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ORIGINAL COMMUNICATION

Accumulative risk of clinical event in high-risk radiologically isolated syndrome in Argentina: data from the nationwide registry RelevarEM

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Abstract

Introduction We aimed to analyze the accumulative risk of MRI and OB factors for evolution from RIS to MS in subjects included in the Argentinean MS registry (NCT03375177).

Methods RIS subjects were identified according to RIS diagnosis criteria. Subjects were longitudinally followed with clinical and MRI at intervals of 6 months. Time from RIS identification to the first clinical event was estimated using Kaplan–Meier. Multivariable Cox regression models were created to assess the independent predictive value of demographic characteristics, as well as clinical, OB and MRI data on time to the first clinical event. The single and increased risk factor of evolution of RIS was quantified.

Results A total of 88 RIS subjects, mean follow-up time 42 ± 4 months were included. 39 (44.3%) and 23 (26.1%) had a new MRI lesion or a clinical event, respectively, during the follow-up. OB (HR 5.9, 95% CI 1.29–10.1, $p = 0.004$), infratentorial lesions (HR 3.7, 95% CI 1.09–7.5) and spinal cord lesions (HR 5.3, 95% CI 1.4–8.2, $p = 0.01$) at RIS identification were independent predictors associated with a subsequent clinical event. The accumulative risk showed that when two of the three factors (OB, infratentorial or spinal cord lesions) were present the HR was 10.4, 95% CI 4.4–22, $p < 0.001$, and when three factors were present, it was HR 15.6, 95% CI 5.7–28, $p < 0.001$ for a relapse.

Conclusion The presence of three factors significantly increased the risk of clinical event; high-risk subjects should probably be managed by a different approach than those used for individuals without high-risk factors.

Keywords Radiologically isolated syndrome · Multiple sclerosis · Clinical progression · Radiological activity · Argentina · Registry

Introduction

The widespread use of brain magnetic resonance imaging (MRI) has greatly increased findings of asymptomatic brain and spinal cord abnormalities of uncertain clinical significance [1]. Some of these findings have the morphology, size, location, and distribution highly suggestive of multiple sclerosis (MS) [1]. This has led to the definition of radiologically isolated syndrome (RIS) to describe those asymptomatic subjects with brain MRI abnormalities suggestive of MS and the absence of prior clinical demyelinating events or an identifiable better explanation for the observed findings on MRI [2, 3].

A first multinational effort, led by the RIS Consortium, reported that the estimated 5-year risk of developing a first clinical event was 34% overall, with increased risk for males, younger subjects (≤ 37 years), oligoclonal bands (OB) in cerebrospinal fluid (CSF), and the presence of spinal cord lesions on MRI [4]. It has also been shown that in pediatric and adult RIS, the presence of OB significantly increases the possibility of having MS [5, 6].

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As a result, some groups have suggested that RIS + OB should be classified as high-risk MS subjects, such as clinically isolated syndromes (CIS), and should be treated with disease-modifying treatment (DMT) to prevent the clinical manifestation of MS and disease progression [7, 8]. However, scarce data exist concerning the risk of developing a clinical event or a new MRI lesion during follow-up in the "high-risk RIS" (MRI + OB) group [1].

Considering that longitudinal studies on subjects with RIS can provide valuable insights into the history of RIS, which may inform management strategies for clinicians [6], we performed the following study to analyze the accumulative risk of clinical or radiological activity in high-risk RIS subjects included in the Argentinean MS and NMOSD registry (RelevarEM, NCT03375177).

Methods

RelevarEM is a longitudinal, strictly observational MS and neuromyeltis optica spectrum disorders (NMOSD) registry in Argentina [9, 10]. It is open to all practicing neurologists and MS specialists and their teams across the country. The registry tracks the outcomes of routine clinical practice of patients with MS and NMOSD in a web-based platform that allows researchers to register and follow up their patients. The primary objective of the registry was to create an MS physician network in Argentina that captures pragmatic and relevant information from MS patients in terms of clinical and demographic aspects [9, 10].

Any patient diagnosed with MS, CIS, RIS, or an NMOSD as defined by validated diagnostic criteria (for MS and NMOSD) [2, 11, 12] can be entered into the registry. To ensure the correct use of the diagnostic criteria for MS and NMOSD in each center, the executive committee invited the participation of all MS centers and physicians involved in the care of affected patients in Argentina. To reduce the possibility of bias in the selection, each participating physician was required to include all patients seen in their practice or clinic. Detailed information and methodology of RelevarEM has been previously published elsewhere [8].

