, they are open to some biases. Therefore, we did perform sub-analyses accounting
23 for this variability in clinical practice, and specificity and sensitivity did not differ from the whole
24 cohort. We also initially included subjects exposed to DMT at the RIS stage for the same reasons.

25 Our proposed revised RIS criteria have low specificity as they combine the 2009 RIS Group and
26 Group 1-2 with risk factors. The specificity increases in scenarios where at least two risk factors,
27 either from 2009-RIS criteria or Group 1-2 subjects, are added, resulting in a higher AUC. This is
28 explained by the low number of patients with enough follow-up data and no risk factors and the
29 inclusion of fewer than 20 individuals classified as negative within the revised RIS criteria.

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

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

17

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25 **Competing interests**

26 CLF has participated in international meetings. Expert in academic boards and Speaker honoraria
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1 She did not receive any financial compensation for her participation in the scientific committee of
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17 CLC reports no competing interest.

18 CJA has received grant support from the National Multiple Sclerosis Society and the National
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22 LM reports no competing interest.

23 CCD has received honoraria or consulting fees from Novartis, Sanofi and Merck in the last three
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25 HZ has no competing interest regarding this study. Unrelated to this study, HZ received personal
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28 CL has received a research grant from the ARSEP foundation, Neuratris, and Biogen. In the last
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3 ELP reports no competing interest.

4 CB has received consulting honoraria from Alexion, Sanofi, Merck, Biogen, BMS, Novartis,
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13 DAL has participated in advisory boards for Alexion, Merck, Novartis and Roche in the last three
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16 OC reports no competing interest.

17 GM reports no competing interest.

18 JDS reports no competing interest.

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26 MC reports no competing interest.

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4 OHK reports no competing interest.
5

6 **Supplementary material**

7 Supplementary material is available at *Brain* online.
8

9 **Appendix 1**

10 **Consortium collaborators**

11 Full details are provided in the Supplementary material.
12

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11 Naila Makhani, Darin T. Okuda.

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13 **References**

- 14 1. Okuda DT, Mowry EM, Beheshtian A, et al. Incidental MRI anomalies suggestive of multiple
15 sclerosis: the radiologically isolated syndrome. *Neurology* 2009; 72(9): 800-5.
- 16 2. Lebrun C, Bensa C, Debouverie M, Wiertlevski S, Brassat D, deSeze J, et al on behalf CFSEP.
17 Association between clinical conversion to multiple sclerosis in radiologically isolated
18 syndrome and magnetic resonance imaging, cerebrospinal fluid, and visual evoked potential:
19 follow-up of 70 patients. *Arch Neurol* 2009; 66(7), 841-846.
- 20 3. Siva A, Saip S, Altintas A, Jacob A, Keegan BM, Kantarci OH. Multiple sclerosis risk in
21 radiologically uncovered asymptomatic possible inflammatory-demyelinating disease. *Mult*
22 *Scler* 2009; 15(8): 918-27.
- 23 4. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005
24 revisions to the "McDonald Criteria". *Ann Neurol* 2005; 58(6), 840–846.
- 25 5. Barkhof F, Filippi M, Miller DH, et al. Comparison of MRI criteria at first presentation to
26 predict conversion to clinically definite multiple sclerosis. *Brain* 1997;120:2059-2069.

