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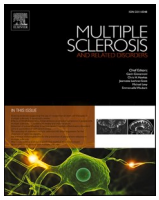

Clinical characterization of long-term multiple sclerosis (COLuMbus) patients in Argentina: A cross-sectional non-interventional study

Norma Deri [a], Andres Barboza [b], Carlos Vrech [c], Roberto Rey [d], Marcos Burgos [e], Marcela Fiol [f], Cristian CalvoVildoso [g], Liliana Patrucco [h], Gustavo Jose [i], Paula Aliberti [j], Daniela Chirico [j], Maria B. Federico [j], Gustavo Seifer [j], Raul Piedrabuena [k,*]

[a] Centro de Investigaciones Diabaid, Autonomous City of Buenos Aires, Argentina
[b] Neurología Clínica, Mendoza, Argentina
[c] Centro Integral de Diagnóstico por Imágenes Marchegiani, Córdoba, Argentina
[d] Neurology Department, Instituto Argentino de Investigación Neurológica (IADIN), Buenos Aires, Argentina
[e] Consultorios AMUGENAL, Salta, Argentina
[f] Department of Neurology, Institute for Neurological Research (FLENI) Buenos Aires, Argentina
[g] Centro de Neurología Rosario, Santa Fe, Argentina
[h] Centro de Esclerosis Múltiple de Buenos Aires, Hospital Italiano de Buenos Aires, Argentina
[i] Centro Médico Privado de Reumatología, Tucumán, Argentina (currently known as Centro de Investigaciones Médicas Tucumán), Argentina
[j] Novartis Argentina S.A., Buenos Aires, Argentina
[k] Instituto Modelo de Neurología Privado, Córdoba, Argentina

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ABSTRACT

Background: Most Multiple Sclerosis (MS) clinical trials fail to assess the long-term effects of disease-modifying therapies (DMT) or disability.
Methods: COLuMbus was a single-visit, cross-sectional study in Argentina in adult patients with ≥10 years of MS since first diagnosis. The primary endpoint was to determine patient disability using the Expanded Disability Status Scale (EDSS). The secondary endpoints were to evaluate the distribution of diagnoses between relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS), patient demographics, disease history, and the risk of disability progression. The relationship between baseline characteristics and the current disability state and the risk of disability progression was assessed.
Results: Out of the 210 patients included, 76.7 % had a diagnosis of RRMS and 23.3 % had been diagnosed with SPMS, with a mean disease duration of 17.9 years and 20.5 years, respectively. The mean delay in the initial MS diagnosis was 2.6 years for the RRMS subgroup and 2.8 years for the SPMS subgroups. At the time of cut-off (28May2020), 90.1 % (RRMS) and 75.5 % (SPMS) of patients were receiving a DMT, with a mean of 1.5 and 2.0 prior DMTs, respectively. The median EDSS scores were 2.5 (RRMS) and 6.5 (SPMS). In the RRMS and SPMS subgroups, 23 % and 95.9 % of patients were at high risk of disability, respectively; the time since first diagnosis showed a significant correlation with the degree of disability.
Conclusions: This is the first local real-world study in patients with long-term MS that highlights the importance of recognizing early disease progression to treat the disease on time and delay disability.

1. Introduction

Multiple Sclerosis (MS) is a chronic, autoimmune and heterogeneous disease of the central nervous system (CNS) (Filippi et al., 2018). Since 1990, there has been a 10.4 % increase in the global prevalence of MS, as reported in 2016 by the Global Burden of Disease collaborator group (Wallin et al., 2019). Approximately 2.2 million cases of MS have been reported worldwide. Local researchers have reported varying prevalence ratios (23.8–48.3/10^5 (Cristiano et al., 2020; Luetic and Menichini, 2021; Mellinger et al., 2018)) in different regions of Argentina. A 22-year study in Buenos Aires reported an increasing incidence of MS in women (from 1/10^5 to 4.9/10^5) between 1992 and 2013 (Cristiano

* Corresponding author.
E-mail address: raulpiedrabuena@gmail.com (R. Piedrabuena).

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et al., 2016).

