Radiologically Isolated Syndrome: 10-Year Risk Estimate of a Clinical Event

Running Head: RIS prognosis

Christine Lebrun-Frenay[1], MD, PhD, Orhun Kantarci[2], MD, Aksel Siva[3], MD, Maria Pia Sormani[4,5], PhD, Daniel Pelletier[6], MD, and Darin T Okuda[7] MD, for the 10-year RISC study group on behalf of SFSEP, OFSEP.

[1]Côte d'Azur University, UR2CA, Pasteur 2 Hospital, Nice, France
[2]Mayo Clinic, Rochester, MN, USA
[3]Istanbul University Cerrahpasa School of Medicine - Department of Neurology, Turkey
[4]Statistic Unit, University of Genoa, Genoa, Italy
[5]IRCCS Ospedale Policlinico San Martino, IRCCS, Genoa, Italy
[6]University of Southern California, Los Angeles, CA, USA
[7]University of Texas Southwestern Medical Center, Dallas, TX, USA

Corresponding author: Christine Lebrun-Frenay, MD, PhD, FAAN. CRCSEP, UR2CA Neurology, Nice Cote d'Azur University. Pasteur[2] Hospital. 30 voie Romaine. 06002. Nice. France.
Lebrun-frenay.c@chu-nice.fr
Phone: (33) 4 92 03 85 27
Fax: (33) 4 92 03 80 15

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Abstract

Objective

We have previously identified male sex, younger age, and the presence of spinal cord lesions as independent factors that increase the 5-year risk for evolution from radiologically isolated syndrome (RIS) to multiple sclerosis. We investigate here risk factors for the development of a clinical event using a 10-year, multi-national, retrospectively-identified RIS dataset.

Methods

RIS subjects were identified according to 2009 RIS criteria and longitudinally followed as part of a worldwide cohort study. We analyzed data from 21 individual databases from 5 different countries. Associations between clinical and MRI characteristics, and the risk of developing a first clinical event were determined using multivariate Cox regression models.

Results

Additional follow-up data was available in 277/451 RIS subjects (86% female). Mean age at RIS diagnosis was 37.2 y (range:11-74 y) with a median clinical follow-up of 6.7 years. The cumulative probability of a first clinical event at 10 years was 51.2%. Age, positive CSF, infratentorial lesions on MRI, and spinal cord lesions, were baseline independent predictors associated with a subsequent clinical event. The presence of gadolinium enhancing lesions during follow-up was also associated with the risk of a seminal event. Reason for MRI and gadolinium enhancing lesions at baseline did not influence the risk of a subsequent clinical event.

Interpretation

Approximately half of individuals with RIS experience a first clinical event within 10 years of the index MRI. The identification of independent predictors of risk for symptom onset may guide education and clinical management of individuals with RIS.

Keywords: Radiologically isolated syndrome. MRI. Multiple sclerosis

Abbreviations: CIS: Clinically Isolated Syndrome; CNS: Central Nervous System; CSF: Cerebrospinal fluid; DMT: Disease-modifying treatment; MRI: Magnetic resonance imaging MS: Multiple sclerosis; OCB: Oligoclonal bands; PP: Primary Progressive; RIS: Radiologically isolated syndrome; RR: Relapsing remitting.

Introduction

Radiologically isolated syndrome (RIS) was formally defined in 2009 to describe individuals with brain magnetic resonance imaging (MRI) findings that are similar to those observed in patients with multiple sclerosis (MS), but are identified incidentally (i.e. without a clinical history of neurological symptoms suggestive of central nervous system (CNS) demyelination)[1]. Before the description of this entity, which represents one of the earliest identifiable groups within the spectrum of CNS demyelinating disorders, several case reports and case series had suggested that individuals with these incidental MRI findings were at a high risk of developing a relapsing remitting (RR) multiple sclerosis[2-6]. It has since been reported that some individuals with RIS develop progressive rather than acute symptoms of demyelinating disease, fulfilling criteria for primary progressive MS (PPMS)[7]. RIS has recently been described even in children[8]. The cumulative incidence of RIS, calculated from autopsy studies, and actual registries of MRI data is approximately 0.1% in adults[9].