- 1 6. Okuda DT, Siva A, Kantarci O, et al. Radiologically Isolated Syndrome: 5-Year Risk for an
2 Initial Clinical Event. *PLoS ONE* 2014; 9(3), e90509. doi:10.1371/journal.pone.0090509.s005.
- 3 7. Lebrun C, Kantarci O, Siva A, Sormani MP, Pelletier D, Okuda D and the 10 years RISC Group
4 on behalf of SFSEP and OFSEP. Radiologically Isolated Syndrome: 10-Year Risk estimate of
5 a clinical event. *Ann Neurol* 2020 ; Jun 4. doi: 10.1002/ana.25799.
- 6 8. Kantarci OH, Lebrun C, Siva A, et al., on behalf of RISC and CFSEP. Primary Progressive
7 Multiple Sclerosis Evolving From Radiologically Isolated Syndrome. *Ann Neurol* 2016
8 Feb;79(2):288-94.
- 9 9. Thompson AJ, Banwell BL, Barkhof F, et al. diagnosis of multiple sclerosis: 2017 revisions of
10 the McDonald criteria. *Lancet Neurol* 2018;17(2):162-173.
- 11 10. De Stefano ND, Giorgio A, Tintore M, et al. Radiologically isolated syndrome or subclinical
12 multiple sclerosis: MAGNIMS consensus recommendations. *Mul Scler* 2017 **24**, 214–221.
- 13 11. Lebrun-Fréney C, Rollot F, Mondot L et al. Risk factors and time to clinical symptoms of
14 multiple sclerosis among patients with a radiologically isolated syndrome. *JAMA Netw Open*.
15 2021;4(10): e2128271. doi:10.1001/jamanetworkopen.2021.28271
- 16 12. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010
17 revisions to the McDonald Criteria. *Ann Neurol* 2011; 69: 292–302.
- 18 13. Okuda DT, Kantarci OH, Lebrun-Frenay C et al. Multi-center, Randomized, Double-blinded
19 Assessment of Dimethyl Fumarate in Delaying the Time to a First Attack in Radiologically
20 Isolated Syndrome. *Ann Neurol* 2022 Nov 18. doi: 10.1002/ana.26555.
- 21 14. Lebrun C, Siva A, Kantarci O, et al., on behalf of RISC and SFSEP. Multicenter, randomised,
22 double-blinded assessment of teriflunomide in extending the time to a first clinical event in
23 radiologically isolated syndrome (RIS): TERIS study. ECTRIMS Online Library. London. Sep
24 14, 2016; 145587.
- 25 15. Zeydan B, Kantarci OH. Progressive forms of multiple sclerosis: distinct entity or age-
26 dependent phenomena. *Neurol Clin* 2018; 36:163-171.
- 27 16. Kantarci O. Phases and phenotypes of multiple sclerosis. *Continuum* 2019; 25:636-654.
- 28 17. Okuda DT, Mowry EM, Cree BA, et al. Asymptomatic spinal cord lesions predict disease

- 1 progression in radiologically isolated syndrome. *Neurology* 2011; 76(8): 686-92.
- 2 18. Zeydan B, Kantarci OH. Impact of Age on Multiple Sclerosis Disease Activity and Progression.
3 *Current Neurology and Neuroscience Reports* 20, 1–7 (2020).
- 4 19. Makhani N, Lebrun C, Siva A et al. Oligoclonal bands increase the specificity of MRI criteria
5 to predict multiple sclerosis in children with radiologically isolated syndrome. *Mult Scler Exp*
6 *Trans Clin* 2019; 5(1), 205521731983666–9. <http://doi.org/10.1177/2055217319836664>.
- 7 20. Lebrun C, Cohen M, Chausseot A, et al. A Prospective Study of Patients with Brain MRI
8 Showing Incidental T2 Hyperintensities Addressed as Multiple Sclerosis: a Lot of Work to do
9 Before Treating. *Neurol Ther* 2014; Dec 13;3(2):123-32. doi:10.1007/s40120-014-0024-7.
- 10 21. Solomon AJ, Bourdette DN, Cross AH, et al. The contemporary spectrum of multiple sclerosis
11 misdiagnosis. A multicenter study. *Neurology* 2016; 87:1393–9.
- 12 22. Calabrese M, Gasperini C, Tortorella C, et al. "Better explanations" in multiple sclerosis
13 diagnostic workup. *Neurology* 2019 ;92(22), e2527–e2537.
- 14 23. Gaitan MI, Yanez P, Padai-Formenti ME et al. SWAN-Venule: An Optimized MRI Technique
15 to Detect the Central Vein Sign in MS Plaques. *AJNR* 2020; **21**, 1039–5.
- 16 24. Suthiphosuwat S, Sati P, Absinta M et al. Paramagnetic Rim Sign in Radiologically Isolated
17 Syndrome. *JAMA Neurol* 2020; 1–3. doi:10.1001/jamaneurol.2020.0124.
- 18 25. Oh J, Suthiphosuwat S, Sati P et al. Cognitive impairment, the central vein sign, and
19 paramagnetic rim lesions in RIS. *Mult Scler* 2021. 1–10 doi:10.1177/13524585211002097.
- 20 26. Okuda DT, Moog T, Mac Creary M et al. Utility of shape evolution and displacement in
21 classifying chronic multiple sclerosis lesions. *Sci Rep* 2020; **10**, 1–8.
- 22 27. Rival, M, Galoppin M & Thouvenot E. Biological Markers in Early Multiple Sclerosis: The
23 Paved Way for Radiologically Isolated Syndrome. *Front Immunol* 2022; **13**, 866092.
- 24 28. Giorgio A, Battaglini M, Rocca MA, et al; MAGNIMS Study Group. The location of brain
25 lesions predicts the conversion of clinically isolated syndromes to multiple sclerosis.
26 *Neurology* 2013;80: 234–41