MS disease indicator is the buildup of regions of demyelination in the CNS but the development of this disease is diverse (Filippi et al., 2018) with several distinct clinical phenotypes (Lassmann et al., 2012). Approximately 85 % of patients are diagnosed with relapsing-remitting MS [RRMS] (Klineova and Lublin, 2018), a phase of MS characterized by episodes of neurological deficits called "relapses", with full or partial recovery. Over time, clinical disability and its progression might become permanent, which is a characteristic of the secondary progressive phase of MS (SPMS) (Filippi et al., 2018). The probability of progressing into the SPMS phase increases proportionally with disease duration, with a 2-fold increase per decade, and approximately 50 %–60 % of patients with RRMS develop SPMS within 15–20 years of the onset of RRMS (Giovannoni et al., 2016; Scalfari et al., 2014). There is no distinct demarcation between the two phases of MS (leading to a delay in SPMS diagnosis) and DMTs cannot prevent the transition from RRMS to SPMS (Gajofatto and Benedetti, 2015; Lublin and Reingold, 1996; Oh et al., 2019; Scalfari et al., 2014). As disability progresses since the early stage of the disease, the neurologist may miss the best therapeutic window to treat MS with disease-modifying therapies (DMTs) (Alkhawajah and Oger, 2011; Jones and Coles, 2010; Lublin et al., 2022; Scalfari et al., 2013).

As there are no clear clinical, immunological, pathological or imaging-based criteria to determine the transition from RRMS to SPMS (Katz Sand et al., 2014), neurologists usually wait till the accumulation of considerable disability and the cessation of episodic disease activity before confirming a diagnosis of SPMS (Lorscheider et al., 2016). Besides, physicians may be hesitant to diagnose SPMS due to the associated psychological burden (Davies et al., 2016; O'Loughlin et al., 2017). The diagnosis of SPMS is usually retrospective, mostly based on the history of worsening after the initial relapsing disease course (Lublin et al., 2014; Oh et al., 2019), and has often been delayed in clinical practice (Katz Sand et al., 2014). In Argentina, a diagnostic uncertainty period of 3.3 years regarding the transition from RRMS to SPMS has been recently reported by Rojas et al. (Rojas et al., 2021). Due to this diagnostic uncertainty, neurologists have to look for objective measures of progression to detect transition from RRMS to SPMS over time. MSProDiscuss™, was a physician-completed digital tool based on a set of weighted questions that include information on patient relapses, symptoms and impacts experienced within the past 6 months (Ziemssen et al., 2020). This tool has been developed a couple of years ago and validated by experienced MS neurologists, patients, and empirical assessments of real-world evidence. A traffic-light system within the MSProDiscuss™ tool facilitates the discussion on the risk of disability progression from RRMS to SPMS.

As MS is a chronic disease that progresses through the years and most clinical trials have a short follow-up duration, it is difficult to assess disability and DMTs effectiveness in the long term (Goodin et al., 2002). Thus, collection of real-world data after several years of disease can clarify the status of those patients, supporting clinical practice and ensuring those long-term patients can receive the appropriate treatment. To this end, we conducted a cross-sectional study in Argentina to determine the level of disability in patients with ≥10 years of disease duration since the first diagnosis of MS. In addition, the risk of disability progression, the distribution of diagnoses between RRMS and SPMS, patient demographics, and disease history have been evaluated.

2. Methods

2.1. Study design and setting

This was a cross-sectional, single-visit, non-interventional study. Patients were enrolled through a non-probability consecutive sampling. Any treatment decisions, including the prescription of DMTs for MS, were made regardless of any decision to include a patient in the study. Ten well-known MS sites from major cities (Buenos Aires, Córdoba, Santa Fe, Salta, Mendoza, and Tucumán) in Argentina participated in this study. These neurological sites with academic affiliation and extensive experience in managing patients with MS are designated as second-opinion referral sites and/or have large clinical practice with MS patients. Data were collected for up to 6 months, until the last patient was interviewed. The last patient last visit was on May 28, 2020, and the database was locked on November 11, 2020.

After the eligibility assessment, patients were interviewed and underwent a neurological examination to assess the disability score, determine the disease phase (RRMS or SPMS) and collect all variables, including epidemiological and clinical variables taken from the medical records, in the electronic case report/record form.

2.2. Participants

All patients included in the study had to be ≥18 years old and had to comply with the 2017 McDonald criteria (Thompson et al., 2018) for MS. These patients were also required to have ≥10 years of MS disease duration since the first diagnosis. Patients with any major neurological or psychiatric disorder that could interfere with proper protocol compliance were excluded from the study. Any patient who had received an investigational drug or therapy within 30 days or five half-lives of the visit — whichever was longer — was also excluded from the study visit. Written informed consent was obtained from each patient.

