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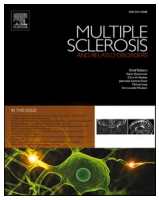

Evaluation of the times of disability progression and related factors in patients with primary progressive multiple sclerosis from Argentina

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A B S T R A C T

Background PPMS (primary progressive multiple sclerosis) patients represent less than 10% of MS patients in Argentina, men and women were similarly affected and most of them had a severe functional impairment. More rapid progression has been reported in males, but this is not the case in all datasets. The main objective of our study was to determine the time to EDSS (Expanded disability Status Scale) 4, 6 and 7 in PPMS patients. We also compared the times to reach these EDSS in men and women and aimed to identify factors associated with the disability progression.

Method This cohort of patients with diagnosis of PPMS ($n = 253$) was selected from follow-up recorded in the RelevarEM registry database.

Result The median times to EDSS 4, 6 and 7 were 24 (IQR 12–48), 72 (IQR 36–96) and 96 (IQR 60–120) months, respectively. Comparison of the survival curves to EDSS 4, 6 and 7 according to gender did not show significant differences ($p = 0.33$, $p = 0.55$ and $p = 0.59$). There is no evidence of an association between the clinical adjustment variables (sex, age >40 years at diagnosis, EDSS > 3 at onset and multifocal MS symptoms at disease onset) and the time of arrival at the EDSS 4, 6 and 7.

Conclusion Severe disability was observed six years after the onset of symptoms. No association was found between the studied factors and the time to arrival to severe disability.

1. Introduction

Primary progressive multiple sclerosis (PPMS) is an infrequent phenotype, with prevalence ranging from 10% to 20% of all multiple sclerosis (MS) phenotypes, according to different series worldwide (Ontaneda, 2019). PPMS patients represent less than 10% of all? MS

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patients in Argentina, men and women were similarly affected and most of them had a severe functional impairment (Ricardo et al., 2020). This phenotype is characterized by accrual of disability independent of clinical relapses, the key pathological features being the meningeal inflammation, axonal damage and glial reaction among other mechanisms (Correale et al., 2017). PPMS presents traits that distinguish it from relapsing forms, such as a relative resistance to T-cell directed disease-modifying treatment, a worse prognosis, a higher relative frequency in men, an older age of onset and, moreover, there are MRI differences reported in these patients (Dastagir et al., 2018).

There is an increasing need to identify those patients who will have a more severe clinical outcome in the long-term. In the last years, different studies described clinical and imaging measures, including the early changes in Expanded Disability Status Scale (EDSS) score and T1 and T2-weighted images lesions and percentage of brain volume loss in MRI as predictors of clinical outcome (Rocca et al., 2017). Regarding gender, more rapid progression has been reported in males, but this is not the case in all datasets (Khaleeli et al., 2008; Koch et al., 2009; Sastre-Garriga et al., 2005; Tremlett et al., 2005).

Until now, the identification of variables that predict progression and the characteristics of the clinical course in patients with PPMS is still under investigation. Additionally, there is scarce research on this topic in Latin America. The main objective of our study was to determine the time to EDSS 4, 6 and 7 in PPMS patients from Argentina. We also compared the times to reach these EDSS in men and women and aimed to identify factors associated with the disability progression.

2. Methods

2.1. Data source

RelevarEM is a longitudinal, non-mandatory, strictly observational MS and neuromyelitis optica spectrum disorders (NMOSD) registry in Argentina. The registry is open to all practicing neurologists and to MS specialists and their teams across the country. It 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 (Rojas et al., 2019). Any patient diagnosed with MS, a clinically isolated syndrome, a radiologically isolated syndrome, or an NMOSD defined by validated diagnostic criteria can be enrolled in the registry. To reduce the possibility of bias in the selection, each participating physician was required to include all patients seen in their practice or clinic. Data from each participating physician are collected by a standardized database management system and anonymized datasets are then periodically uploaded to the RelevarEM server. The objectives, methods and operational details of the RelevarEM database have previously been described by Rojas et al. (Rojas et al., 2019). Until March 2021 the total of MS patients' data uploaded to RelevarEM were $n = 3.434$. Patient's data came from 43 centers and 57 physicians distributed throughout Argentina, who were taking part in the Registry.