27

1 **Figure legends**

2 **Figure 1 Flow chart of the cohort.**

3

4 **Figure 2 Kaplan-Meier survival analysis with the endpoint of time to the first acute or**
5 **progressive event.** The graph compares the group with the current definition of 2009-RIS
6 fulfilling 3 or 4 of 4 DIS criteria⁵ (green line) with Group 1 fulfilling 1 of 4 DIS criteria⁹ (blue
7 line); Group 2 fulfilling 2 of 4 DIS criteria⁹ (orange line). There was a difference overall between
8 the survival distributions of Group 1 (DIS 1), Group 2 (DIS 2) and 2009-RIS (DIS 3/4) ($p=0.0255$).
9 At 2 years, the risk of a clinical event was 13% (event-free survival 87% (95% CI: 43-73) for
10 Group 1 (DIS 1), 14% for group 2 (event-free survival 86% (95% CI: 61-80) for Group 2 (DIS 2)
11 and 16% (event-free survival 84% (95% CI: 79-87) for 2009-RIS. There was no difference
12 between the survival distributions of Group 1 (DIS 1) and Group 2 (DIS 2) ($p=0.351$). At 2 years,
13 the clinical event-free survival was 87% (95% CI: 76-93) for Group 1 (DIS 1) and 86% (95% CI:
14 78-91) for Group 2 (DIS 2). At 5 years, the risk of a clinical event was 29% (event-free survival
15 71% (95% CI: 76-93) for Group 1 (DIS 1), 28% for group 2 (event-free survival 72% (95% CI:
16 78-91) for Group 2 (DIS 2) and 45% (event-free survival 55% (95% CI: 48-62) for 2009-RIS.
17 There was no difference between the survival distributions of Group 1 (DIS 1) and Group 2 (DIS
18 2) ($p=0.479$). At 2 years, the clinical event-free survival was 87% (95% CI: 76-93) for Group 1
19 (DIS 1) and 86% (95% CI: 79-91) for Group 2 (DIS 2).

20

21 **Figure 3 Kaplan-Meier survival analysis with the endpoint of time to the first acute or**
22 **progressive event comparing the current definition of 2009-RIS fulfilling 3 or 4 of 4 DIS**
23 **criteria⁵ (red line) with risk factors at the index scan.** Group 1 and 2 subjects fulfilling 1 or 2
24 of 4 DIS criteria⁹ AND (presence of oligoclonal bands AND presence of spinal cord lesions) (blue
25 line); Group 1 and 2 subjects fulfilling 1 or 2 of 4 DIS criteria WITHOUT (oligoclonal bands OR
26 spinal cord lesions) (green line); Group 1 and 2 subjects fulfilling 1 or 2 of 4 DIS criteria AND
27 (presence of oligoclonal bands OR spinal cord lesions) (orange line). There was a difference
28 between survival distributions of group 1/2 WITH OCB AND spinal cord lesion, group 1/2 WITH
29 OCB OR SC lesion, group 1/2 WITHOUT OCB AND SC lesion and RIS ($p=0.0319$). At 2 years,