2.3. Study endpoints

The primary endpoint was to determine the disability level of patients with ≥10 years of MS disease duration since the first diagnosis and the primary variable was current disability, as measured by the Expanded Disability Status Scale (EDSS).

The secondary endpoints were as follows:

a) To evaluate the distribution of diagnoses of RRMS and SPMS among the patients. Patients with SPMS were classified based on the criteria for an initial relapse-remitting course, followed by progression of a 1-point increase in the EDSS for patients with an EDSS score of ≤5.5, or a 0.5-point increase in the EDSS for patients with an EDSS score of ≥6 (over a period of at least 6 months) in the absence of a relapse.
b) To describe patient demographics and epidemiological and clinical data.
c) To evaluate the risk of patient disability progression using the MS Progression Discussion tool (MS ProDiscuss™), which categorizes the risk in low, medium and high.

The exploratory endpoints were as follows:

a) To assess the relationship between current disability, as measured by the EDSS (dependent variable), and demographic characteristics, subgroups of patients with RRMS/SPMS (independent variables), risk of disability progression, as assessed by the MSProDiscuss™ tool, and suitable baseline characteristics.
b) To assess the relationship between the risk of disability progression, as assessed using the MSProDiscuss™ tool (dependent variable), and demographic characteristics, subgroups of patients with RRMS/SPMS (independent variables), suitable baseline characteristics and EDSS score.

2.4. Study size

There was no methodology to calculate the sample size required for the primary objective of the study because there was no predefined effect to be found in the target sample. However, considering the MS prevalence of twenty-five cases per 100,000 inhabitants (the total number of patients with MS was estimated to be approximately 8,000 in

Argentina), an inclusion of 240 patients was considered adequate for the primary objective. This sample size was planned to provide a confidence interval (CI) that was narrow enough for the primary endpoint. The original plan was to collect data for 240 patients; however, as patients could not visit the health centers due to the COVID-19 pandemic, the database was locked earlier than planned and data were collected for 224 patients.

2.5. Statistical methods

Statistical outputs were produced using SAS® Version 9.4 on the Full Analysis Set (FAS), which included all patients with MS enrolled in the study. For continuous variables, summary statistics included *n* (number of patients with information about the variable), mean, standard deviation, median, 25th and 75th percentiles, interquartile range (IQR), minimum and maximum, and the two-sided 95 % CI and *p* values were presented, where applicable. Categorical variables were shown as frequencies and percentages. In this case, if applicable, the two-sided 95 % CI of proportion was provided. A missing category was presented only when there were patients with missing data. All descriptive statistics were provided by group (patients with RRMS and SPMS) and in total for demographics, baseline characteristics, risk of disability progression, and current EDSS. The number and percentage of patients with a signal of risk of disability progression as gathered by the MSProDiscuss™ tool were presented. A logistic regression model was used to evaluate the relationship between subgroups of patients with RRMS/SPMS and demographics and the risk of disability, as assessed using the MSProDiscuss™ tool. A multivariate regression model was used to assess the relationship between the current disability and demographics, subgroups of patients with RRMS/SPMS (independent variables), MSProDiscuss™ tool, and suitable baseline characteristics.

3. Results

3.1. Participants

Out of the 224 patients screened, 223 patients were enrolled (One patient was considered as a screening failure due to protocol deviation). Finally, the FAS included a total of 210 patients (13 patients were excluded due to protocol deviations).

3.2. Patient demographics, distribution of diagnosis, and disease history

Out of the 210 patients included in the study, 161 (76.7 %) had a diagnosis of RRMS and 49 (23.3 %) had a diagnosis of SPMS (Table 1). Overall, the mean (SD) age of patients was 49.2 (10.9) years, with patients with SPMS being older than patients with RRMS. Most patients were female (63.3 %). At study entry, the mean (SD) disease duration since the first symptom was 18.5 (6.7) years (17.9 [6.6] years for RRMS and 20.5 [6.4] years for SPMS). Overall, the mean (SD) delay in diagnosis was 2.7 (4.4) years, and the mean (SD) delay in the initial MS diagnosis for the RRMS and SPMS subgroups was 2.6 (4.4) years and 2.8 (4.7) years, respectively. There was no other relevant medical history.