Despite being a relatively common diagnostic entity faced by MS clinicians, a number of issues persist, including misdiagnosis of RIS and uncertain prognosis, especially given the autopsy evidence that some patients may remain asymptomatic, presumably for the rest of their lives. Misdiagnosis of RIS is a significant problem that can result from the inappropriate application of RIS diagnostic criteria due to either an incomplete neurological history that misses prior clinical events of demyelinating disease, or a misinterpretation of white matter MRI lesions in terms of their actual etiology or spatial characteristics[10]. Because RIS is diagnosed in individuals without clinical signs or symptoms, MRI interpretation remains integral to an accurate diagnosis. In particular, the presence of characteristic spinal cord lesions, or other para-clinical data (e.g. cerebrospinal fluid (CSF) findings) can increase the specificity for a CNS demyelinating disease. In addition, once RIS is correctly diagnosed, there are no widely accepted guidelines for surveillance or prophylactic treatment of RIS individuals[11]. Longitudinal studies of subjects with RIS can provide valuable insights into the 'natural history' of RIS, which may inform management strategies for clinicians.

A first multinational effort, led by the RISConsortium, reported that the estimated 5-year risk of developing a first clinical event was 34% overall, with increased risk for males, younger subjects (age ≤ 37 years), and presence of spinal cord lesions on MRI[14]. To date, the risk of developing clinical symptoms beyond this 5-year time period is unknown. Our objectives were to estimate the risk of a clinical event at 10 years, and to assess the association of demographic, clinical, and radiological characteristics with this risk.

Methods

Ethics Statement

This study was approved by the following regulatory authorities and ethics committees: Committee on Human Research (University of California, San Francisco, San Francisco, California, U.S.A.), Mayo Clinic Institutional Review Board (Mayo Clinic, Rochester, Minnesota, U.S.A.), Institutional Review Boards of Mt. Sinai School of Medicine (Mt. Sinai School of Medicine, New York, New York, U.S.A.), University of Texas Southwestern at Dallas (Dallas, Texas U.S.A), Institutional Review Board of Val d'Hebron Research Institute (MS Center of Catalunya CEMCAT, Barcelona, Spain), Institutional Review Board of the University of Siena (University of Siena, Siena, Italy), Istanbul University Cerrahpasa School of Medicine Ethical Committee for Clinical Research and Studies (Istanbul, Turkey), and the Comité de Protection des Personnes (Hôpital Pasteur[2], Nice, France) for the French MS Observatory (Observatoire Français de la Sclérose En Plaques-OFSEP). Written informed consent was acquired from all study subjects.

Study design and participants

All 451 of the subjects contained within the original RIS cohort reported in 2014 were included in this analysis[14]. Subjects originated from 21 clinical sites within 5 countries. All subjects had initial brain MRI studies dated after 1990 that revealed incidental anomalies suggestive of demyelinating disease meeting 2009 criteria for RIS (i.e. 2005 criteria for DIS)[1]. In all individuals, demographic characteristics, family history of MS, detailed historical and current clinical data, comprehensive neurological examination results, brain and spinal cord MRI findings, and CSF analysis were collected at study entry. Subjects were longitudinally followed with clinical and MRI evaluations at intervals that varied according to each center's clinical discretion. Standardized data collection sheets

were provided to each center to record the onset and characteristics of relapsing or progressive neurologic symptoms, and the presence and location of new gadolinium enhancing lesions that occurred during the follow-up period. For this current analysis, updated data were gathered to ascertain clinical and MRI events that occurred subsequent to the initial 2014 publication[14]. These updated data were used when available (277 subjects, or 61.4% of the overall study cohort). For the remaining 141 subjects from two centers unable to provide updated follow-up, data originally used in the 2014 analysis were retained and analyzed (Supplementary Table 1).

Neuro-Imaging Studies

All study subjects underwent one or more MRI studies of the brain that initially fulfilled MRI criteria for RIS (i.e 2005 criteria dissemination in space-DIS)[1]. Follow-up images were obtained using non-uniform protocols from different MRI scanners and magnetic field strengths (1.5 or 3.0 Tesla). All MRI examinations included T1 and T2-weighted sequences in multiple planes of view (axial, coronal, and sagittal) with or without 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 were initially identified by a local neuroradiologist, and independently reviewed by an MS specialist to ensure MRI criteria for RIS were met[1].

