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Longitudinal trajectories of EDSS in primary progressive MS patients – A latent class approach



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Multiple Sclerosis

- Chronic and degenerative multifactorial disease
- During years patients show a great quantity of symptoms (fatigue, visual problems and loss of balance), very general and with a great heterogeneity between patients
- These symptoms cause an increasing disability up to a complete stillness
- Disability in multiple sclerosis is measured by a scale, called EDSS, that range between 0 and 10.

Stages of disease

- **Clinically Isolated Syndrome (CIS):** first episode of neurologic symptoms that lasts at least 24 hours; can be followed by clinical confirm of multiple sclerosis
- **Relapsing-remitting (RR):** about 85% of patients begin with this form of disease; relapses are alternate with remission
- **Secondary-progressive (SP):** gradual worsening of disability; more than 50% of RR go in this form after an heterogeneous number of years.
- **Primary progressive (PP):** progressive worsening of disease from onset; can be not active (without relapses during follow-up) or active.

Introduction

- ❑ Primary progressive multiple sclerosis (PPMS)
observed in 10-15% of MS patients
- ❑ Worst prognosis
- ❑ No evident prognostic factors
- ❑ First treatment (Ocrelizumab) formally approved soon
- ❑ Hot topic PPMS → Treatment strategies

Introduction

New biomarkers

Sensitive clinical outcomes

**DISABILITY ACCUMULATION
(EDSS)**

Time to EDSS 4

5 to 8 years
from onset

Time to EDSS 6

7.1 to 14 years
from onset

**LARGE
HETEROGENEITY**

Aim

- ❑ To model heterogeneity of disability accumulation trends among PPMS patients
- ❑ To identify clusters of PPMS patients with different trajectories of disability accrual over time
- ❑ To classify PPMS patients prognosis using short term disability time trend from first visit (1, 3 and 5 years)
- ❑ To find demographic and clinical characteristics associated to PPMS prognostic classes

Methods

Data

- **MSBase International Registry**
- **Inclusion criteria:** Primary progressive MS patients (active and not active), minimal dataset (birth, sex, onset, centre, disability), first visit with EDSS within 5 years from disease onset

Outcome

- Expanded Disability Status Scale (EDSS)

Statistical model

- Unsupervised advanced statistical approach
- Longitudinal growth curve mixed model with latent classes
- To model heterogeneity among patients by classifying them into unobserved groups (latent classes)
- Linear and non linear (quadratic, square root) functions of time since onset

Linear Mixed Model

For subject i at occasion j (and binary covariate c)

$$\begin{aligned} Y_{ij} = Y_i(t_{ij}) = & \beta_0 + \beta_1 \times t_{ij} + \beta_2 C_i + \beta_3 C_i \times t_{ij} && \longleftarrow \text{POPULATION LEVEL} \\ & + u_{0i} + u_{1i} \times t_{ij} && \longleftarrow \text{INDIVIDUAL LEVEL} \\ & + \epsilon_{ij} \end{aligned}$$

With $u_i \sim \mathcal{N}(0, B)$ and $\epsilon_{ij} \sim \mathcal{N}(0, \sigma^2)$

Variable C can represent an observed variable but also a non observed one.

If C is not observed this variable is «latent» → **latent class**

Linear Mixed Model with latent classes

Population of N subjects ($i, i=1, \dots, N$)

- Y_{ij} repeated measure of the outcome for subject i at occasion j ($1, \dots, N$)
- T_{ij} time of measurement at occasion j
- X_i vector of time-independent covariates

G latent homogeneous classes ($g, g=1, \dots, G$)

- C_i discrete latent variable for the latent group structure: $c_i = g$ if subject i belong to class g
- Every subject belongs to only one latent class

Two submodel

- Model for probability of latent class membership
- Model for the class-specific trajectory of characteristic (i.e.: biomarker)

Linear Mixed Model with latent classes

Probability of latent class membership explained according to covariates X_i :
→ *multinomial logistic regression*