3.3. Disease-modifying treatments

Most of the patients (98.6 %) were reported to have been on DMTs (prior or current DMT status; 98.1 % in the RRMS subgroup and 100 % in the SPMS subgroup) (Table 2). Patients had a mean (SD) of 1.5 (0.8) and 2 (1.0) of prior DMTs for RRMS and SPMS subgroups, respectively. Overall, 182 patients (86.7 %) were receiving DMTs, and had been under treatment therewith for a mean (SD) time of 68.1 (61.7) months. In the RRMS and SPMS subgroups, 90.1 % and 75.5 % of patients were receiving DMTs, respectively. The mean (SD) time since the start of current DMTs was 69.7 (64.2) months for patients with RRMS and 61.8 (50.1) months for patients with SPMS. (Table 2).

Table 1
Patient demographics and disease history.

Variable	RRMS $N = 161$	SPMS $N = 49$	Total $N = 210$
Age (years), mean (SD)	48.1 (10.8)	53.1 (10.5)	49.2 (10.9)
Sex, Male, n (%)	60 (37.3)	17 (34.7)	77 (36.7)
Female, n (%)	101 (62.7)	32 (65.3)	133 (63.3)
Ethnicity, Asian, n (%)	1 (0.6)	0	1 (0.5)
Multiple*, n (%)	1 (0.6)	0	1 (0.5)
White, n (%)	159 (98.8)	49 (100.0)	208 (99.0)
Disease duration since first symptom (years)			
mean (SD)	17.9 (6.6)	20.5 (6.4)	18.5 (4.9)
Disease duration since first diagnosis (years)			
mean (SD)	15.2 (4.6)	17.7 (5.1)	15.8 (4.9)
Delay in initial MS diagnosis (years)			
mean (SD)	2.6 (4.4)	2.8 (4.7)	2.7 (4.4)

Percentages are calculated considering N as denominator for the corresponding row.
FAS, Full Analysis Set; n, number of patients available for this particular variable/category; N, total number of patients (FAS); RRMS, Relapsing Remitting Multiple Sclerosis; SPMS, Secondary Progressive Multiple Sclerosis.
* One patient had mentioned two races (American Indian or Alaska native and white) in the eCRF, so this was considered as 'multiple'.

Table 2
Disease modifying therapies.

Variable	RRMS $N = 161$	SPMS $N = 49$	Total $N = 210$
Patients treated with DMTs at some point since diagnosis (currently or previously), n (%)	158 (98.1)	49 (100.0)	207 (98.6)
Number of prior DMTs, mean (SD)	1.5 (0.8)	2.0 (1.0)	1.6 (0.9)
Patients currently treated with DMTs, n (%)	145 (90.1)	37 (75.5)	182 (86.7)
Patients currently treated with their first DMT, n (%)	17 (10.6)	2 (4.1)	19 (9.1)
Time since start date (months)*	69.7 (64.2)	61.8 (50.1)	68.1 (61.7)

* This represents time since ongoing medication start date, where medications start date is available for a patient. FAS, Full Analysis Set; n, number of patients available for this particular variable/category; N, total number of patients (FAS); RRMS, Relapsing Remitting Multiple Sclerosis; SPMS, Secondary Progressive Multiple Sclerosis.

3.4. Current disability

The summary of the current EDSS score is shown in Fig. 1. The median (IQR) EDSS score reported in all patients was 4.0 (2.0–6.0). The median (IQR) EDSS score was 2.5 (1.5–4.0) for the RRMS subgroup and 6.5 (6.0–7.0) for the SPMS subgroup. When the relationship between current disability (as measured by the EDSS) and the type of MS (RRMS or SPMS) was assessed, the inferential analysis (Table 3) found a significant correlation with the types of MS ($p = 0.0003$)). In addition, the current disability (EDSS) was associated with the risk of disability progression, as evaluated by the MSProDiscuss™ tool, ($p < 0001$). Furthermore, work status was significantly related to the EDSS score ($p < 0.0001$).