Study population, cohort selection and variables included

RIS subjects were identified according to RIS diagnosis criteria [2]. In all individuals, demographic characteristics, detailed historical and current clinical data, neurological examination results, brain, and spinal cord MRI findings at identification of the subject, and OB detection (defined as the presence of ≥ 2 unique OB in the CSF that were not present in a corresponding serum sample) were collected at study entry. Subjects were longitudinally followed with clinical and MRI evaluations at approximate intervals of 6 months. Standardized data collection was provided to record the onset and characteristics of relapsing or progressive neurologic symptoms and the presence and location of new T2 or gadolinium-enhancing (GAD+) lesions. A clinical event was defined as the appearance of a new neurological symptom that lasts more than 24 h in the absence of clinical intercurrence, followed by a period of clinical stability or improvement of at least 30 days. Follow-up images were obtained using non-uniform protocols from different MRI scanners and magnetic field strengths (1.5 or 3.0 T). All MRI examinations included T1- and T2-weighted sequences in multiple planes of view (axial, coronal, and sagittal) with the administration of gadolinium-based contrast agents. Spinal cord imaging protocols were also heterogeneous but generally included T1- and T2-weighted sequences in axial and sagittal planes, with or without contrast. All abnormalities within the brain or spinal cord identified by the MRI specialist were confirmed and reported by the MS specialist in the standardized data collection developed for the study.

For the inclusion of subjects in the analysis, demographic data (age and gender) and MRI data (cerebral and spinal cord MRI) had to be obtained. Also, the MRI at baseline and follow-up at each center had to be done in the same scan keeping the standardized protocol sequences.

Ethics committee approval was obtained for each participating center, and a written informed consent (according to each committee, if necessary) was obtained from all participants before data collection.

Statistical analysis

Baseline characteristics of the cohort were reported in percentages for categorical data and in median and range or mean ± SD for continuous data.

Time from RIS identification to the clinical event or a new MRI lesion was estimated using Kaplan–Meier survival analyses. Multivariable Cox regression models were created to assess independent variables (age at RIS identification, gender, the presence of OB, GAD+ lesion and number, infratentorial lesions and spinal cord lesions at baseline MRI) to the first symptomatic event or new MRI lesion. A complete case analysis of the regression model was done considering demographic and MRI data at baseline. The single and accumulative increased risk factor of a clinical event or a new MRI lesion was quantified by hazard ratios (HR) along with their 95% confidence intervals (CI). A p value of < 0.05 was considered significant.

Results

A total of 88 RIS subjects were included (75% females, mean age 43.1 ± 4.2 [range 34–52], mean follow-up time 42 ± 4 months, range 21–57 months, interquartile range 38.7 months). In 65 subjects (73.8%), lumbar punctures were performed and OBs were present in 27 (41.5%). Spinal cord lesions were identified in 18 subjects (20.4%). The first brain MRI was usually ordered by the general practitioner for various medical events, including headache ($n = 35$), migraine ($n = 14$), craniocerebral trauma ($n = 12$), depression ($n = 6$), anxiety (6), tinnitus ($n = 6$), syncope ($n = 6$), cognitive complaint ($n = 2$) and anosmia ($n = 1$).

The remainder of baseline characteristics are displayed in Table 1. During the follow-up, 39 (44.3%) and 23 (26.1%) had a new MRI lesion or a clinical event, respectively (Table 1). The presence of OB (HR 5.9, 95% CI 1.29–10.1, $p = 0.004$), infratentorial lesions (HR 3.7, 95% CI 1.09–7.5, $p = 0.03$) and spinal cord lesions (HR 5.3, 95% CI 1.4–8.2, $p = 0.01$) at RIS identification were independent predictors associated with a subsequent clinical event. Despite a trend to increased risk for the male gender, this was not significant (Table 2). These factors were also related to radiological activity during follow-up; however, gender was not identified as a trend in the risk of radiological activity as it was observed for a clinical event (Table 3). When we added factors, we found that 15 patients presented two out of three identified risk factors (OB, spinal cord and infratentorial lesions). The accumulative risk showed that when two of the three factors were present, HR was 10.4, 95% CI 4.4–22, $p < 0.001$ (Fig. 1). A total of 8 patients had all three risk factors present; the risk of clinical event in that group was HR 15.6, 95% CI 5.7–28, $p < 0.001$ (Fig. 2). The risk of a new MRI lesion in the presence of two factors was HR 9.4, 95% CI 4.3–15, $p < 0.001$, and for three factors, HR 14.3, 95% CI 5.2–21, $p < 0.001$. On the contrary, all subjects with OB, spinal cord and infratentorial lesions (high-risk RIS) had a clinical event during follow-up, with a mean time to event of 14 ± 4 months (range 3–18) (Fig. 3).