Procedures

The primary objectives for this investigation were to estimate the 10 year risk of a first clinical event, and to assess the impact of baseline demographic, clinical, and radiological metrics on the time to the first clinical event after prolonged follow-up. A seminal event was defined as the development of an acute or progressive neurological episode localized to the optic nerve, brainstem, cerebellum, spinal cord, or long sensory or motor tracts, lasting more than 24 hours in the absence of fever or acute illness and followed by a period of symptom improvement, or the onset of a clinical symptom with the temporal profile revealing at least a 12-month progression of neurological deficits evaluated by the Expanded Disability Status Scale (EDSS) score. Subgroups were defined based on demographic characteristics (e.g. age at the time of RIS diagnosis, sex, ethnicity), clinical data (i.e. MS family

history, CSF profiles, reason for MRI, use of disease-modifying treatments (DMTs)), and imaging data (e.g. total number of T2 lesions contained within the infratentorial, juxtacortical, and periventricular regions on brain MRI, presence of gadolinium-enhancing lesions on the index MRI and during the follow-up, involvement of the spinal cord). Positive CSF was defined as an IgG index>0.7 or the presence of ≥ 2 unique oligoclonal bands (OCB) in the CSF that were not present in a corresponding serum sample.

Statistical Analysis

Statistical analyses were performed (co-author M.P.S.) using SPSS for Windows, version 25.0 (SPSS, IBM, Armonk, New York, U.S.A.). Means with standard deviations (SD) were calculated to summarize the demographic, clinical, and radiological data, when appropriate. The time from RIS diagnosis to the first acute, or progressive clinical symptom was estimated using univariate Kaplan-Meier survival analyses. Log-rank tests were used to compare survival data between subgroups in univariate analysis. Multivariable Cox regression models were created to assess the independent predictive value of demographic characteristics, clinical data, and imaging data on the time to the first symptomatic event. The association of each covariate with time to the first clinical symptom was quantified by hazard ratios (HR) along with their 95% confidence intervals (CI). A p-value <0.05 was considered significant. The association of radiological activity during follow-up with the risk of a clinical event was evaluated by a Cox model with radiological activity as a time dependent variable.

Data availability

Individual participant data will be available, including data dictionaries and individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices) will be shared. Study protocol, statistical analysis plan, analytic code will be available, beginning 9 months and ending 36 months following article publication with Investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose, to achieve aims in the approved proposal.

Results

Clinical characteristics

The study cohort of 451 RIS subjects was principally composed of women (86.5%) who were mostly white (86%). Mean age at RIS diagnosis was 37.2 years (y) (SD:11.1 y). In the 277 subjects (61.4% of the overall study cohort) with updated data, the mean clinical follow-up time overall was 7.2 y (median: 6.7 y, range: 1-26.6 y). The individuals with updated data available were similar to those without updated data in terms of a familial history of MS or personal history of auto-immune disease [14] (Table 1). Neurological examinations were performed at baseline, and at least one follow-up visit for each patient. Twelve individuals (2.6%) were diagnosed with RIS at age<18 years. Reasons for the index brain MRI that led to the diagnosis of RIS were diverse, with headache being the most common (42%; Table 2 and Supplementary Table 2). CSF results were available for 300/451 subjects and were abnormal in 194 (65%). Among these 194 individuals, 59 had positive OCBs, 15 had elevated IgG index only, and 120 had positive results for both tests (6 were reported positive without details) (Table 3).

The cumulative probability of a clinical event at 10 years was 51.2% (standard error=2.5%) (Fig.1). Of the 173 patients who developed symptoms, 21 individuals (11.7%; 62% female) fulfilled criteria for primary progressive MS[7] (median age at baseline: 43.8 y; range: 20–74). We did not find any predictive factors that could predict a PP vs. a RR clinical course.

In univariate analysis, factors associated with increased risk of a first clinical event were a younger age at RIS diagnosis, positive CSF, and presence of either infratentorial or spinal cord lesions (Table 3). Radiological activity during follow-up was also associated with increased risk of a clinical event (HR=1.81, 1.31-2.52, p<0.001). Unlike the findings previously reported at 5 years[14], sex was no longer a prognostic factor for clinical evolution [HR for male sex: 1.24 (95% CI=0.88-1.77), p=0.25]. A positive family history (first degree relative) for MS was observed in 10.0% of the study group and was not predictive for clinical evolution (Table 3).

