Prognostic Indicators in Pediatric Clinically Isolated Syndrome

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Italian iMedWeb Registry and MSBase Registry collaborators are available as an online supplementary file.

Additional supporting information can be found in the online version of this article.

Objective: To assess prognostic factors for a second clinical attack and a first disability-worsening event in pediatric clinically isolated syndrome (pCIS) suggestive of multiple sclerosis (MS) patients.
Methods: A cohort of 770 pCIS patients was followed up for at least 10 years. Cox proportional hazard models and Recursive Partitioning and Amalgamation (RECPAM) tree-regression were used to analyze data.
Results: In pCIS, female sex and a multifocal onset were risk factors for a second clinical attack (hazard ratio [HR], 95% confidence interval [CI] = 1.28, 1.06–1.55; 1.42, 1.10–1.84, respectively), whereas disease-modifying drug (DMD) exposure reduced this risk (HR, 95% CI = 0.75, 0.60–0.95). After pediatric onset MS (POMS) diagnosis, age at onset younger than 15 years and DMD exposure decreased the risk of a first Expanded Disability Status Scale (EDSS)-worsening event (HR, 95% CI = 0.59, 0.42–0.83; 0.75, 0.71–0.80, respectively), whereas the occurrence of relapse increased this risk (HR, 95% CI = 5.08, 3.46–7.46). An exploratory RECPAM analysis highlighted a significantly higher incidence of a first EDSS-worsening event in patients with multifocal or isolated spinal cord or optic neuritis involvement at onset in comparison to those with an isolated supratentorial or brainstem syndrome. A Cox regression model including RECPAM classes confirmed DMD exposure as the most protective factor against EDSS-worsening events and relapses as the most important risk factor for attaining EDSS worsening.
Interpretation: This work represents a step forward in identifying predictors of unfavorable course in pCIS and POMS and supports a protective effect of early DMD treatment in preventing MS development and disability accumulation in this population.

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Patients with pediatric onset (before the age of 18 years) multiple sclerosis (POMS) represent 3 to 10% of the total multiple sclerosis (MS) population.[1–12] An onset before age 10 is even less frequent, accounting probably for <1% of total MS cases.[9,13–15] The estimated annual incidence of POMS ranges between 0.13 and 0.6 in 100,000 in different countries.[10,12,15–18] POMS usually starts with the occurrence of a first attack of demyelination, termed pediatric clinically isolated syndrome (pCIS),[19] characterized by a monofocal or multifocal clinical central nervous system event of presumed inflammatory demyelinating cause with acute or subacute onset in the absence of encephalopathy, not explained by fever or systemic illness and that does not meet the 2010 McDonald MS criteria on baseline magnetic resonance imaging (MRI).[20] The majority of children with pCIS experience a second clinical attack and consequently convert to clinically definite MS (CDMS) within a variable time ranging between 11 and 71.3 months.[6,8–10,21–23]

POMS subjects tend to have higher relapse rate,[24,25] higher MRI lesion accrual,[26] and more prominent cognitive deficits[27] early in their disease course than adult onset MS (AOMS).

Although time to conversion to a secondary progressive (SP) course is longer in POMS than in AOMS, SP patients' median age is lower in POMS in comparison to AOMS, suggesting that POMS is not a more benign disease[7,9] in comparison to AOMS. Recent MRI data have demonstrated that POMS patients have a smaller overall brain volume than would be expected for age,[28] suggesting that demyelinating lesions may impact brain growth and development. For this reason, although the currently available disease-modifying drugs (DMDs) are not licensed for POMS, their off-label prescription is increasing in this subpopulation.[29,30]

Prognostic demographic, topographic, clinical (age, sex, symptoms at first presentation, relapses after the first attack), MRI (number of brain T2 lesions), and laboratory (cerebrospinal fluid–restricted IgG oligoclonal bands [CSF OB]) factors predicting conversion to CDMS or the risk of disability accumulation over time have been extensively studied in adult CIS.[9,31–46]

As POMS is a rare disease, very few studies on small populations tried to determine which patients with pCIS are at highest risk for CDMS and disability worsening. Predictors for an increased risk of time to second attack in the KIDMUS study,[8,9,47] the largest prospective series of pCIS to date, included demographic (age > 10 years) and topographic (optic neuritis [ON]) characteristics, and MRI features (multiple well-defined periventricular or subcortical lesions suggestive of MS) at onset. Myelitis or altered mental status impairment at onset were associated with a decreased risk of conversion to CDMS.[8,47] Abnormal cranial MRI, presence of CSF OB, and age were confirmed as independent predictors of conversion to CDMS in a series of children with isolated ON.[48]

Occurrence of severe disability and SP course in pCIS[8,9,47,48] were more frequently found in children with disability sequelae after the first attack, a short interval between the first 2 demyelinating episodes, a large number of relapses, and progressive onset. However, there was no consistent correlation between gender, age at onset, or a polysymptomatic versus monosymptomatic onset in disease course prognosis,[6,47,49,50] so that it is still challenging to identify children who could benefit from very early initiation of a DMD treatment.