Class-specific trajectory : linear trajectory example with observed covariates :

$$Y_{ij}|c_i=g = u_{0ig} + u_{1ig}t_{ij} + \beta_1 X_i + \beta_2 X_i t_{ij} + \epsilon_{ij}$$

with $u_{ig} = u_i|c_i=g = (u_{0ig}, u_{1ig})' \sim \mathcal{N}((\mu_{0g}, \mu_{1g})', B_g)$ class-specific RE
and $\epsilon_{ij} \sim \mathcal{N}(0, \sigma^2)$, $\epsilon_{ij} \perp u_{ig}$

- μ_{0g} and μ_{1g} class-specific mean intercept and slope
- B_g class-specific variance-covariance

Results: Patient characteristics

Characteristics	N=853
EDSS at first visit , median (IQR)	4 (2.5 – 5.5)
Time to diagnosis from onset , years (mean(SD); range)	2.2 (1.8)
Disease duration at first EDSS assessment , mean(SD)	2.4 (1.5)
Follow-up , median (range)	6.9 (0.03 – 35.1)
N. of EDSS obs. , median (range)	10 (2-52)
Relapses during f-up	
1	185 (21.7)
≥2	73 (8.6)
Turkey	6%
Others (Czech Republic, India, Iran, Kuwait, Argentina)	20.2%
Year of entry in registry	
<1980	0.6%
1980-1989	0.9%
1990-1999	13.1%
2000-2009	60.9%
2010-2015	24.5%

Results: EDSS trajectories

Mild class : n=143 (16.8%)

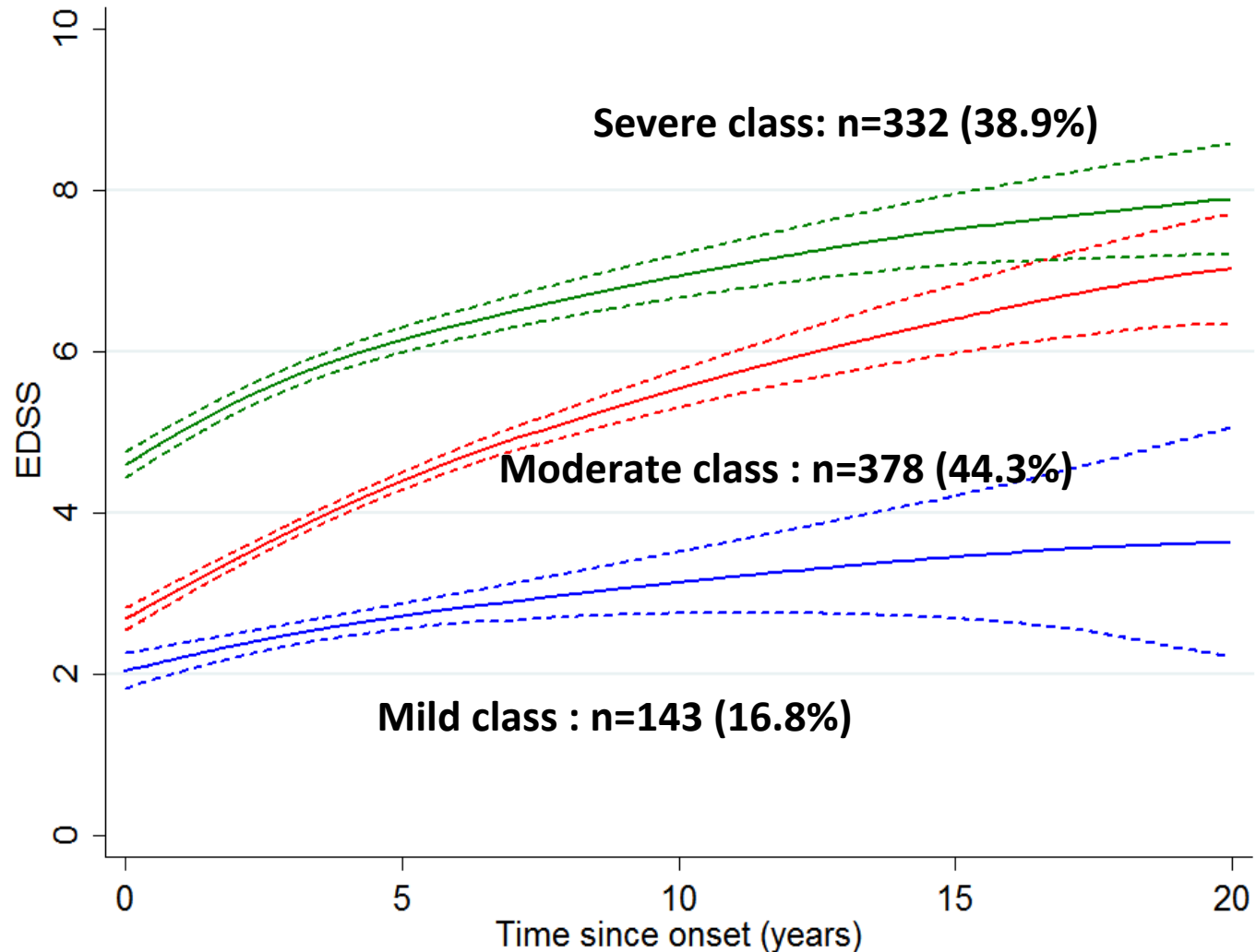
Moderate class : n=378 (44.3%)