In multivariable analysis, adjusted for center and date of the RIS index MRI, the risk of a clinical event increased with younger age at RIS diagnosis [HR: 0.96 (95% CI: 0.95-0.98); *p*<0.001] (Fig.2a). In other words, the risk of developing a clinical event decreased by 4% for every additional year of age. Positive CSF [HR=2.17 (95%CI: 1.40-3.36), p=0.004], presence of infratentorial lesions [HR:

1.39 (1.00-1.95); *p*=0.048] and presence of spinal cord lesions [HR: 2.33 (1.66-3.27) ; *p*<0.001] (Fig.2b, Fig.3a,b) were also identified as independent predictors of evolution to clinical symptoms in adjusted models.

Treatment with an approved MS disease modifying therapy (DMT) prior a first clinical episode occurred in 73/451 (16.2%) of RIS individuals. The mean treatment time was 4.3 y (SD: 4.3 y, range=0-18 y). Off-label treatments included IFNb1a, IFNb1b, glatiramer acetate, fingolimod, and natalizumab; a few individuals were exposed to more than one treatment. Treatment decisions were made at the individual level and at the discretion of the referring physician. DMT exposure in RIS subjects was not significantly associated with the risk of developing a first clinical event in univariate analysis [HR=0.84, (0.53-1.33), p=0.46].

MRI characteristics

Spinal cord imaging was performed at the discretion of the treating physician at each study site. Cervical MRIs were available in 326 subjects (72.3%) and thoracic MRIs in 171 subjects (37.9%). At least one spinal cord lesion was observed in 36% of subjects (138 of 383 available scans). The presence of a spinal cord lesion [HR: 2.33 (1.66-3.27) (Figure 3a); *p*<0.001], or an infratentorial lesion [HR: 1.39 (1.00-1.95); *p*=0.048] (figure 3b) were independently associated with the development of a first clinical event in a multivariable models adjusted for center and date of index MRI.

Data on the presence or absence of gadolinium enhancement at baseline was available for 381/451 subjects (84.5%). Contrast enhancement on the index MRI was observed in 108 cases (28.3%). The presence of contrast enhancement at baseline was not associated with risk of conversion to a first clinical event [HR= 0.84 (0.59-1.2), p=0.32]. Throughout the follow-up period, 226 patients (50%) had contrast enhancement at at least one point in time. Of these subjects, 146 (65%) remained asymptomatic at last follow-up. Among the 173 individuals who had a clinical event, 78 (45%) had contrast enhancement before conversion. Having gadolinium enhancing lesions during follow-up was significantly associated to the risk of a clinical event [HR=1.81, 1.31-2.52, p<0.001].

Index MRI scan and reasons for MRI

The date of the index MRI scan (RIS diagnosis date) was significantly related to the probability of a first clinical event (Fig.4), with subjects diagnosed in the last 15 years showing a higher rate of conversion after 5 years (33%), and after 10 years (52%) as compared to subjects with a RIS diagnosis date greater than 15 years (conversion rate 22% at 5 years, and 45% at 10 years, p=0.039). Survival analyses did not reveal different patterns of conversion to a first symptomatic event (p=0.09) between participating centers. In addition, there were no significant differences related to the reasons why RIS subjects received an MRI scan (p for heterogeneity=0.43) or an association between reason for MRI and the rate of a first clinical event (p=0.71) (Supplementary Table 2). In particular, headache was not identified as a risk factor for developing a clinical episode [HR: 0.91 (95% CI: 0.67-1.24); *p=0.56*] (Table 3).

Risk Stratification at baseline

Considering the 4 independent risk factors for a clinical event emerging from the multivariable analysis (Table 3), younger age, positive CSF, and infratentorial or spinal cord lesions on baseline MRI, the probability of a first clinical event at 10 years follow-up was 29% for subjects with at least 1 risk factor. There were stepwise increases in the probability with the number of risk factors present: 54% for individuals with 2 risk factors, 68% with 3 risk factors, and 87% with all 4 risk factors (Fig.5).