Table 1 Baseline characteristics of included patients

	$N = 88$
Mean age, SD (range)	43.5 ± 4.2 (34–52)
Female gender, *n* (%)	66 (75%)
Mean follow-up time ± SD (months)	42 ± 4
Lumbar puncture, *n* (%)	65 (73.8)
OB, *n* (%)	27 (41.5)
GAD+, *n* (%)	18 (20.5)
Mean GAD+, *n* (%)	0.46 ± 1.1 (0–7)
Infratentorial lesions, *n* (%)	36 (40.9)
Spinal cord lesions, *n* (%)	18 (20.4)
New MRI lesion during follow-up, *n* (%)	39 (44)
Mean time to new MRI lesion ± SD (months)	14 ± 7
Clinical event, *n* (%)	23 (26.1)
Mean time to clinical event ± SD (months)	15 ± 7

OB oligoclonal bands, *GAD+* gadolinium-enhancing lesions, *SD* standard deviation

Table 2 Regression analysis assessing risk factors of clinical event in RIS

Variable	HR	*p* value	95% confidence interval
Age	1.65	0.15	0.55–2.88
Male gender	2.1	0.09	0.88–3.23
OB	5.9	0.004	1.29–10.1
GAD+ at baseline MRI	2.3	0.11	0.67–4.65
Number of GAD+ at baseline MRI	1.11	0.34	0.73–1.98
Infratentorial lesions at baseline MRI	3.7	0.031	1.09–7.5
Spinal cord lesions on baseline MRI	5.3	0.01	1.4–8.2

Cox regression analysis was done based on complete case analysis, so, despite demographic and MRI data were complete in all, OB data were present in 65 subjects

OB oligoclonal bands, *GAD+* gadolinium-enhancing lesions

Discussion

This is the first study performed in Latin America to evaluate the risk of clinical events during follow-up in RIS with specific focus on high-risk RIS. A total of 26.1% of subjects had a clinical event and 44% a new MRI lesion during almost 4 years of follow-up. We found that OB, infratentorial lesions and spinal cord lesions were independently

Table 3 Regression analysis assessing risk factors of new MRI lesion in RIS

Variable	HR	*p* value	95% confidence interval
Age	1.61	0.17	0.60–2.43
Male gender	1.7	0.18	0.65–2.68
OB	5.2	0.001	1.67–12.5
GAD+ at baseline MRI	1.8	0.26	0.55–4.87
Number of GAD+ at baseline MRI	1.08	0.22	0.66–1.22
Infratentorial lesions at baseline MRI	4.1	0.01	1.22–8.2
Spinal cord lesions on baseline MRI	4.6	0.008	1.34–10.2

*Cox regression analysis was done based on complete-case analysis, so, despite demographic and MRI data were complete in all, OB data were present in 65 subjects