Although several randomized clinical trials (RCTs)[51–56] and their extension phases[57,58] demonstrated that early treatment with DMDs can delay conversion to CDMS and accumulation of medium to long-term disability in adult onset CIS patients, comparable evidence is currently lacking in pCIS.

The aim of this multicenter, collaborative study was to assess prognostic factors, including DMD exposure, for time

to second clinical attack and a first disability-worsening event in a large cohort of pCIS prospectively collected and followed up for up to 10 years in 2 large registries: the Italian iMedWeb Registry and the MSBase Registry.

Patients and Methods

Ethics Statement

The Italian iMedWeb Registry was approved by the Polyclinic of Bari Ethics Committee and by the local ethics committees at all participating centers. The MSBase Registry was approved by the Melbourne Health Human Research Ethics Committee and by the local ethics committees at all participating centers. Written informed consent was obtained from all enrolled patients, or in the case of pediatric patients from their parents, in accordance with the Declaration of Helsinki.

Study Population

This was a large, multicenter, retrospective observational study performed on prospectively acquired data. Longitudinal data from pCIS patients, with an age at onset < 18 years and with a first clinical visit within 1 year from the disease onset, were extracted from the Italian iMedWeb Registry and the MSBase Registry in June 2015.

All the participating centers use iMed software to collect uniform information about all patients with MS who have been examined as outpatients or inpatients. Information is collected by well-trained neurologists in a retrospective manner at the first visit, and prospectively every 6 months thereafter. Quality assurance through online certification of Expanded Disability Status Scale (EDSS) competency is required at each participating site.

Patients included in this analysis had a diagnosis of pCIS or POMS.[19] Patients with a diagnosis of monophasic or recurrent acute disseminated encephalomyelitis (ADEM) were not included in the analysis, whereas patients with an ADEM-like onset and a second nonencephalopathic clinical attack were considered.[19]

Patients with a progressive disease course from onset were excluded from this study.

Baseline data included demographics, date of onset and topography of pCIS (isolated ON, isolated spinal syndrome, isolated supratentorial syndrome [including ADEM-like onset], isolated brainstem syndrome; or multifocal if > 2 of these locations were involved), and disability level according to the EDSS score. Brain MRI features as well as CSF data regarding presence/absence of OB were also extracted, if available.

Follow-up data collected approximately biannually included date of visit, date of MS diagnosis, EDSS score, relapses, and DMD treatment prescription (date of start and end of each treatment) since the patient's last visit. Date of brain MRI follow-up was also recorded.

A minimum of 3 visits per patient spanning a minimum 9 months, with full EDSS evaluation, was required to define a minimum 3-month confirmed disability-worsening event.

Disability worsening was defined as a minimum 1-point increase in EDSS score above a baseline value if the baseline EDSS was 1 to 5.5, or $1\frac{1}{2}$-point increase if the baseline EDSS was zero, or half-point increase above baseline EDSS scores ≥ 6.0. A confirmation at repeat assessment at least 3 months later was required to confirm the EDSS-worsening event. EDSS scores recorded during relapses were excluded. Brain MRI data were included as a prognostic factor if performed within 1 year from the onset and before the occurrence of a second attack or the first EDSS-worsening event. Brain MRI T2 lesion load was classified according to the following criteria: 0 to 2 lesions or > 2 lesions. CSF data were also retrieved. CSF data were recorded as presence/absence of CSF OB.

Statistical Analyses

In descriptive analyses, continuous covariates were summarized as median and interquartile range (IQR), and categorical variables were expressed as frequency and percentage. Median times from onset to each outcome were based on Kaplan–Meier estimates.

Univariate and multivariate Cox proportional hazard regression models were performed to identify predictive factors for shorter time to second attack or a first confirmed EDSS-worsening event.

For the analysis to the second attack, the date of onset was considered as time of origin in the Cox model. For the analysis to a first confirmed EDSS-worsening event, the date of MS diagnosis was used as time of origin to more properly evaluate predictor factors of disability worsening after excluding pCIS patients who did not convert to MS during the follow-up and thus with lower probability of having disability worsening. Times to events were calculated from the date of origin to the date of outcome occurrence or last follow-up.

In both univariate and multivariate analysis models, the following covariates were tested: sex, age at onset ($\leq$12, 12–15, and $>$15 years), symptoms at onset (isolated ON, isolated myelitis, isolated supratentorial syndrome, isolated brainstem syndrome, or multifocal symptoms), brain MRI T2 lesions ($\leq$2 and $>$2), CSF OB (positive and negative), and decade of birth and treatment (handled as time-dependent covariates). For the time to a first confirmed EDSS-worsening event, relapses occurring before disability progression were included as a time-dependent covariate, and relapses (1 vs 2) and DMD exposure (yes vs no) before the MS diagnosis were also considered.