Discussion

We report herein the 10-year estimated risk of subjects with RIS evolving to an initial clinical event from an international, multi-center, longitudinal cohort. This cohort, which includes longitudinally-acquired clinical and MRI data, is currently the largest and longest published study of RIS individuals. The estimated 10-year risk from RIS diagnosis to a first clinical event, defined as the development of either an acute episode or progressive neurological worsening, was 51.2%. This trend towards symptom evolution also appeared to extend out beyond 10 years. Four key risk factors at diagnosis were identified that increase the risk of evolution to clinical symptoms: younger age, a positive CSF profile, the presence of spinal cord or infratentorial lesions, and the occurrence of gadolinium enhancing lesions during follow-up.

These data are largely consistent with previously published findings[1,2]. We and others have demonstrated that age and spinal cord lesions strongly predict development of clinical symptoms[13], and as reported in clinically isolated syndrome (CIS) subjects[15], infratentorial lesions were also a predictive factor. As expected, the presence of at least one gadolinium enhancing lesion during MRI follow-up at any time was also significantly associated with the risk of a clinical event. Different than our prior findings, in this work we did not find that male sex was significantly associated with the risk of a first clinical event.

A strength of our study was the ascertainment of detailed and standardized clinical data. This is important as a significant issue that potentially confounds the diagnosis of RIS is inaccurate clinical historical data that may miss possible symptoms of demyelination. As in many other chronic illnesses, signs of impending disease may be observed in the months to years preceding the documented seminal event. Neurologists should be meticulous in determining if a subject with incidental brain anomalies suggestive of MS is and has always been asymptomatic[10]. The 'isolated' part of the definition of RIS refers to the absence of neurological symptoms suggestive of CNS demyelination, including symptoms which could be considered as MS prodromes. To fulfill this aspect, the diagnostic questioning needs to be extensive, as it has been shown that nearly 30% of patients thought to present with their first demyelinating clinical event have had previous symptoms suggestive of demyelination[16].

Another strength of our study is the dual reading of MRIs using standardized definitions. This ensured correct application of the validated 2009 RIS criteria. We cannot extend our conclusions to what could have been found with another set of RIS criteria[17]. With the widespread use of MRI technology, it is not uncommon that healthy individuals without signs of neurological disease will have MRI scans that reveal unexpected white matter T2 hyperintense lesions. In these instances, it is of paramount importance that the T2 abnormalities be deemed highly suggestive of demyelination based on their size, location, and morphology. As the origins of T2 hyperintensities are heterogeneous, the future inclusion of additional imaging modalities such as central vein imaging, the evaluation of hypointense rims, or 3-dimensional phenotyping may increase the specificity for CNS demyelinating lesions. In

addition, an accurate diagnosis of RIS may help avoid the inappropriate use of DMT in individuals with an alternate etiology for their white matter hyperintensities. Recent literature on MS misdiagnosis suggests that more than 45% of misdiagnoses were represented by nonspecific neurological symptoms and MRI abnormalities more consistent with a migraine or small vessel ischemic changes, and that many of these patients were unnecessarily treated with MS DMTs[18,19].

Whether to treat RIS subjects off-label with DMTs is a matter of debate. The impact of subclinical white matter lesions on measures of neurological function that are not traditionally considered in MS diagnostic criteria remains controversial. Two prospective research studies have demonstrated that a significant proportion of individuals with RIS demonstrate cognitive impairment compared to healthy controls matched for age, sex, and level of education[20,21]. Fatigue and quality of life have also been shown to be impacted in subjects with RIS[22]. In a nationwide prospective Norwegian study, evidence of pre-clinical disease activity was demonstrated on cognitive and physical performance decline up to 20 years prior to the first demyelinating symptom of MS[23]. In a large Canadian matched cohort study, patients who developed MS had more frequent use of healthcare resources than controls in the 5 years preceding their first clinical demyelinating event, implying that clinical disease might be manifest earlier than could be diagnosed based on conventional criteria for MS diagnosis[24]. These studies enhance the suspicion that MS may start several years prior to diagnosis, with cognitive impairment, fatigue, or lower physical performance being potentially early signs of demyelinating disease. Lastly, as all the RIS subjects fulfill the 2005 MS criteria for dissemination in space on their index scan, it is commonly considered that, when a clinical event finally occurred they fulfilled the diagnostic criteria for MS.