OB oligoclonal bands, *GAD+* gadolinium-enhancing lesions

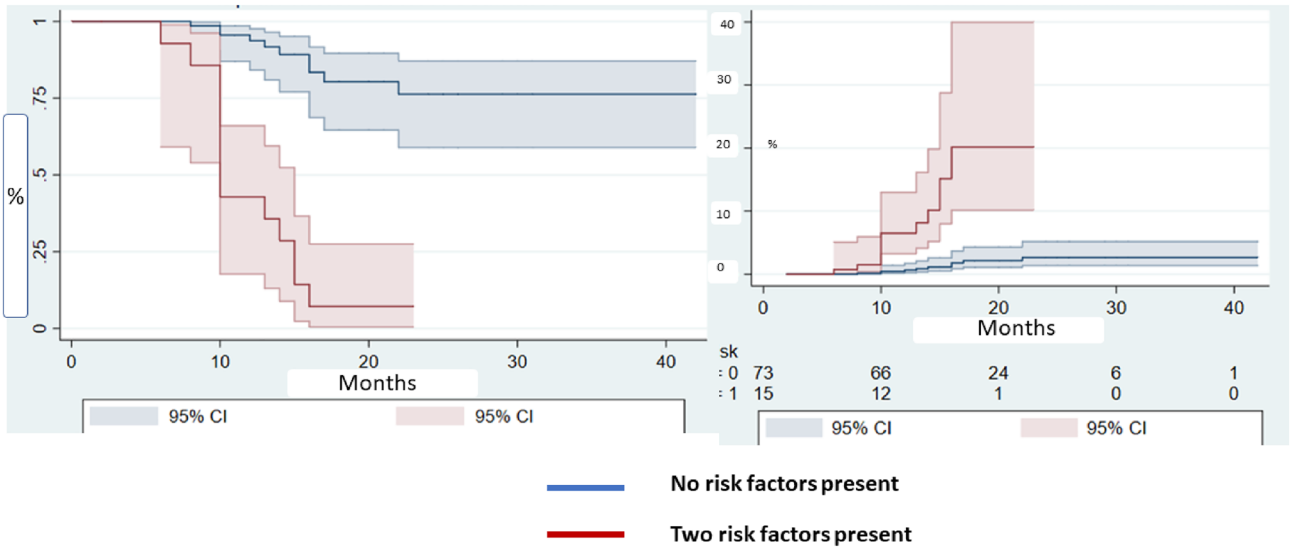

Fig. 1 Survival curves of clinical events in RIS when two high-risk factors were present

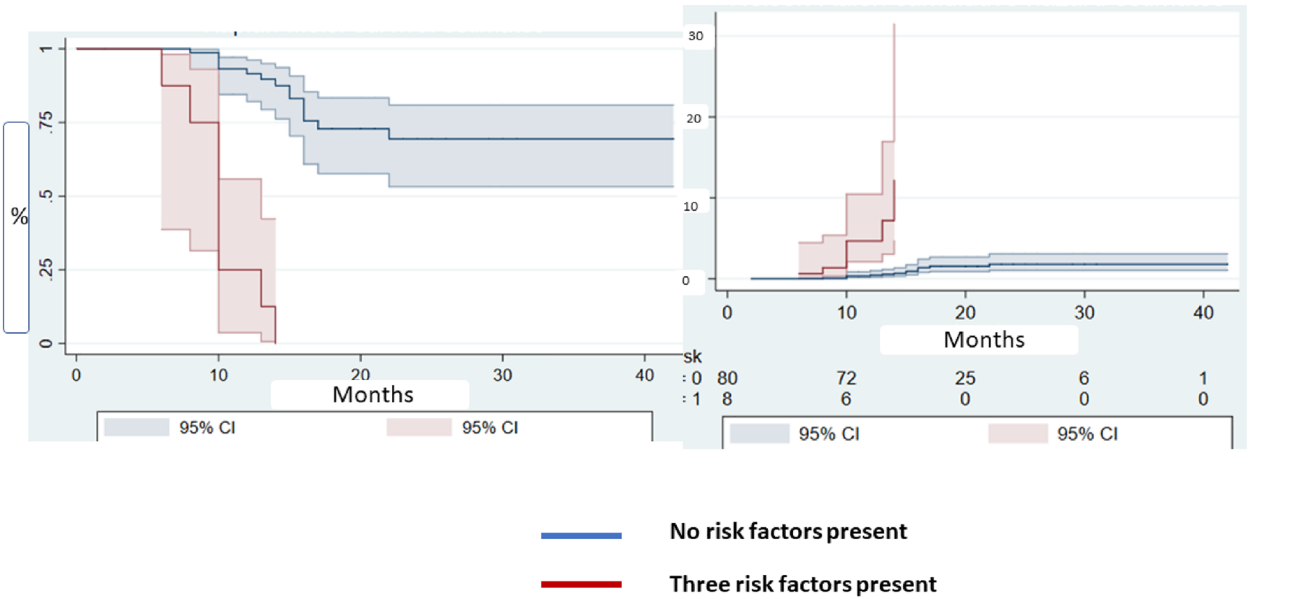

Fig. 2 Survival curves of clinical events in RIS when three high-risk factors were present

associated with an increased risk of a clinical event or a new MRI lesion during follow-up. When the risk factors were added in a subject, the risk of a clinical event or a new MRI lesion increased significantly, from 5 to nearly 15 times. All subjects with the three main risk factors (OB, spinal cord and infratentorial lesions) had a clinical event during the first 2 years after subject identification.