For the multivariate models, multiple imputation with expectation maximization (EM) and bootstrapping was used to overcome the presence of missing data.[59]

The missing values of the brain MRI T2 lesions and of the CSF OB were imputed based on a multivariate linear model using all the covariates included in the multivariate Cox proportional hazard regression models for each outcome. MRI T2 lesions and CSF OB status, respectively, were included as dependent variables in the multivariate linear regression models. For the covariates that were not normally distributed, a transformation has been performed to make them roughly continuous and unbounded.

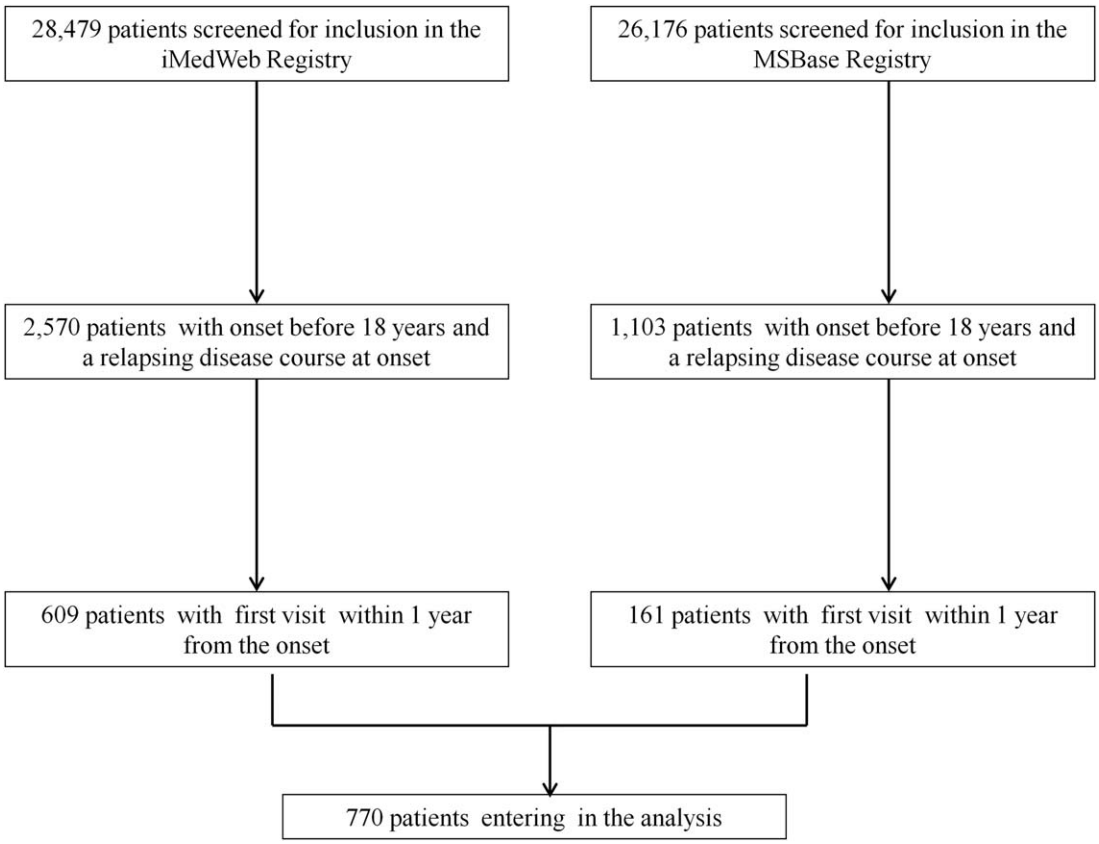


FIGURE 1: Patients' disposition.

The multiple imputation with EM and bootstrapping was performed using the Amelia Package for R. This R package implements different algorithms. First, a dataset with the same dimension as the original data is obtained by a bootstrap (n = 1,000) procedure. Second, the algorithm estimates the sufficient statistics (with priors if specified) by EM, and then imputes the missing values of sample. It repeats this process *m* times to produce the *m* complete datasets where the observed values are the same and the unobserved values are drawn from their posterior distributions. Finally, utilizing each of the multiply-imputed datasets separately, we carry out statistical analyses and combine the results of the *m* (in our case 15) statistical analyses to calculate a point estimate.

The assumptions we have applied (number of imputations = 15, bootstraps = 1,000) ensure a missing imputation with a relative efficiency > 95% and robust estimates.[60]

Results were expressed in terms of hazard ratios (HRs) with 95% confidence intervals (95% CIs).