2.2. Patients

The cohort of patients with diagnosis of PPMS ($n = 253$) were selected from follow-up recorded in the RelevarEM registry database. For this research, the database lock occurred in March 2021. Those patients who met the inclusion criteria were selected. Inclusion criteria were 1) adults (older than 18 years) diagnosed with PPMS (based on validated diagnosis criteria)(Thompson et al., 2018), at least 48 months of follow-up and last medical visit less than 12 months before study initiation. Exclusion criteria were inability to undergo magnetic resonance imaging (MRI) examination, presence of other neurologic disorders besides MS that may influence the patient's disability. Data regarding demographic and clinical characteristics of PPMS were obtained from the anonymized patient medical records. Clinical variables included were duration of the disease, disability measured by the Expanded Disability Status Scale (EDSS), clinical relapses, modified disease treatments, baseline and during follow-up MRI data (new or enlarging T2-hyperintense lesions or gadolinium enhancing lesions).

2.3. Statistical analysis

Epidemiological data at baseline were evaluated using descriptive statistics. A survival analysis was performed to estimate the time to EDSS 4, 6 and 7 and the Long Rank Test to compare men versus women. Kaplan–Meier plots were generated for disability outcomes. Multivariate analysis was conducted using the Cox proportional hazards model. Sex, age >40 years at diagnosis, EDSS > 3 at onset and multifocal MS symptoms at disease onset were used as covariates for the analysis. The Stata software package, version 10 was used. (StataCorp. Stata statistical software: Release 10. College Station. TX, USA: StataCorp LP, 2007.) All p values were two tailed; $p < 0.05$ was considered significant.

2.4. Ethics statement

RelevarEM Registry was approved by local ethics committees in all participating centers. If required, written informed consent was obtained from enrolled patients. [10]

3. Results

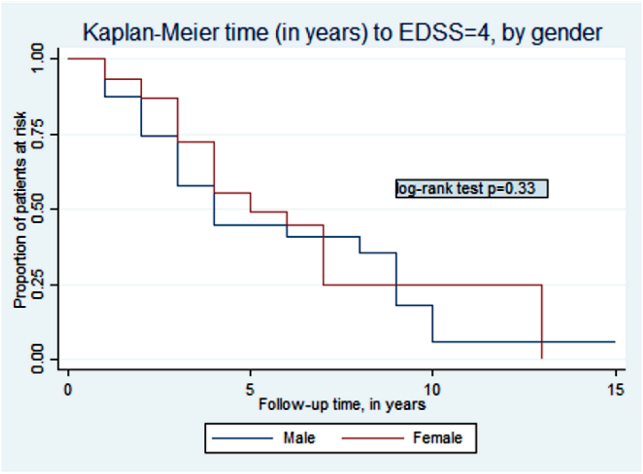
Of the 253 registered PPMS patients, 142 (56%) met the inclusion criteria. Demographic characteristics of these patients are summarized in Table 1. Overall, mean age at onset of PPMS was 41 years (standard deviation (SD) ± 11), and mean duration of PPMS was 11 years ± 5.9). The male/female ratio was 1.05. At the time of study inclusion, 59.9% of PPMS patients had no treatment and 33.8% were on treatment with ocrelizumab. The median of the first and last EDSS were 3 (IQR 2–4) and 6 (IQR 5–7) respectively (delta-EDSS 3; IQR 1.5 - 4). At disease onset, 61.3% of PPMS patients presented multifocal MS symptoms. The presence of relapses during the first year of diagnosis were reported in 4.9% PPMS patients and 29% showed new or enlarging T2-hyperintense lesions and/or gadolinium enhancing lesions on brain MRI at 12 months of diagnosis. No difference was found in the baseline clinical characteristics between men and women. However, women had a longer duration of MS compared to men (Table 1).