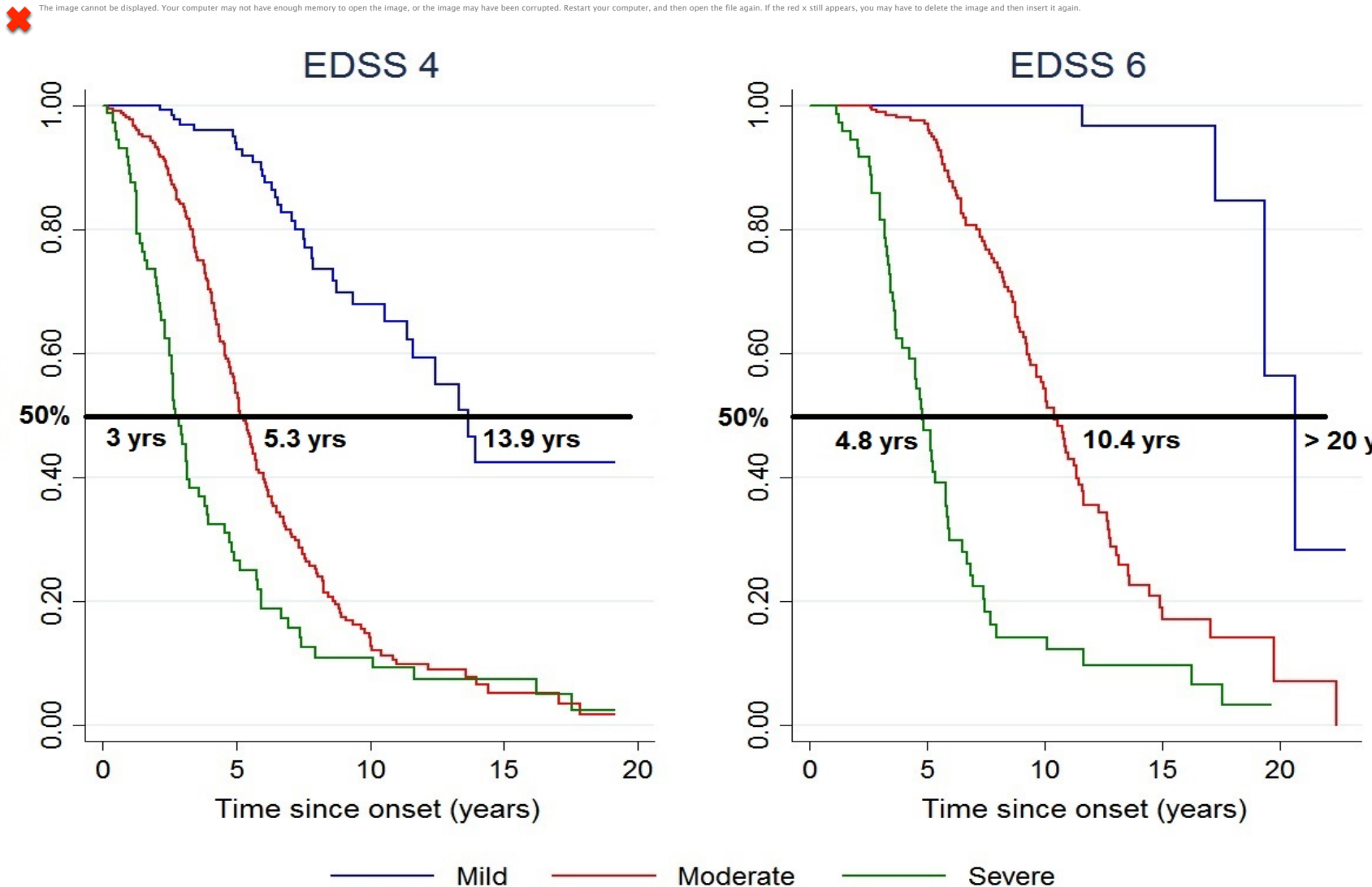
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Severe class: n=332 (38.9%)