Furthermore, the Recursive Partitioning and Amalgamation (RECPAM) method[61,62] was used as an exploratory analysis to identify distinct and homogeneous subgroups of patients at different risk of EDSS progression, using as time of origin the date of MS diagnosis. This tree-based method integrates the advantages of main effects of standard Cox regression and tree-growing techniques. At each partitioning step, the method chooses the covariate and its best binary split to maximize the difference in the risk of reaching the outcome. The algorithm stops when user-defined conditions (stopping rules) are met. In the RECPAM model, we tested the same set of variables used in the Cox regression analysis, except for the time-dependent variables (treatment and relapses before progression) that were added in the final Cox model. In our RECPAM analysis, a minimum set of 0 confirmed progression of EDSS after MS diagnosis and 20 subjects per node were considered. A final exploratory Cox regression analysis including the RECPAM classes was carried out. Probability values were 2-sided, and values < 0.05 were considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.2.0.

Results

A cohort of 770 patients with pCIS was extracted from the Italian iMedWeb Registry (44 contributing MS centers) and the MSBase Registry (32 contributing MS centers) in June 2015 (Fig 1). See Supplementary Table 1 for the complete list of participating centers. Demographic and clinical characteristics of this cohort are shown in Table 1. Four hundred ninety-three (64.0%) patients underwent a CSF tap, and 494 (64.2%) had an MRI examination recorded within 1 year of onset symptoms.

The median (IQR) follow-up was 5.4 (1.9–10.8) years. Six hundred two (78%) patients experienced a

TABLE 1. Demographic and Clinical Characteristics of Patients with pCIS

Baseline Features	Value
Sex, F/M	544/226
Age at onset, yr, median (IQR)	16.0 (14.1–17.2)
Classes of age at onset, No. [%]	
0–≤12 years	92 [12.0]
>12–≤15 years	190 [24.7]
>15–≤18 years	487 [63.3]
pCIS topography, No. [%]	
Isolated optic neuritis	196 [26.2]
Isolated brainstem syndrome	149 [19.9]
Isolated spinal syndrome	101 [13.5]
Isolated supratentorial syndrome	173 [23.1]
Multifocal	129 [17.3]
Patients with CSF examination, No. [%]	493 [64.0]
Patients with CSF OB, positive OB/total, No. [%]	399/493 [80.9]
Patients with MRI examination, No. [%]	494 [64.2]
Patients with number of brain MRI T2 lesions = 0–2, No. [%]	58 [11.7]
Patients with number of brain MRI T2 lesions > 2, No. [%]	436 [88.3]
First EDSS evaluation, mean {SD}	1.9 {1.4}
Follow-up features	
Follow-up, yr, median (IQR)	5.4 (1.9–10.8)
Patients with a 2nd attack during the follow-up, No. [%]	602 [78.2]
Patients with an EDSS worsening during the follow-up, No. [%]	299 [24.3]
Patients treated with at least 1 DMD during the follow-up, No. [%]	614 [79.7]
Patients with a first drug prescription before 2nd attack, No. [%]	200 [26.0]
Patients with a first drug prescription before first EDSS worsening event, No. [%]	156 [52.2]

CSF = cerebrospinal fluid; DMD = disease-modifying drug; EDSS = Expanded Disability Status Scale; F = female; IQR = interquartile range; M = male; MRI = magnetic resonance imaging; OB = oligoclonal bands; pCIS = pediatric clinically isolated syndrome; SD = standard deviation.

second attack, and 299 (24.3%) experienced a confirmed EDSS-worsening event during follow-up. Five hundred twenty-one (66.7%) patients received 1 or more DMDs during follow-up; 200 (26.0%) of these received their first DMD prescription before the second clinical attack (79.0% interferon beta, 6.5% glatiramer acetate, 5.0% natalizumab, 9.5% other immunomodulators/immunosuppressive drugs) and 468 (60.8%) before the first EDSS-worsening event (76.7% interferon beta, 4.7% glatiramer acetate, 4.5% natalizumab, 3.0% azathioprine, 11.1% other immunomodulators/immunosuppressive drugs).

Second Attack

The median (IQR) time between the onset and the second attack was 0.7 (0.3–2.2) years.