3.5. Risk of disability progression

Based on the MSProDiscuss™ tool assessment, overall, 40 % of patients were at a higher risk of disability progression and 23.3 % and 36.7

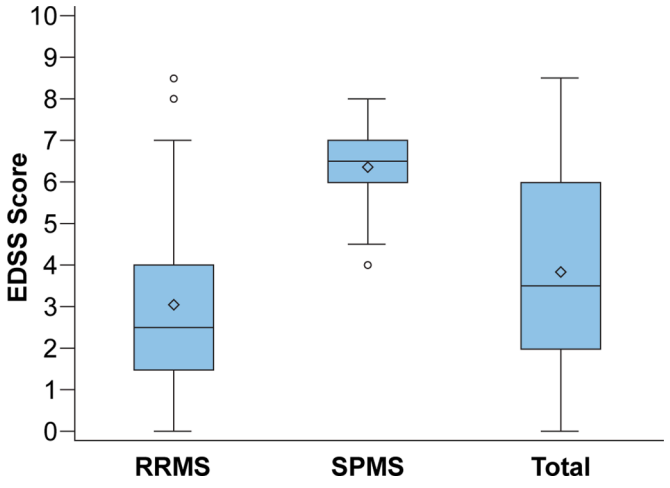

Fig. 1. Current summary of EDSS. Baseline is Visit 1. Diamonds represent the mean and circles represent values outside of the 1.5*IQR. Lower and upper whiskers extend to the most extreme points within the 1.5*IQR of Q1 and Q3, respectively. EDSS, Expanded Disability Status Scale; FAS, Full Analysis Set; IQR, Interquartile Range; n, patients with ≥10 years of MS disease duration since the first diagnosis and with a non-missing valid EDSS value at baseline; N, total number of patients (FAS); RRMS, Relapsing-Remitting Multiple Sclerosis, SPMS, Secondary Progressive Multiple Sclerosis.

Table 3
Inferential analysis of current disability as measured by the EDSS.

Independent variables	Estimate	Standard error	Interval	P value
Intercept	−2.1	1.0	(−4.10, −0.11)	0.0385
Age	0.0	0.0	(−0.03, 0.00)	0.1154
Sex	−0.3	0.2	(−0.69, 0.02)	0.0668
Race	0.4	0.9	(−1.31, 2.14)	0.6377
Work status	1.0	0.2	(0.63, 1.39)	<0.0001
Type of Multiple Sclerosis	0.9	0.2	(0.41, 1.38)	0.0003
MSProDiscuss™ tool	1.6	0.1	(1.37, 1.90)	<0.0001
Number of prior DMTs	0.1	0.1	(−0.06,0.29)	0.2026
Disease duration since first diagnosis	0.0	0.0	(−0.00, 0.01)	0.1019
Disease duration since first symptom	0.0	0.0	(−0.00, 0.00)	0.7506

$n = 210$, EDSS as a dependent variable.
Multivariate regression model was used for the analysis. The model was as follows: current EDSS = demographics + subgroup of RRMS patients/SPMS patients + suitable baseline characteristics (EDSS as a dependent variable).
FAS, Full Analysis Set; n, number of patients with non-missing value for the corresponding independent variable.

% of patients were at medium and lower risk of disability progression, respectively (Fig. 2). The RRMS subgroup had 29.2 % patients in the medium-risk category and 23 % in the high-risk category, whereas 95.9 % of patients in the SPMS subgroup were at a high risk of disability progression.

It was found that work status and number of prior DMTs were not associated with the risk of disability progression as assessed by the MSProDiscuss™ tool (Table 4). While the time of disease duration since the first symptom was not associated with the risk category (OR 1.0 for both medium- and high-risk categories), the high-risk group was significantly associated with time since first diagnosis (OR 1.0, $p = 0.0367$). The inferential analysis between the RRMS/SPMS subgroups with demographic characteristics and the risk of disability progression is shown in Table 5.