The median times to EDSS 4, 6 and 7 were 24 (IQR 12–48), 72 (IQR 36–96) and 96 (IQR 60–120) months respectively. Comparison of the survival curves to EDSS 4, 6 and 7 according to gender did not show significant differences ($p = 0.33$, $p = 0.55$ and $p = 0.59$) (Figs 1-3).

There is no evidence of an association between the clinical adjustment variables and the time of arrival at the EDSS 4, 6 and 7 (Tables 2-

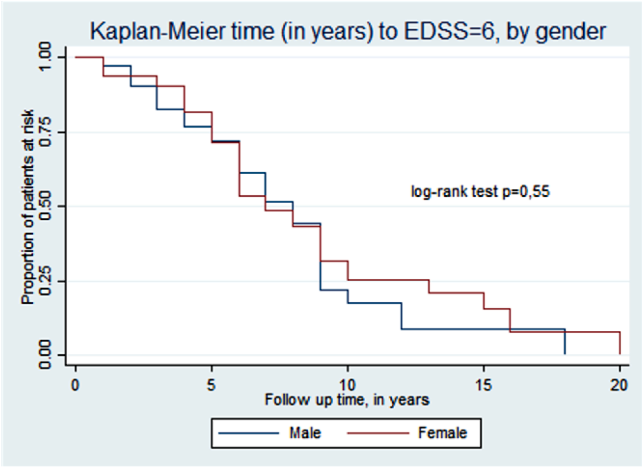
Table 1
Demographic characteristics in men and women with PPMS.

Variable	Women, $n = 69$	Men, $n = 73$	P
Mean age at onset (SD)	42.14 (10.5)	39.81 (10.95)	0.19
Mean duration of PPMS (SD)	12.52 (6.56)	10 (5.13)	**0.01**
Multifocal MS symptoms at beginning,%	65.2	57.5	0.34
Median EDSS at diagnosis (IQR)	3 (2–4)	3 (2–4)	0.71
OBC positive,%			
Relapses at beginning	10.2	10.8	0.56
New or enlarging T2-hyperintense lesions and/or gadolinium lesions on brain MRI at 12 months of diagnosis	28.2	29.8	0.62
Current treatment. N (%)			
- Ocrelizumab	19 (27.5)	29 (39.7)	–
- Rituximab	2 (2.9)	1 (1.4)	–
- Glatiramer acetate	0	2 (2.9)	–
- Fingolimod	2 (2.9)	0	–
- Dimetylfumarate	1 (1.4)	1 (1.4)	–
- No treatment	40 (54.8)	45 (65.2)	–



Comparison of the survival curves up to EDSS = 4 or higher according to gender did not show statistically significant differences (p = 0.33).

Fig. 1. Time to EDSS 4 in a patient with PPMS according to gender. Comparison of the survival curves up to EDSS = 4 or higher according to gender did not show statistically significant differences ($p = 0.33$).



Comparison of the survival curves up to EDSS = 4 or higher according to gender did not show statistically significant differences (p = 0.55).

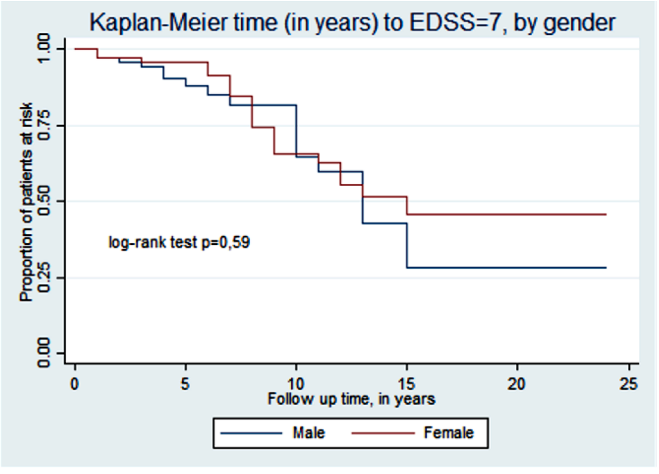
Fig. 2. Time to EDSS 6 in a patient with PPMS according to gender Comparison of the survival curves up to EDSS = 4 or higher according to gender did not show statistically significant differences ($p = 0.55$).