Results: EDSS trajectories

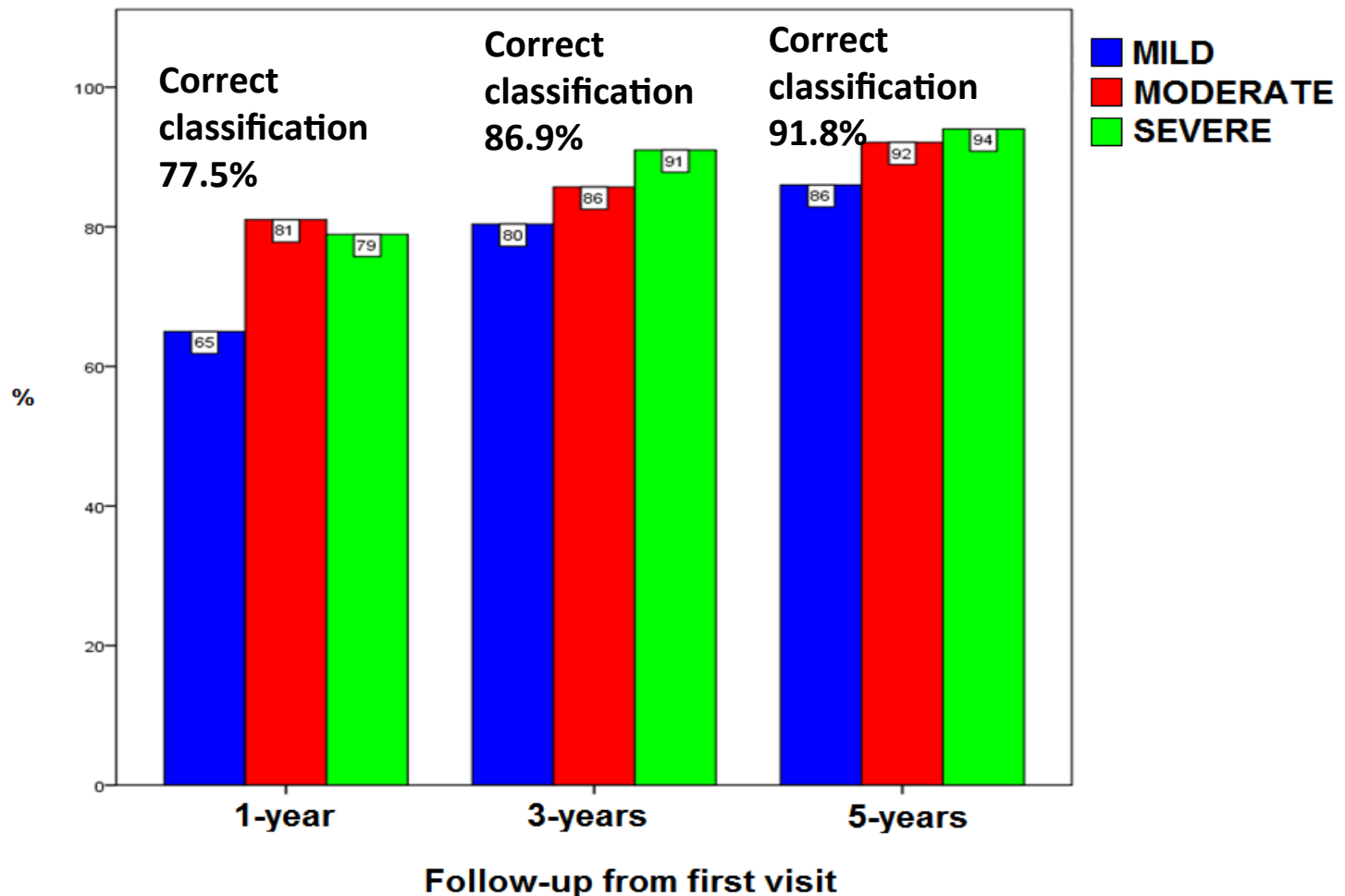


Results: Time to EDSS milestones



Prediction of final prognostic class by short-term observation

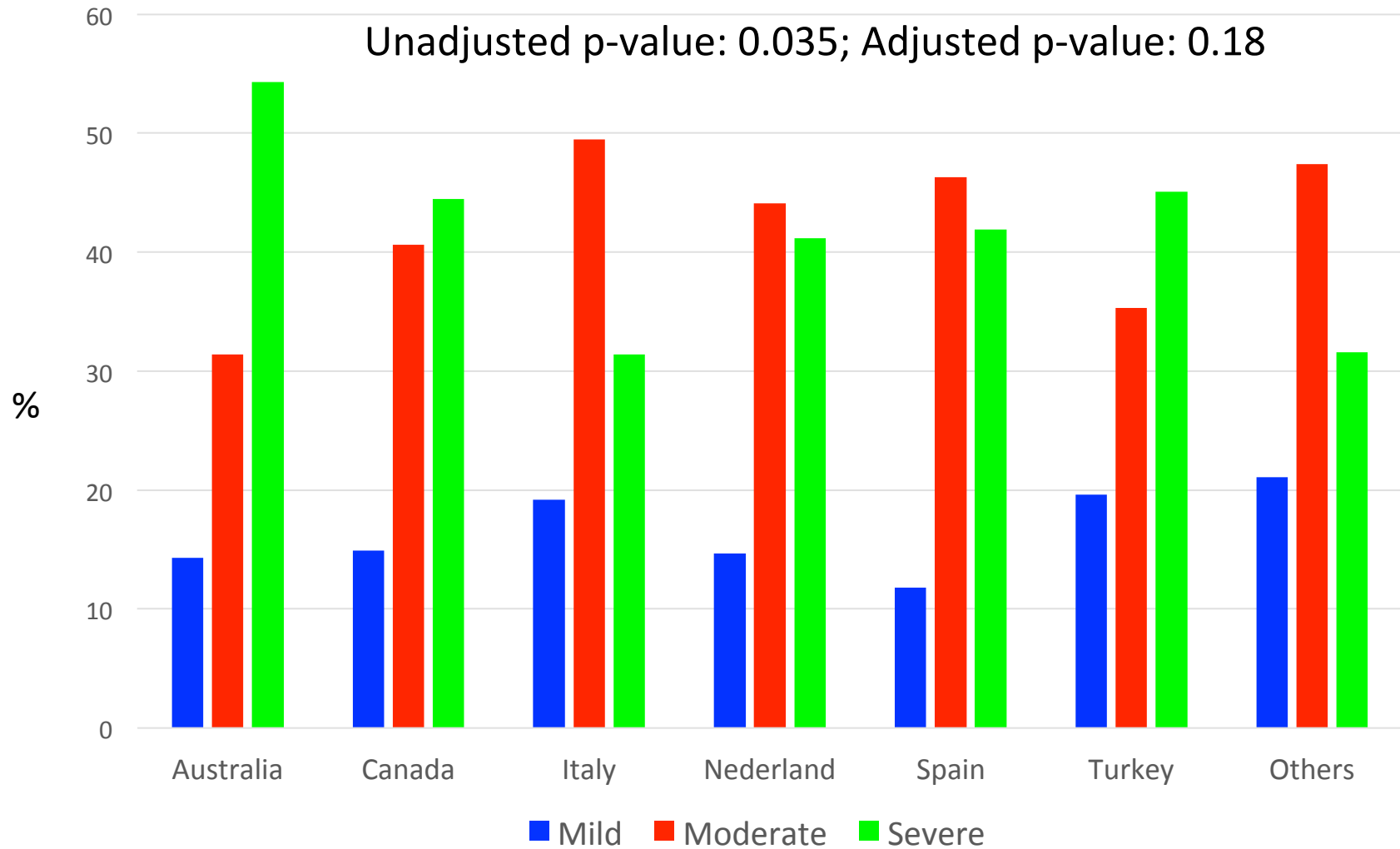
PATIENTS WITH THE SAME FINAL CLASSIFICATION AFTER A SHORT-TERM FOLLOW-UP



Clinical and demographic predictors

Characteristics	Mild (n=143)	Moderate (n=378)	Severe (n=332)	Univariable (p-value)	Multivariable (p-value)
Age at onset, mean(SD)	41.3 (11.1)	42.6 (10.3)	42.8 (11.3)	0.24	
Males	64 (44.8)	180 (47.6)	168 (50.6)	0.22	
Time to diagnosis from onset, years (mean(SD); range)	2.7 (2.2; 0.1-11)	2.3 (1.8; 0-12.7)	1.6 (1.4; 0-10)	<0.001	<0.001