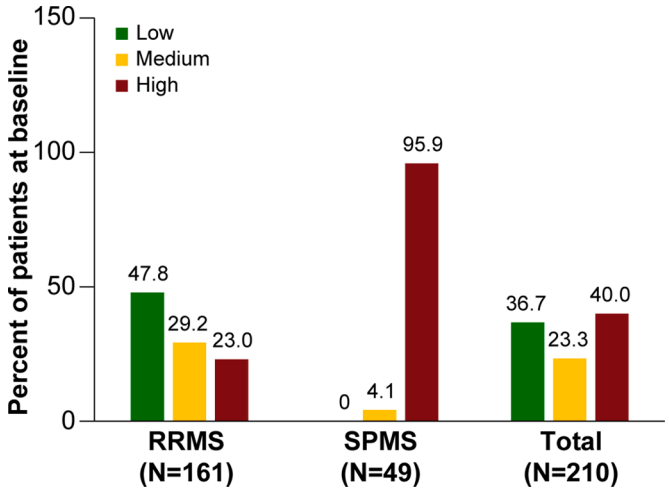

Fig. 2. Risk of disability progression as measured by the MSProDiscuss™ tool. Baseline is visit 1. Data presented for patients with ≥10 years of MS disease duration since the first diagnosis and with non-missing valid EDSS value at baseline. Green: low risk, Amber: medium risk, Red: high risk. RRMS, Relapsing Remitting Multiple Sclerosis; SPMS, Secondary Progressive Multiple Sclerosis.

4. Discussion

This was a cross-sectional, single-visit, non-interventional study conducted in Argentina to evaluate patients with ≥10 years of MS disease duration since first diagnosis. Over time after disease diagnosis, a significant number of patients may enter the so-called transition phase, characterized by the appearance or increase of disability progression and the conversion into the SPMS phenotype. This transition phase from RRMS to SPMS can be a complex process and, sometimes, difficult to recognize. On the one hand, since there are no clear and unique criteria for SPMS diagnosis and identification in clinical practice is not sufficient, there is an urgency to define a prospective diagnosis. On the other hand, as most DMTs used in RRMS patients have not been able to prove effectiveness in SPMS patients, a discussion for a potential treatment switch is another point to be taken into consideration. Hence, we conducted this study to evaluate the characteristics of those patients who could be in this particular stage of the disease and describe their current status.

After 10 years or more since diagnosis, 76.7 % of recruited patients presented the RRMS phenotype and 23.3 % had a diagnosis of SPMS. At study entry, the mean disease duration for RRMS and SPMS was 17.9 years and 20.5 years, respectively. In our study, 75.5 % of patients with SPMS diagnosis were currently on DMTs, which represents a considerably higher percentage than that reported previously in other countries (Gross and Watson, 2017; Muller et al., 2020). In a study conducted in Germany, a total of 33.9 % of patients with SPMS were found to be receiving immunomodulatory agents (Muller et al., 2020). In another real-world study in the United States, it was reported that 50 % of patients with SPMS were receiving DMTs (Gross and Watson, 2017). It can be assumed that more patients have access to DMTs now as compared to the first decade of this century or that more patients with SPMS are being treated nowadays. Considering that the association of SPMS with poor prognosis could be due to the use of DMTs not proven to have efficacy in the progressive stage (Lorscheider et al., 2016; Scalfari et al., 2013), it is really important to choose a DMT that has proven evidence to be effective for this stage of the disease.

Delay in disability progression with DMTs has also been observed in short-term studies in the past (De Angelis et al., 2018; Goodin et al., 2002). The disability progression impacts on daily life activities, which is evidenced, for example, in employment status .(Conradsson et al., 2020; Smith and Arnett, 2005) In our study, the inferential analysis showed a correlation between the EDSS and the work status.

Table 4
Inferential analysis of the risk of disability progression, measured using MSProDiscuss™ Tool.

Independent variables	Independent variable category	Response category	Estimate	Standard error	Odds ratio	P value
Intercept		Medium risk	−3.9	1.1	..	0.0004
		High risk	−10.1	1.9	..	<0.0001
Sex	Male	Medium risk	−0.6	0.3	0.3	0.0139
	Male	High risk	−0.4	0.4	0.4	0.2439
Work status	No	Medium risk	0.1	0.2	1.1	0.8107
	No	High risk	0.2	0.4	1.4	0.6466
Number of prior DMTs		Medium risk	−0.6	0.3	0.6	0.0586
		High risk	−0.4	0.4	0.7	0.3187
EDSS Score		Medium risk	1.0	0.2	2.5	<0.0001
		High risk	1.9	0.3	6.4	<0.0001
Disease duration since first diagnosis		Medium risk	0.0	0.0	1.0	0.2937
		High risk	0.0	0.0	1.0	0.0367
Disease duration since first symptom		Medium risk	0.0	0.0	1.0	0.5361
		High risk	0.0	0.0	1.0	0.8142

$n = 210$, n1 = 161.
General linear mixed model was used for the analysis.
The model was as follows: logit (proportion of patients in each group of MSProDiscuss™ tool response) = demographics + suitable baseline characteristics + EDSS score.
P values are calculated using MSProDiscuss™ tool disability progression = low (green), Sex = female, Work status = yes, as a reference category in the model. MSProDiscuss™ tool as a dependent variable.
The SPMS category was removed due to zero count in one of the response categories.
For patients who answered "no medication to report", number of prior DMTs is considered as 0.
Current DMT was also removed from the model as it had an imbalance in count for various categories.
Odds ratio >1 indicates that the event is more likely to occur as the predictor EDSS increases.
FAS, Full Analysis Set; n, number of patients with non-missing value for the corresponding independent variable; n1, number of observations used in this model.