4).

4. Discussion

Characteristics of PPMS patients included in this work are in line with a prior epidemiological study from our group (Ricardo et al., 2020). These data show that the characteristics of our sample represent the population of patients with PPMS included in RelevarEM. Additionally, other studies from North America, Europe and Asia, have shown similar clinical and radiological characteristics of PPMS patients (Evans et al., 2013; Maghzi et al., 2007; McDonnell and Hawkins, 1998; Tremlett et al., 2005).

In this long-term longitudinal study, the mean time to severe disability (unilateral assistance required to walk) was observed six years after the onset of symptoms. Comparison of the survival curves to EDSS 4, 6 and 7 according to gender did not show significant differences.



Comparison of the survival curves up to EDSS = 4 or higher according to gender did not show statistically significant differences (p = 0.59).

Fig. 3. Time to EDSS 7 in a patient with PPMS according to gender. Comparison of the survival curves up to EDSS = 4 or higher according to gender did not show statistically significant differences ($p = 0.59$).

Table 2
Cox proportional hazards model between sex, age at diagnosis, MS symptoms at onset and time to EDSS 4.

Variable	HR	p value	CI95%
Multifocal MS symptoms at beginning	0,67	0,15	0,39–1,15
Age ≥ 40 years at diagnosis	1,36	0,26	0,79–2,34
Female gender	0,82	0,48	0,48–1,41
Time elapsing between clinical onset of MS and the diagnosis	0,93	0,11	0,86–1,01

HR: Hazards ratio. MS: multiple sclerosis. IC95%: 95% confidence interval.

Table 3
Cox proportional hazards model between sex, age at diagnosis, EDSS at onset, MS symptoms at onset and time to EDSS 6.

Variable	HR	p value	CI95%
Multifocal MS symptoms at beginning	1,29	0,32	0,77–2,15
EDSS ≥ 3 at onset	1,63	0,059	0,98–2,73
Age ≥ 40 years at diagnosis	1,28	0,33	0,76–2,15
Female gender	0,77	0,32	0,47–1,27
Time elapsing between clinical onset of MS and the diagnosis	1,01	0,91	0,91–1,1

HR: Hazards ratio. MS: multiple sclerosis. IC95%: 95% confidence interval.

Table 4
Cox proportional hazards model between sex, age at diagnosis, EDSS at onset, MS symptoms at beginning and time to EDSS 7.

Variable	HR	p value	CI95%
multifocal MS symptoms at onset	0,87	0,71	0,44–1,71
EDSS ≥ 3 at onset	1,06	0,85	0,54–2,07
Age ≥ 40 years at diagnosis	1,14	0,69	0,57–2,26
Female gender	0,86	0,66	0,44–1,68
Time elapsing between clinical onset of MS and the diagnosis	0,97	0,7	0,84–1,11

HR: Hazards ratio. MS: multiple sclerosis. IC95%: 95% confidence interval.

Furthermore, we did not find association between the clinical adjustment variables such as sex, age at diagnosis, EDSS at onset, multifocal MS symptoms at onset and time elapsing between clinical onset of MS with the time to arrival at the EDSS 4, 6 and 7.