Supplementary Table 2 reports demographic and clinical characteristics of patients with and without a second clinical attack during follow-up. The univariate analysis showed that female patients (HR = 1.23, 95% CI = 1.02–1.48), patients with a multifocal disease onset (HR = 1.32, 95% CI = 1.03–1.70), and patients with at least 3 brain MRI T2 lesions (HR = 1.72, 95% CI = 1.11–2.64) were at higher risk of developing a second attack. Neither presence of OB nor early DMD

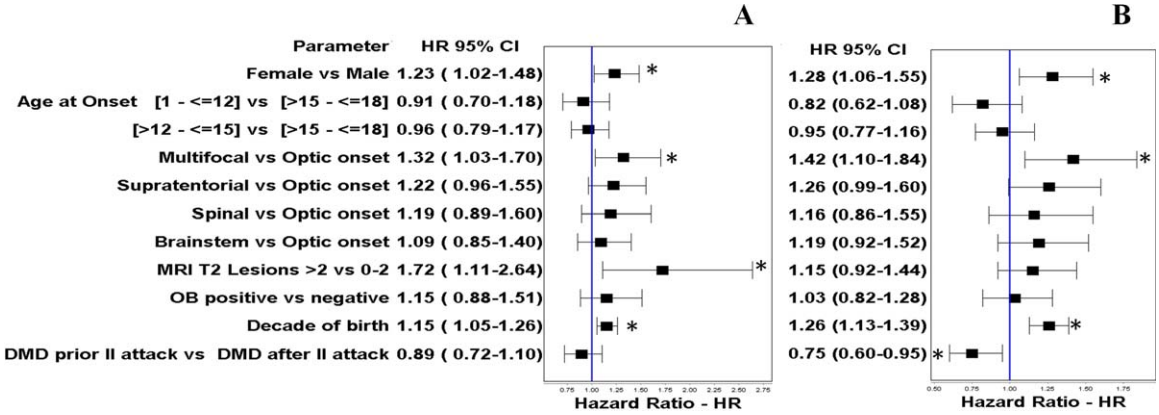


FIGURE 2: Risk of a second clinical attack during follow-up in pediatric clinically isolated syndrome patients. (A) Univariate and (B) multivariate Cox proportional hazard regression models. CI = confidence interval; DMD = disease-modifying drug; MRI = magnetic resonance imaging; OB = oligoclonal bands. *$p < 0.05$. [Color figure can be viewed at www.annalsofneurology.org]

treatment were predictive of time to a second attack (Fig 2).

In the multivariate model, female patients (HR = 1.28, 95% CI = 1.06–1.55) and a multifocal disease onset (HR = 1.42, 95% CI = 1.10–1.84) were confirmed as independent risk factors for the second attack. Moreover, this model showed a significantly lower risk for a second attack in patients who started DMDs (from the time of initiation of DMDs), relative to patients who did not start DMDs (HR = 0.75, 95% CI = 0.60–0.95; see Fig 2).

First Confirmed EDSS-Worsening Event

The median (IQR) time between MS diagnosis and the first EDSS-worsening event was 3.2 (1.1–6.7) years. Demographic and clinical characteristics of all pCIS patients and pCIS patients who converted to MS, stratified by the occurrence of a first confirmed EDSS-worsening event, are shown in Supplementary Table 3. In Figure 3, the univariate and multivariate Cox models are reported.

In the univariate model, the occurrence of relapse was a strong determinant of an increased risk of a first EDSS-worsening event (HR = 4.48, 95% CI = 3.11–6.46), whereas an age at onset < 15 years and a supratentorial syndrome at onset were found to be protective (HR = 0.69, 95% CI = 0.50–0.96; HR = 0.67, 95% CI = 0.45–0.98, respectively). No effect of sex, CIS topography, brain MRI T2 lesions, OB, and DMD exposure was detected in the univariate model.

In the multivariate Cox model, age at onset < 15 years (HR = 0.59, 95% CI = 0.42–0.83) and DMD exposure before the first confirmed EDSS worsening event (HR = 0.75, 95% CI = 0.71–0.80) prolonged the time to this outcome, whereas the occurrence of relapse was a strongly significant risk factor associated with a shorter time to a first EDSS worsening event (HR = 5.08, 95% CI = 3.46–7.46).