1 the risk of the clinical event was 24% (event-free survival was 76% (95% CI: 51-89) for group 1/2
2 WITH OCB AND SC lesion, 18%(event-free survival was 82% (95% CI: 71-89) for group 1/2
3 WITH OCB OR SC lesion, 10% (event-free survival was 90% (95% CI: 78-95) for group 1/2
4 WITHOUT OCB AND SC lesion and 16% (event-free survival was 84% (95% CI: 79-87) for
5 2009-RIS. At 5 years, the risk of the clinical event was 34% (event-free survival was 62% (95%
6 CI: 35-80) for group 1/2 WITH OCB AND SC lesion, 24% (event-free survival was 76% (95%
7 CI: 51-89) for group 1/2 WITH OCB OR SC lesion, 13% (event-free survival was 87% (95% CI:
8 74-94) for group 1/2 WITHOUT OCB AND SC lesion and 42% (event-free survival was 58%
9 (95% CI: 50-64) for 2009-RIS.

10

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

15

16

17

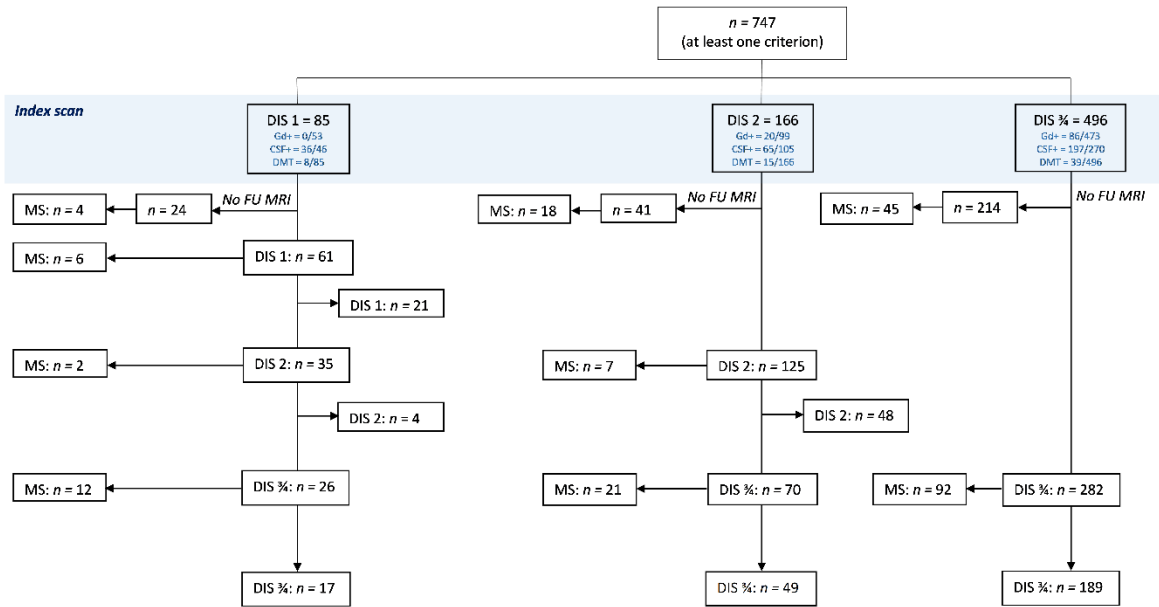
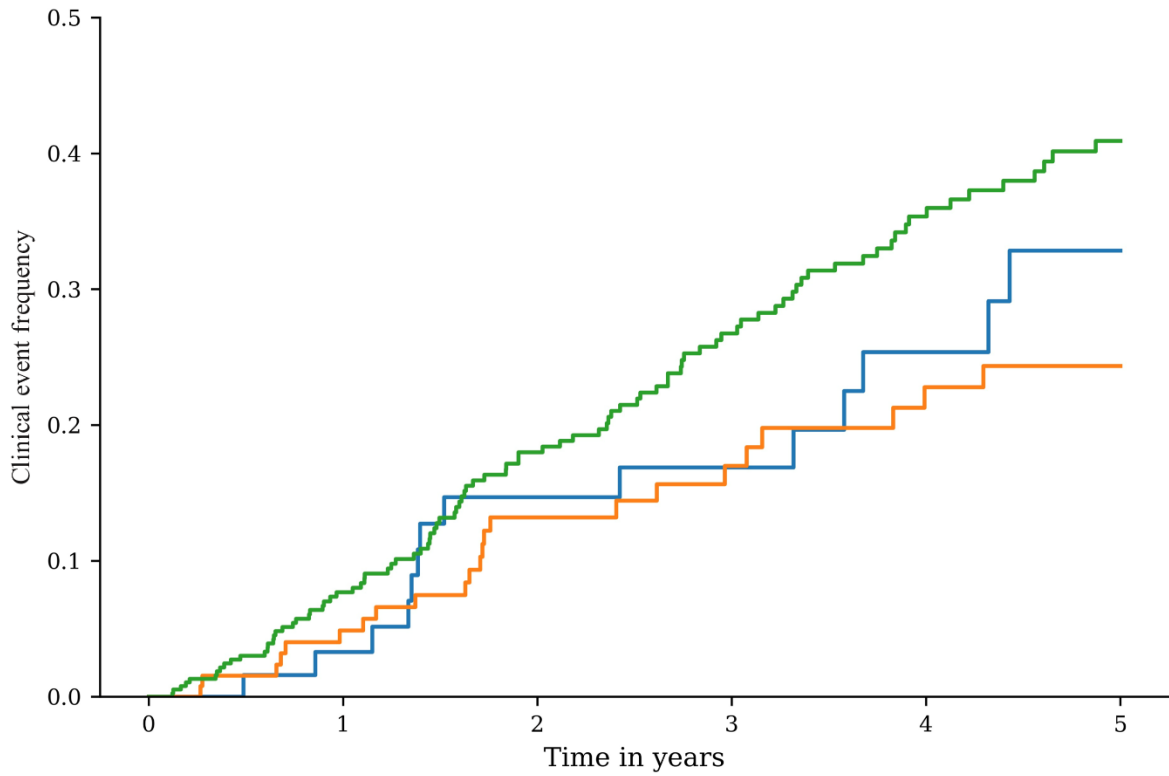