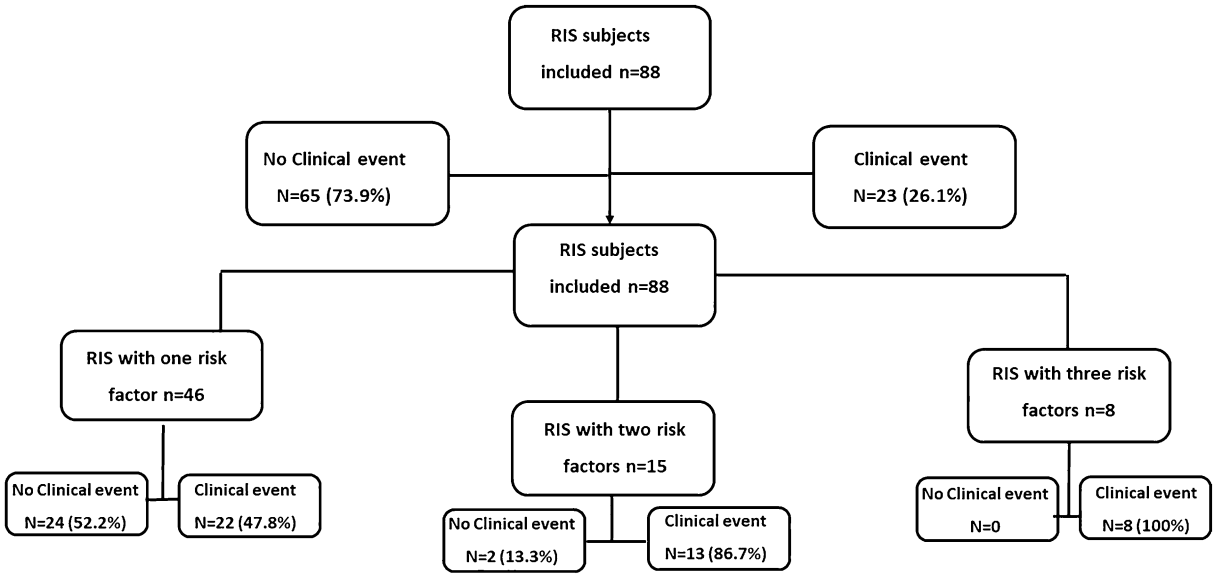

Fig. 3 Flow diagram of clinical event based on the presence of risk factors identified

Our results are in line with previous studies. In 2009, Lebrun et al. first described a cohort of 70 RIS subjects and the predictive clinical, imaging, and electrophysiological factors associated with a clinical event [13]. During follow-up, 23 out of 70 patients were found to have clinical conversion to the following conditions: optic neuritis ($n=6$), myelitis ($n=6$), brainstem symptoms (diplopia or internuclear ophthalmoplegia) ($n=5$), sensitive symptoms (paresthesias in lower or upper limbs) ($n=4$), cerebellar symptoms ($n=1$) and cognitive deterioration ($n=1$) [13]. No progressive form of MS was detected in that study; the mean time between the first brain MRI and CIS was 2.3 years (range, 0.8–5.0 years). In the multivariate analysis, the MRI criteria for MS, added to CSF abnormalities alone or to a VEP abnormality, were associated with an increased risk of a clinical event [13]. The group recently communicated the risk of a clinical event at 10 years and assessed the association of demographic, clinical, and radiological characteristics with this risk [6]. To that purpose, they analyzed the data of 21 individual databases from five countries. Follow-up data were available in 451 RIS subjects (86% female); mean age at RIS diagnosis was 37.2 years (range, 11–74 years), with a median clinical follow-up of 6.7 years [6]. The cumulative probability of a first clinical event at 10 years was 51.2%. A younger age at RIS diagnosis, the presence of OB, infratentorial lesions on MRI, and spinal cord lesions were baseline independent predictors associated with a subsequent clinical event [6]. The group also found that gadolinium-enhancing lesions during follow-up were also associated with the risk of an event [6]. A sub-analysis of that cohort identified 15 RIS subjects who evolved to primary progressive MS [14]. The median time to PPMS was 3.5 years (range, 1.6–5.4). Subjects with a RIS that evolved to PPMS were frequently men ($p<0.005$) at an older age ($p<0.001$) who had more spinal cord lesions (100%) before symptomatic evolution than those who developed CIS/MS (64%) and those who remained asymptomatic (23%) within the follow-up period ($p<0.005$) [14]. Previous findings were also replicated in pediatric populations. Makhani et al. described clinical and radiologic outcomes of 38 children with RIS [5]. In that study, during the mean follow-up time of 4.8 years, a first clinical event occurred in 16/38 children (42%; 95% CI 27–60%) in a median of 2.0 years (interquartile range [IQR] 1.0–4.3 years) [5]. Radiologic evolution was observed in 23/38 children (61%; 95% CI 44–76%) with a median of 1.1 years (IQR 0.5–1.9 years) [5]. The presence of OB in CSF (HR 10.9, 95% CI 1.4–86.2, $p=0.02$) and spinal cord lesions on MRI (HR 7.8, 95% CI 1.4–43.6, $p=0.02$) was associated with an increased risk of a first clinical event after adjustment for age and sex [5].