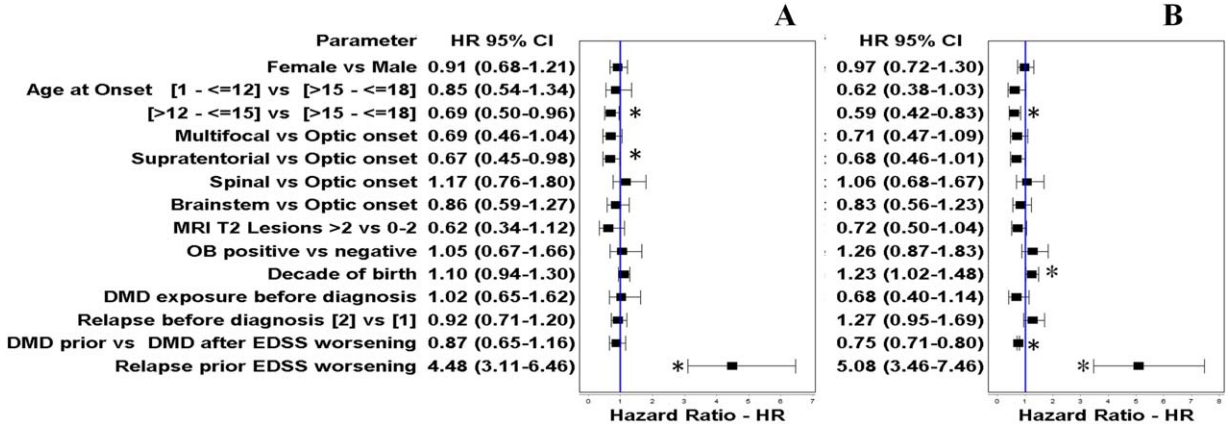
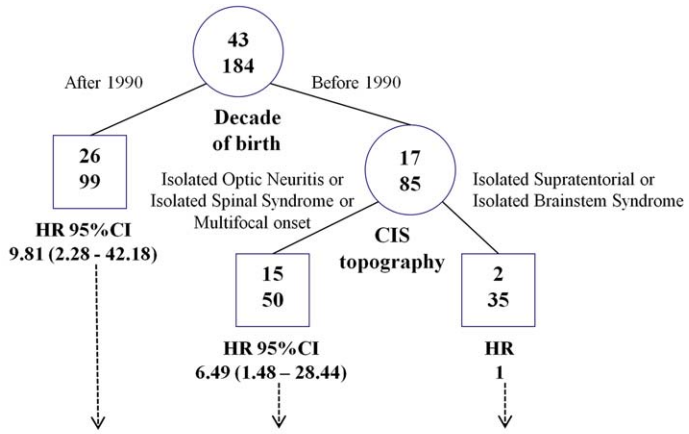


FIGURE 3: Risk of attaining a first confirmed EDSS-worsening event during follow-up. (A) Univariate and (B) multivariate Cox proportional hazard regression models in pediatric onset multiple sclerosis patients. CI = confidence interval; DMD = disease-modifying drug; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; OB = oligoclonal bands. *$p < 0.05$. [Color figure can be viewed at www.annalsofneurology.org]



VARIABLE	Class 1	Class 2	Class 3	*p*
Females, *n* (%)	73 (73.7)	38 (76.0)	29 (82.86)	0.5537
Classes of Age at Onset, years, *n* (%)				
0 - ≤12	19 (19.2)	3 (6.0)	0 (0.0)	0.0048
> 12 - ≤15	28 (28.3)	11 (22.0)	7 (20.0)	
> 15 - ≤18	52 (52.5)	36 (72.0)	28 (80.0)	
CIS topography, *n* (%)				
Isolated Optic Neuritis	20 (20.2)	21 (42.0)	0 (0.0)	<0.0001
Isolated Brain-Stem Syndrome	24 (24.2)	0 (0.0)	17 (48.6)	
Isolated Spinal Syndrome	16 (16.2)	8 (16.0)	0 (0.0)	
Isolated Supratentorial Syndrome	17 (17.2)	0 (0.0)	18 (51.4)	
Multifocal	22 (22.2)	21 (42.0)	0 (0.0)	
First DMD prescription before EDSS worsening, *n* (%)	84 (84.9)	40 (80.0)	29 (82.3)	0.7557
Patients with > 2 Brain MRI T2 lesions, *n* (%)	90 (91.0)	48 (96.0)	34 (97.1)	0.3066
OB Positive	90 (91.0)	44 (88.0)	30 (85.7)	0.6667
Relapse/s before EDSS Worsening, *n* (%)	18 (18.2)	1 (2.0)	1 (2.9)	0.0027

FIGURE 4: RECPAM (Recursive Partitioning and Amalgamation) risk classes from a "pruned" tree for a first confirmed EDSS worsening event in pediatric onset multiple sclerosis patients. Circles represent nodes; squares represent leaves. The first number in each figure represents the total number of patients with the event; the second number represents the total number of patients included in the group. CI = confidence interval; CIS = clinically isolated syndrome; DMD = disease-modifying drug; EDSS = Expanded Disability Status Scale; HR = hazard ratio; MRI = magnetic resonance imaging; OB = oligoclonal bands. [Color figure can be viewed at www.annalsofneurology.org]

RECPAM Analysis for a first Confirmed EDSS-Worsening Event

An exploratory RECPAM analysis was used to identify distinct and homogeneous subgroups of POMS patients at different risk of reaching a first EDSS-worsening event. RECPAM analysis led to the identification of 3 heterogeneous risk classes from a "pruned" tree (Fig 4).

The most important variable in discriminating this risk was the decade of birth, followed by the pCIS topography, with the lowest incidence in patients born before 1990 followed by those with a supratentorial or a brainstem syndrome at onset (reference category: class 3; HR = 1).

In comparison with patients belonging to class 3, those born before 1990 but with isolated ON or spinal syndrome, or multifocal symptoms at onset, had a 6-fold increased risk (class 2; HR = 6.49, 95% CI = 1.48–28.44), and those born after 1990 (class 1; HR = 9.81, 95% CI = 2.28–42.18) had a 10-fold higher incidence of EDSS progression. The characteristics for each class were reported in Figure 4.