Figure 1
159x86 mm (x DPI)

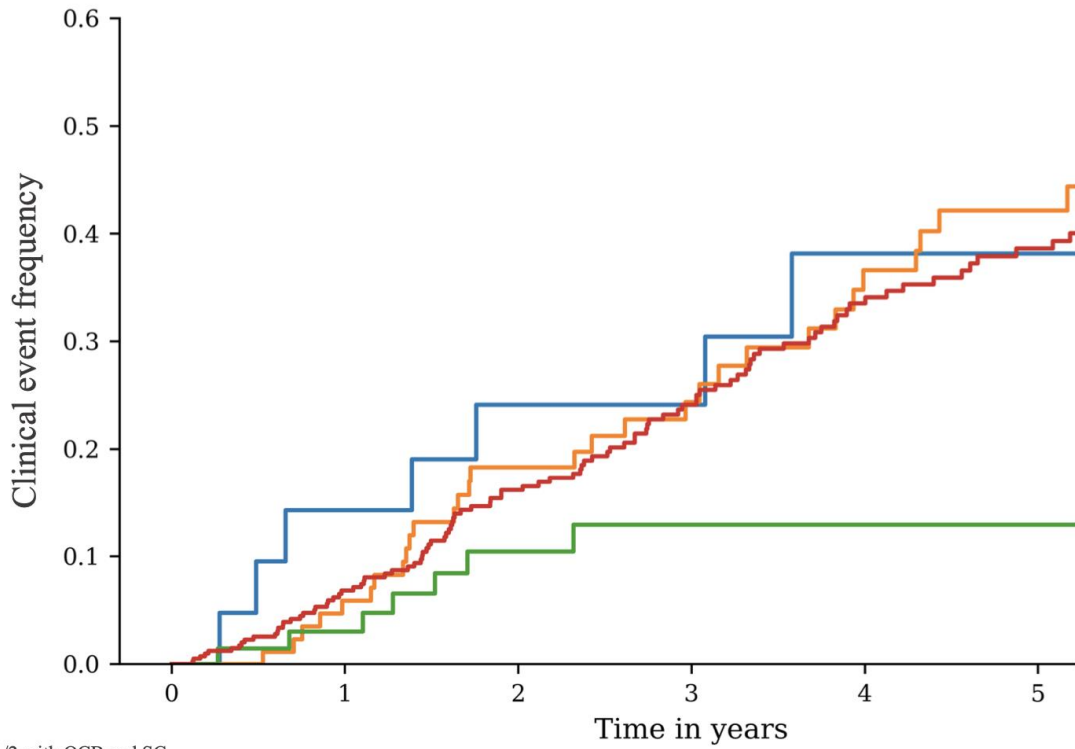
- 1
- 2
- 3
- 4



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)

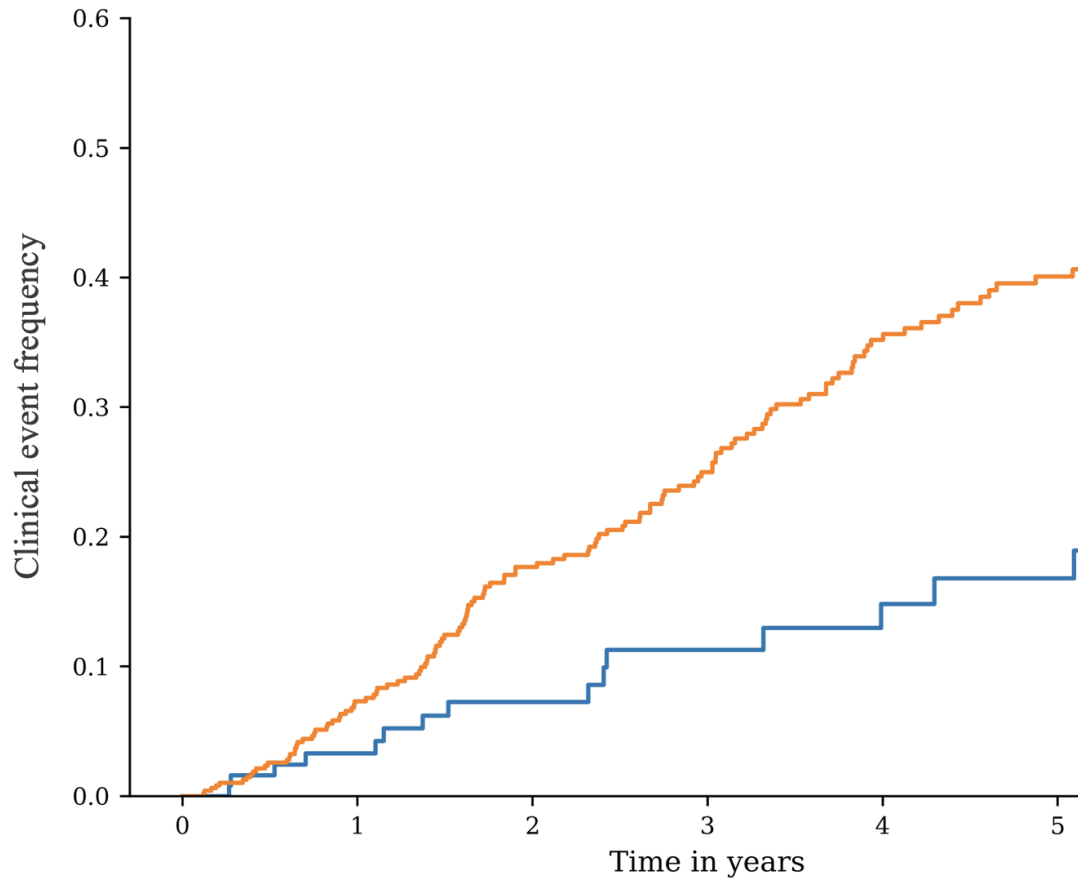
1
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Group 1/2 with OCB and SC						
At risk	21	18	14	12	8	7
Censored	0	0	2	4	6	7
Events	0	3	5	5	7	7
Group 1/2 with BOC or SC						
At risk	98	79	59	45	35	27
Censored	3	17	27	37	40	45
Events	0	5	15	19	26	29
Group 1/2 without OCB and SC						
At risk	76	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)