It is currently a matter of debate whether to treat RIS subjects from time of identification, considering the possibility of delaying or avoiding conversion to MS [1, 8]. A survey of MS neurologists in Europe showed that only a few respondents would initiate treatment in RIS if an initial MRI revealed one or more gadolinium-enhancing (Gd+) lesions in the brain (29%) or spinal cord (30%) or one new or enlarging T2 lesion in the brain (40%) [15]. However, a finding of more than one new or enlarging T2 brain lesion

in a follow-up scan would lead a majority (51%) to initiate treatment [15]. Respondents who chose not to initiate treatment generally agreed (94%) that they would perform a follow-up MRI, and if lesions were then found, the decision to treat would increase based on the type, number, and location of lesions [15]. Another study of 239 MS experts in the United States showed that initiation of treatment would not be appropriate (79%) in RIS subjects [16]. However, there was consensus (80% [71.9–87.7%]) to initiate treatment if > 2 gadolinium-enhancing lesions were observed [16]. All neurologists in that survey agreed to obtain a follow-up brain MRI, with 82% doing so within 12 months [16]. Finally, in Argentina, a survey of 66 MS neurologists showed that most respondents would not start DMTs in RIS subjects even though the RIS patient showed positive OB (65.5%), a GAD+ spinal cord lesion (56.3%) or one brain lesion that was GAD+ at identification (54.2%) [17]. However, most respondents would start treatment if MRI showed one (61%) or more Gd+ (30.5%) lesions in the brain and/or spinal cord during the follow-up [17]. Likewise, some responders would initiate DMTs if one new or enlarging T2 lesion (47.5%) or more Gd− (40.7%) lesions were observed on brain MRI [17].

There is consistency between the different cohort studies regarding MRI (spinal cord, infratentorial and GAD+ lesions) and OB findings and the risk of a clinical event in RIS subjects [15–17]. In those subjects in whom most of these risk factors are identified, without red flags suggestive of an alternative diagnosis, the possibility of subclinical MS may be considered and the use of treatments would be justified [7]; however, current evidence does not support treatment in RIS subjects [1]. Ongoing randomized controlled trials could define the role of DMTs in this population [1].

Our study has several limitations, including the retrospective design, the MRI analysis (given that different MRI scanners between centers (but not intra centers) and field strengths were employed), the absence of an external evaluation to confirm a relapse, and the period of follow-up. Nonetheless, the standardized collection of the data, the MS specialists involved in data collection, and the power of the study in terms of the number of included subjects strengthen the observation.

In conclusion, we found that OB, infratentorial lesions and spinal cord lesions were independently associated with an increased risk of a clinical event or a new MRI lesion and that the presence of all factors increased the risk of a clinical event by up to 15 times. A close monitoring of this subject matter should be maintained in current clinical practice.

Declarations

Conflicts of interest No potential conflict of interest relating to this paper was reported by the authors.

Ethical approval Ethics committee approval was obtained for each participating center, and a written informed consent (according to each committee, if necessary) was obtained from all participants before data collection.

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