POMS patients belonging to the lowest risk class (class 3) compared to those belonging to class 1 and 2 less frequently had an age at onset younger than 12 years (0% vs 19.2% and 6%) and isolated ON (0% vs 20.2% and 42%), spinal syndrome (0% vs 16.2 and 16%), or multifocal involvement (0% vs 22.2% and 42%) at onset, whereas they more frequently had an isolated supratentorial (51.4% vs 17.2% and 0%) or brainstem syndrome (48.6% vs 24.2% and 0%) at onset. Notably, POMS patients belonging to the highest risk class (class 1) more frequently had relapses before EDSS worsening than those in classes 2 and 3 (18.2% vs 2.0% and 2.9%).

The final Cox regression model, including RECPAM classes, confirmed DMD exposure as the most important protective factor (HR = 0.33, 95% CI = 0.14–0.77) and relapses after diagnosis as the most

TABLE 2. Post-RECPAM Cox Regression Model for a first EDSS-Worsening Event in POMS Patients with RECPAM Classes Included in the Model

Variable	HR (95% CI)	*p*
RECPAM class 1 vs 3	18.66 (4.04–86.15)	0.0002
RECPAM class 2 vs 3	8.42 (1.89–37.43)	0.0052
Female vs male	0.62 (0.32–1.22)	0.1702
Class of age at onset		
0–≤12 years	0.30 (0.10–0.94)	0.0392
>12–≤15 years	0.81 (0.39–1.66)	0.5581
Brain MRI T2 lesions, > 2 vs 0–2	0.80 (0.26–2.46)	0.6992
OB, positive vs negative	2.69 (0.60–11.98)	0.1947
DMD exposure before diagnosis	0.26 (0.06–1.19)	0.082
Relapse before diagnosis, 2 vs 1	1.23 (0.62–2.41)	0.5523
DMD exposure before EDSS worsening	0.33 (0.14–0.77)	0.0103
Relapses prior to EDSS worsening	5.91 (2.47–14.14)	<0.0001

CI = confidence interval; DMD = disease-modifying drug; EDSS = Expanded Disability Status Scale; HR = hazard ratio; MRI = magnetic resonance imaging; OB = oligoclonal bands; POMS = pediatric onset multiple sclerosis; RECPAM = Recursive Partitioning and Amalgamation.

important risk factor (HR = 5.91, 95% CI = 2.47–14.14) for EDSS-worsening events in this POMS population (Table 2). Moreover, this model confirmed a higher risk of an EDSS-worsening event for patients belonging to RECPAM classes 1 and 2 in comparison to patients belonging to RECPAM class 3 (HR = 18.66, 95% CI = 4.04–86.15; HR = 8.42, 95% CI = 1.89–37.43, respectively), and a lower risk for patients with an age at onset younger than 12 years in comparison to those with an age at onset older than 15 years (HR = 0.30, 95% CI = 0.10–0.94; see Table 2).

Discussion

Our study is the first attempt to evaluate predictors, including DMD exposure, for the risk of a second attack and a first EDSS-worsening event in a cohort of >700 patients with pCIS, prospectively followed for a median of >5 and up to 10 years in 2 large MS registries: the Italian iMedWeb Registry and the MSBase Registry. In accordance with previous studies,[4–6,9,21,30,63] about 80% of our patients experienced a second attack in a median time of 0.7 years with a range between 0.3 and 2.2 years. About a quarter of them experienced an EDSS-worsening event in a median time of 3.4 years, and 67% of them received at least 1 DMD treatment. In line with other reports,[64,65] we found that 81% of pCIS patients who underwent CSF examination showed a positive CSF OB status and 88% of those who underwent MRI examination had at least 3 MRI brain lesions.

Comparing demographic and clinical characteristics between patients with and without a second clinical attack during the follow-up, we found greater percentages of females and patients with CSF OB and a lower frequency of patients with a first DMD prescription in the group of pCIS patients who experienced a second attack. These results are in accordance with previous studies in adult onset and pediatric onset CIS patients.[37,39,40,50] The univariate analyses for the risk of a second attack confirmed that female patients have a higher risk, but also highlighted an increased risk in patients with a multifocal disease onset and with at least 3 MRI T2 brain lesions as already demonstrated in adult onset CIS[39] and in other series of pCIS.[8,47]

The multivariate model further confirmed the higher risk for a second clinical attack in females and in patients with multifocal onset, but also showed a significant impact of DMD exposure in patients who started DMDs before the second attack. The prognostic implications of gender in determining the risk of a second clinical attack have already been demonstrated in adult CIS,[39] whereas results regarding CIS topography are at best mixed in pediatric populations.[65]

Several previous studies of adult onset CIS as well as of pCIS showed that the presence of T2 brain lesions was associated with a higher risk of future clinical

events.[36,37,41,42,48] In our multivariate model, a trend for a higher risk of a second attack was found in patients with at least 3 MRI T2 brain lesions, but this did not reach a statistical significance.