Table 5
Inferential analysis of the subgroup of RRMS patients.

Independent variables	Independent variable category	Response category	Estimate	Standard error	P value
Intercept		RRMS	3.4	1.146	0.0029
Sex	Male	RRMS	0.1	0.240	0.7917
Work status	No	RRMS	−0.1	0.292	0.6535
Number of prior DMTs		RRMS	−0.2	0.203	0.4462
EDSS score		RRMS	−0.5	0.186	0.0166
Disease duration since first definitive diagnosis		RRMS	0.0	0.005	0.5110
Disease duration since first symptom		RRMS	0.0	0.004	0.8830
MSProDiscuss™ tool	High	RRMS	−1.2	0.426	0.0071

$n = 210$, n1=133.
The model was as follows: logit (proportion of patients with each type of Multiple Sclerosis) = demographics + suitable baseline characteristics + EDSS score. RRMS as a dependent variable.
P values were calculated using type of Multiple Sclerosis = SPMS, sex = female, work status = yes as a reference category in the model.
MSProDiscuss™ tool disability progression = low category was removed due to zero count in one of the Multiple Sclerosis (SPMS) categories.
For patients who answered "no medication to report", number of prior DMTs is considered as 0.
Current DMT was also removed from the model as it had an imbalance in count for various categories.
FAS, Full Analysis Set; n, number of subjects within subgroups; n1, number of observations used in this model.

Regarding the level of disability, patients in the SPMS subgroup showed severe disability (median EDSS 6.5) and relied on walking aids, confirming the urgent need to treat the progression of MS as soon as it is identified to stop or delay disability and the consequent worsening of the disease and quality of life.

On the other hand, although patients with RRMS have a low disability score (median EDSS 2.5), half of them show a medium or high risk of disability progression, as assessed by the MSProDiscuss™ tool (29.2 % of patients in the medium-risk category and 23 % in the high-risk category). MSProDiscuss™ was a tool with a high focus on patient-reported outcomes, which is an important aspect that is not usually considered when assessing disability progression. This tool also facilitates a discussion between physicians and patients. The medium/high-risk patient group represents a great challenge and deserves singular attention. It is important to proactively monitor RRMS patients with medium/high signs of disability progression to facilitate early SPMS diagnosis and intervention which, in turn, would lead to better prognosis (Cristiano et al., 2020; Giovannoni et al., 2016). As previously mentioned, a diagnostic uncertainty period of 3.3 years from RRMS to SPMS was reported in Argentina. In the local consensus on the identification and monitoring of SPMS, a panel of expert neurologists recommended that patients with suspected SPMS should be evaluated in an MS Center or by trained professionals in order to optimize care (Cristiano et al., 2021). Moreover, RRMS is the most amendable phase of MS, and early initiation of DMTs during RRMS slows the progression to SPMS (Bergamaschi et al., 2016). As the early detection of disease progression is also largely dependent on the patients (Oh et al., 2019), it is important that they carefully monitor changes in symptoms and report them to their neurologists in a timely manner, to receive adequate and early interventional support to manage MS.

MSProDiscuss™ was used to evaluate the risk to progress from RRMS to SPMS and to assess the relationship with some patient demographics and clinical characteristics. While the time of disease duration since the first symptom was not associated with the risk of disability progression, the time from first diagnosis was found to have a significant correlation with the risk of disability progression, which reconfirms the need to monitor disability as soon as MS is diagnosed. The identification of those patients who have a high probability of disability progression imposes

on physicians the need of close monitoring and earlier therapeutic action.