Disease duration at first EDSS assessment, mean (SD)	2.3 (1.5)	2.5 (1.4)	2.3 (1.5)	0.39	
Year of first visit, median (IQR)	2006 (2001-2010)	2007 (2002-2010)	2007 (2003-2010)	0.22	
Patients with relapse during f-up	53 (37.1)	107 (28.3)	98 (29.5)	0.15	
Mean Relapse rate from onset	0.10 (0.2)	0.10 (1.6)	0.16 (0.6)	<0.001	0.11
Treated	79 (55.2)	197 (52.1)	184 (55.4)	0.64	
Time on treatment over f-up (%), mean (SD)	20 (26.7)	14.9 (22.9)	14.9 (24.1)	0.10	
Median annual visits	1.4 (0. 8-2.4)	1.5 (0.7-2.4)	1.5 (0.7-2.5)	0.93	
F-up from onset, Median (IQR)	7.6 (4.6-11.3)	7.3 (4-12)	6.1 (3.9-9.4)	0.0018	0.25
Gd lesions first visit (n=141), n(%)	8/28 (28.6)	18/57 (31.6)	15/56 (26.8)	0.85	
T2 lesions first visit (n=231), mean(SD; range)	9.6 (11; 0-41)	7.6 (9.5; 0-50)	9.6 (12; 0-60)	0.28	

Country differences



Practical implications and future studies



- Three distinct patterns of disability accumulation that can be characterized after 1-3 years of follow up
- Design of clinical trials in PPMS
- EDSS course from onset of disease
- Early classification of patients
- Classification as inclusion/exclusion criteria or matching parameter
- Dynamic approach with time-dependent predictors