As already demonstrated in RCTs[51–58] and observational cohorts[37,66] of adult CIS patients, we found a significant protective effect of a DMD treatment, started after the first attack, against the occurrence of a second attack.

The presence of CSF OB was not a significant predictor of the time to a second attack in our cohort. So far contradictory results on the effect of OB positivity for time to relapse in selected cohorts of children with isolated ON have been reported by the same group.[48,67]

Both the univariate and multivariate Cox models for attaining EDSS worsening showed that the occurrence of relapse after MS diagnosis was the only significant factor for this outcome. In particular, the presence of at least 1 relapse after MS diagnosis increased this risk almost 5-fold in comparison to patients with no subsequent relapses. The role of relapses in the accumulation of disability is still somewhat controversial in AOMS.[9,31,33,44,45,68] However, a higher number of relapses during the first year or the first 2 years of the disease has been shown to be associated with a higher rate of SP and severe disability milestones in previous studies in AOMS[33,44,45] and POMS.[8,9] It is noteworthy that in the present study we have investigated the role of relapse occurrence as a time-dependent covariate, whereas previous studies usually have included the number of relapses during the first years (eg, the first 2–5 years) of the disease.

A younger age at onset was found to be a significant protective factor against the risk of EDSS worsening, especially for patients with onset between 12 and 15 years. This was confirmed in the multivariate Cox analysis, after adjustment for all other covariates; POMS patients with an onset between 12 and 15 years had a 41% lower risk of EDSS worsening in comparison to patients with a disease onset between 15 and 18 years.

These findings are in line with the results of previous studies of AOMS and POMS in which patients younger than 18 years took 10 years longer than AOMS patients to reach disability milestones and SP course.[7,9] Most important, the most significant protective factor shown by the multivariate models for the risk of EDSS worsening was early DMD exposure.

This finding is novel and clearly demonstrates the importance of early treatment in pCIS and POMS, as already reported for adult CIS.[51–58]

Finally, the RECPAM analysis, which integrates the advantages of main effects of standard Cox regression and tree-growing techniques, allowed us to better identify distinct and homogeneous subgroups of POMS patients at different risk of reaching an EDSS-worsening event.

The most important variable in discriminating this risk was the decade of birth, followed by the pCIS topography, with the lowest incidence in patients born before 1990 followed by those with a supratentorial or brainstem syndrome at onset, and the highest incidence (9.8 times higher) in those born after 1990.

These results seem to support the hypothesis that a first attack with cognitive deficit (included in the supratentorial class) may predict a lower incidence of physical disability accumulation.

Historically, the topography of the first demyelinating event has been deemed an important clinical factor related to MS prognosis in AOMS.[31–33]

The RECPAM analysis revealed that the highest risk class (class 1) included POMS patients who reported additional relapses more frequently than those in classes 2 and 3 (18.2% vs 2.0% and 2.9%).

Notably, the final Cox regression model including RECPAM classes confirmed DMD exposure as the most important protective factor against EDSS worsening, and relapses after diagnosis as the most important risk factor for attaining EDSS worsening in this POMS population.

In conclusion, the strength of this study is its cohort size, one of the biggest ever studied, with acquisition of data performed prospectively. Our pCIS cohort is both multicenter and multinational, enabling, by a rigorous statistical approach, better identification of prognostic indicators. The major limits of this multicenter study are the lack of standardized protocols for CSF analysis and the lack of a systematic MRI acquisition and analysis protocol, and also the quite large amount of missing information on CSF and MRI features, which could be responsible of their poor significance as prognostic factors, unlike the results found in adult onset CIS cohorts collected at a single center.[37]

This work represents a step forward in identifying risk factors for conversion to CDMS in patients with pCIS and disability worsening in POMS. Moreover, for the first time, the results consistently support a beneficial effect of early DMD exposure in preventing a second attack in pCIS and medium- to long-term disability accumulation in POMS. In particular, the multivariate model showed that in patients receiving a DMD, there was a 25% reduction in the risk of EDSS worsening during follow-up compared to untreated patients. This result was further confirmed and reinforced by the Cox

regression model including RECPAM classes, which demonstrated that, independently of the other risk factors, DMD treatment significantly reduces disability worsening.

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Author Contributions

Study conception and design: P.I., M.S., G.Luc., and M.T. Contributed substantially to data acquisition and analysis: all authors. Drafted the manuscript and prepared the figures: P.I., M.S., G.Luc., and M.T. Equal first authors: P.I. and M.S.

Potential Conflicts of Interest

Nothing to report.

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