Historical research in relapsing MS showed that male patients have a shorter time between disease onset and a given disability level when compared to women (Confavreux et al., 2003; Weinshenker, 1994). Furthermore, large studies of MS patients found that male sex was associated with a shorter time to, and a younger age for, conversion to secondary progressive MS, as well as a faster accumulation of disability (Koch et al., 2010; Ribbons et al., 2015). Regarding PPMS, the results are not conclusive. Khaleeli Z. et al. in a long-term study found that male patients were twice as likely to deteriorate on the EDSS as female patients over 10 years (Khaleeli et al., 2008). Conversely, in a large cohort of PPMS patients ($n = 580$), researchers found no sex-associated effects on rate of disability accumulation (Ribbons et al., 2015). In summary, to date, there is no agreement as to whether the progression of disability is associated with the gender of patients with PPMS or not (Khaleeli et al., 2008; Koch et al., 2009; Sastre-Garriga et al., 2005; Tremlett et al., 2005). In relation to symptoms associated with PPMS, it has been reported that depression, cognitive impairment and pain are more frequently reported in women than women?(Rommer et al., 2020). Although these symptoms were not registered in our study, it is important to note that there are clinical manifestations independent of the degree of disability that could affect the quality of life of patients with PPMS.

Regarding the mean time to severe disability, our findings were in agreement with previous studies that reported a similar median time to EDSS 6, although others showed a longer time to reach this disability milestone, which varies between 7 and 14 years from the onset of the disease (Confavreux and Vukusic, 2006; Khaleeli et al., 2008; Koch et al., 2009; Signori et al., 2018). An MSBase observational study showed heterogeneity in the disability trajectories of patients with PPMS. Researchers used the latent class growth curve mixture models (LCMM) to model longitudinal EDSS scores. This model identified three distinct patterns of disability progression among PPMS patients. The EDSS time course of patients grouped in the milder class is represented by a trajectory that never reaches an EDSS 6 during the course of 20 years of follow-up available for analysis after the onset of disease. The most severe trajectory begins with a high EDSS and reaches EDSS 6 within 5 years from onset (Khaleeli et al., 2008; Signori et al., 2018).

Several factors associated with progression of disability have been identified in patients with PPMS. Rocca M. et al. showed that integrating clinical and imaging (conventional brain and cervical cord scan and diffusion tensor brain scans acquired at baseline and after 15 months) predicted long-term disability at 15 years. Moreover, the integration of clinical and imaging measures allows identification of PPMS patients at risk of long-term disease progression 4 years earlier than using clinical assessment alone (Rocca et al., 2017). Regarding clinical variables, Khaleeli Z et al. found that Timed to 25 Walk Test at baseline and EDSS change over 2 years was significant predictor of progression over 10 years. Previous studies reported age at onset as a prognostic factor in PPMS (Harding et al., 2015; Koch et al., 2009; Signori et al., 2018; Tremlett et al., 2005), although other studies did not find this association. Another controversial factor is the presence of relapses: while the London-Ontario study did not find association between relapses and the time to reach disability milestones, in the MSBase study, patients within the most severe trajectory class had the highest rate of superimposed relapses (Khaleeli et al., 2008; Rocca et al., 2017; Signori et al., 2018). Unlike our research, the time elapsing between clinical onset of MS and the diagnosis was reported as an important predictor of disability severity. Research showed that a shorter period between the onset of symptoms and diagnosis predicted a more aggressive disease (Khaleeli et al., 2008; Signori et al., 2018).

We studied a large number of Argentinian patients over a long follow-up period and found that they reach high levels of disability in a relatively short time. Multicenter studies are, however, vulnerable to bias. These findings should be validated on an independent external cohort to generalize our results. Furthermore, since RelevarEM participants are more represented by MS specialist centers in Argentina, we could be expected a larger frequency of more rapidly progressing patients than in a truly population-based cohort. As limitations of our study, we can mention the lack of different parameters of magnetic resonance imaging (MRI) at baseline, such as measurement of brain and spinal volume and MRI longitudinal data. Besides, we could not evaluate the variability of the EDSS (EDSS delta) in the first months / years. Thus, we were not able to estimate the impact of early disability progression as a long-term factor. However, we would like to highlight the large number of Argentinian patients taking into account the low prevalence of MS in our region. Furthermore, the scarcity of data on PPMS in the region highlights the importance of this study.

In conclusion, in this study, severe disability was observed six years after the onset of symptoms. No association was found between the studied factors and the time of arrival to severe disability. More studies are needed in our country and LATAM to be able to corroborate these data.

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Declaration of Competing Interest

None.

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