5. Conclusion

This cross-sectional study conducted in Argentina that evaluated disability in patients with ≥10 years of MS disease duration since the first diagnosis showed that, although RRMS patients were fully ambulatory and without aid, more than half of those patients were at medium or high risk of disability progression and there was severe disability in the SPMS subgroup, where patients relied on walking aids, confirming the urgent need to monitor the progression of MS as soon as it is identified to delay patient disability and improve their quality of life. Identifying those patients who have a high probability of disability progression imposes on physicians the need of close monitoring and earlier therapeutic action. Additional studies need to be conducted in this particular population in order to provide physicians with more accurate tools that help them achieve a prospective and "timely" SPMS diagnosis.

Availability of data and material

Research data will not be shared due to privacy restrictions.

Ethical approval

This study was conducted in accordance with the 18th World Medical Assembly (Helsinki) recommendations and amendments, as well as the guidelines for Good Epidemiological Practice. The study protocol was approved by the Institutional Review Boards and Independent Ethics Committees at all participating study locations; each site ensured compliance with all necessary regulatory submissions in accordance with local regulations, including local data protection regulations. All patients provided their written informed consent according to the local Independent Review Board requirements.

Consent for publication

Written informed consent was obtained from the patients for their anonymized information to be published in this article.

MSProDiscuss Tool™

Due to changes in the regulatory environment for provision of this tool and in an effort to streamline the support offerings to the MS community, Novartis has decided to retire the MSProDiscuss tool. The MSProDiscuss Tool™ was discontinued and unavailable effective since 31 December 2022

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This study was supported by Novartis Argentina S.A., Argentina. This institution participated in the collection, analysis and interpretation of data, and in the decision to submit the article for publication.

CRediT authorship contribution statement

Norma Deri: Conceptualization, Formal analysis, Validation, Writing – original draft, Writing – review & editing. **Andres Barboza:** Writing – original draft, Writing – review & editing, Investigation. **Carlos Vrech:** Writing – original draft, Writing – review & editing, Investigation, Resources. **Roberto Rey:** Resources, Writing – original draft, Writing – review & editing, Investigation. **Marcos Burgos:** Writing – original draft, Writing – review & editing, Investigation. **Marcela Fiol:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Cristian CalvoVildoso:** . **Liliana Patrucco:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Gustavo Jose:** Investigation, Validation, Writing – original draft, Writing – review & editing. **Paula Aliberti:** Data curation, Formal analysis, Supervision, Validation, Writing – original draft, Writing – review & editing. **Daniela Chirico:** Data curation, Formal analysis, Project administration, Validation, Writing – review & editing, Supervision. **Maria B. Federico:** . **Gustavo Seifer:** Conceptualization, Funding acquisition, Project administration, Validation, Writing – original draft, Writing – review & editing, Investigation, Supervision. **Raul Piedrabuena:** Investigation, Resources, Writing – original draft, Writing – review & editing.

Declaration of competing interest

Norma Deri reports grants from Novartis Argentina S.A. during the conduct of the study; grants from Novartis Argentina S.A., Sanofi Aventis and Laboratorios Roche not related to the submitted work. Andres Barboza reports grants from Novartis Argentina S.A. during the conduct of the study. Carlos Vrech reports grants from Novartis Argentina S.A. during the conduct of the study, and personal fees from Merck not related to the submitted work. Roberto Rey reports grants from Novartis Argentina S.A. during the conduct of the study. Marcos Burgos reports grants or contracts from Novartis Argentina S.A. and Biogen not related to the submitted work, personal fees/honoraria, and meeting travel support from Novartis Argentina S.A., Biogen, Teva, Merck and Roche. Marcela Fiol reports grants from Novartis Argentina S. A. during the conduct of the study, and grants from Biogen not related to the submitted work. Liliana Patrucco reports grants from Novartis Argentina S.A. during the conduct of the study, personal fees from Novartis Argentina S.A., Roche, Sanofi-Genzyme, Biogen, Merck, and Biosidus not related to the submitted work. Cristian Calvo-Vildoso reports no conflicts of interest. Gustavo Jose reports personal fees, non-financial support and other from Novartis Argentina S.A. during the conduct of the study, and grants and other from Novartis Argentina S.A. and Amgen not related to the submitted work. Paula Aliberti, Daniela Chirico, Maria B. Federico are employees at Novartis Argentina S.A. Gustavo Seifer was an employee at Novartis Argentina SA at the time of the study. Raul Piedrabuena reports grants from Novartis Argentina S.A. during the conduct of the study, grants from Biogen and Merck, personal fees from Roche, Merck, and Sanofi Genzyme not related to the submitted work.

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