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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)

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1 **Table I Main clinical and MRI characteristics of the whole cohort and subgroups defined according to fulfilling dissemination**
 2 **in space (DIS)^a 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%)	
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

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

5 ^a Percentages represent data availability as not all individuals had all data available.

6 ^bThe following statistics are used as appropriate to compare Group 1, Group 2 and RIS: The association between Groups and variables was
 7 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
 8 heteroskedasticity of data. The difference between Follow-up (months) according to modalities of DIS at baseline was assessed with the Mann-
 9 Whitney. The alpha risk was set to 5% ($\alpha = 0.05$).

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1 **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		

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

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

6 ^bHeadache is chosen as the most common reason for MRI to enter as a variable in the analyses

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1 **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
	Without risk factors <i>n</i> = 299	With risk factors <i>n</i> = 238	Without risk factors <i>n</i> = 299	With risk factors <i>n</i> = 292	Without risk factors <i>n</i> = 299	With risk factors <i>n</i> = 292	
	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)
No of analyzed patients	<i>n</i> = 299	<i>n</i> = 238	<i>n</i> = 299	<i>n</i> = 292	<i>n</i> = 299	<i>n</i> = 292	<i>n</i> = 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]

^aAt least 1 juxtacortical lesion, or at least 1 periventricular lesion, or at least 1 infratentorial lesion, or at least 1 spinal cord lesion.

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Table 4 Radiologically Isolated Syndrome Criteria^a

2009 RADIOLOGICAL SYNDROME CRITERIA	2023 RADIOLOGICAL SYNDROME CRITERIA
<p>A. The presence of incidentally identified CNS white matter anomalies meeting the following MRI criteria:</p> <ol style="list-style-type: none"> 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 <p>CNS anomalies not consistent with a vascular pattern</p> <p>B. No historical accounts of remitting clinical symptoms</p> <p>C. MRI anomalies do not account for clinically apparent impairments</p> <p>D. MRI anomalies are not due to the direct physiological effects of substances</p> <p>E. Exclusion of MRI phenotypes suggestive of leukoaraiosis or extensive WM pathology lacking involvement of the corpus callosum</p> <p>F. MRI anomalies not better accounted for by another disease process</p>	<p>I. RADIOLOGICAL CRITERIA</p> <p>A. MRI with incidental CNS white matter anomalies demonstrating radiological characteristics highly suggestive of demyelinating disease and meeting the following criteria:</p> <ol style="list-style-type: none"> 1. ovoid, well-circumscribed, and homogeneous foci > 3mm² 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 <p>WITH</p> <p>B. Index MRI fulfilling 3 or 4 out of 4 dissemination in space criteria according to the 2005 multiple sclerosis diagnostic imaging criteria.</p> <p>OR</p> <p>C. Index MRI fulfilling at least one of 4 dissemination in space requirements, additionally fulfilling 2 of the following:</p> <ol style="list-style-type: none"> 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 <p>II. EXCLUSION CRITERIA</p> <ol style="list-style-type: none"> 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.

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^aComplementary expert recommendation: Multiple Sclerosis specialty-trained Neurologists to apply these criteria.

^bAt least 1 juxtacortical lesion, or at least 1 periventricular lesion, or at least 1 infratentorial lesion, or at least 1 spinal cord lesion.

^cWithin the brain if a single spinal cord focus was the original incidental anomaly identified.