Expert opinions on monitoring and treating RIS have been proposed in several countries, including the United States, Europe, and Argentina. These guidelines have generally proposed neuraxis imaging, examination of CSF, the use of 2009 RIS diagnostic criteria, and clinical follow-up. Some data suggest that when gadolinium-enhancing lesions were visible on baseline scans or during follow-up, neurologists advised treatment[25,26], despite the fact that DMTs are not currently recommended for individuals with RIS given their asymptomatic state, the risk of misidentification, and the possibility that they may not progress to develop clinical symptoms. According to

McDonald criteria, RIS subjects who experience a seminal clinical event related to CNS inflammation with history of contrast enhancing lesions preceding this episode would fulfill criteria for MS. However, based on findings showing that early initiation of DMTs benefits patients with early relapsing-remitting MS, the impact of DMTs in RIS individuals with gadolinium-enhancing lesions on brain MRI is yet to be established, even in those individuals deemed at high risk for conversion. To that effect, two randomized, placebo-controlled studies with oral DMT are ongoing to evaluate the impact of immuno-intervention on the course of RIS[27,28]. These 2 studies are focused on subjects meeting criteria for RIS and not specifically those fulfilling predictive risk factors reported in this study. Although, a large effect size would be anticipated with the inclusion of subjects with 4 risk factors at baseline, recruitment limitations would be expected given that a lower number of potential individuals would be available.

Our findings should be evaluated in the context of study limitations including the retrospective design, to the validity of MRI data interpretation given the fact that different MRI scanners and variable field strengths were used, the lack of utilization of an adjudication committee for confirming relapses, and incomplete follow-up of some patients at previously participating centers. Potential biomarkers involving MRI, serum, and CSF, including neurofilament-light chain or chitinases, were not considered in this analysis, but are currently subjects of ongoing investigations[29,30]. The limitations of our study underscore the need for future RIS individuals to be evaluated clinically and by MRI, and then followed prospectively at regular intervals according to standardized procedures. Continued efforts to identify an alternate diagnosis for the observed MRI anomalies should also be performed. It is also important to highlight that some RIS subjects in this cohort were exposed to DMT prior to an initial clinical event, which may have impacted our outcomes.

Which rigorous application of RIS diagnostic criteria, approximately half (51%) of subjects experience a first clinical event within 10 years, especially those with infratentorial/spinal cord lesions, younger subjects and those with positive CSF. These factors should assist clinicians counsel patients about individual risk. Randomized clinical trials are ongoing and will help address the question of treatment of individuals with RIS. Individual treatment initiatives are not currently supported despite the extensive literature supporting the association of early MS treatment and reduction in the frequency of clinical attacks.

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Authors Contributions

CLF, OK, AS, MPS, DP, DTO contributed to the conception and design of the study, data acquisition and data analysis, drafted and critically reviewed the manuscript.
All other authors included in the 10-yr RISC Study group contributed substantially to acquisition of data, and commented on, revised, and approved the final version to data acquisition (supplementary table 3).

Potential Conflicts of interests

CLF, OK, AS, MPS, DP and DTO report no conflict of interest which may be affected by the study.
Included in the 10-yr RISC Study group, CJA, MPA, CB, EB, BB, JC, MC, BMK, MI, DAL, ELP, NdS, PL, CL, NM, GM, LM, XM, JP, JdS, ET, MTi, MTu, UU, PV, BW, BZ report no conflict of interest which may be affected by the study.

Appendix: on behalf the 10-year Radiologically Isolated Syndrome Consortium (RISC) study group, Société Francophone de la Sclérose En Plaques (SFSEP), Observatoire Français de la Sclérose En Plaques (OFSEP)

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Legends for Figures

Figure 1: Kaplan-Meier survival analysis with the endpoint of time to the first acute or progressive event at 10-years for the entire RIS cohort. The cumulative probability of a clinical event at 10 years was 51.2% (standard error=2.5%).

Figure 2: Kaplan-Meier survival analysis with (a) age as a prognostic factor and (b) positive CSF as a prognostic factor.

Figure 3: Kaplan-Meier survival analysis with (a) spinal cord lesions as a prognostic factor and (b) infratentorial lesion as a prognostic factor.

Figure 4: Kaplan-Meier survival analysis with the endpoint of time to the first acute or progressive event at 10-years for the entire RIS cohort considering the time of the baseline MRI.

Figure 5: Kaplan-Meier survival analysis with the endpoint of time to the first acute or progressive event at 10-years for the entire RIS cohort considering the number of risk factors.

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