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Clinical and demographic characteristics of male MS patients included in the national registry-RelevarEM. Does sex or phenotype make the difference in the association with poor prognosis?

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Abbreviations: MS, multiple sclerosis; CIS, clinically isolated syndrome; RRMS, relapsing remitting MS; SPMS, secondary progressive MS; PPMS, primary progressive MS; RoMS, relapsing onset MS; PoMS, progressive onset MS; IT, infratentorial lesions without spinal cord involvement; SC, spinal cord lesions without infratentorial involvement; ITSC, infratentorial plus spinal cord involvement.

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ABSTRACT

Background: In multiple sclerosis demographics there is a well-known female prevalence and male patients have been less specifically evaluated in clinical studies, though some clinical differences have been reported between sexes.
Objective: The objective of this study was to assess clinical and demographic differences between male and female patients included in the national Argentine MS Registry-RelevarEM.
Material and methods: This study was observational, retrospective, and was based on the data of 3099 MS patients included as of 04 April 2021. The statistical analysis plan included bivariate analyses with the crude data and also after adjustment for the MS phenotype, further categorized as progressive-onset MS or relapsing-onset MS. In the adjusted analysis, the Mantel-Haenszel odds ratio was compared to the crude odds ratio, to account for the phenotype as a confounder.
Results: The data from 1,074 (34.7%) men and 2,025 (65.3%) women with MS diagnosis were analysed. Males presented primary progressive disease two times more often than women (11% and 5%, respectively). In the crude analyses by sex, the presence of exclusively infratentorial lesions in the magnetic resonance imaging studies was more frequent in males than in females, but after adjustment by MS onset phenotype, such difference was only present in males with relapsing-onset MS ($p = 0.00006$). Similarly, worse Expanded Disability Status Scale scores were confirmed only in men with relapsing-onset disease after phenotype adjustment ($p = 0.02$).
Conclusion: We did not find any statistically significant clinical or demographic difference between sexes when the progressive MS phenotype was specifically considered. However, the differences we found between the clinical phenotypes are in line with the literature and highlight the importance of stratifying the analyses by sex and phenotype when designing MS studies.

1. Introduction

Multiple sclerosis (MS) is a heterogeneous chronic demyelinating and neurodegenerative autoimmune disease of the central nervous system (CNS) and represents the second most frequent cause of disability in young individuals. Its prevalence has been dramatically increasing during the last decades in almost all parts of the world, with a female to male ratio of 3:1. This rising predominance in women, together with pregnancy-related scenarios which require special and careful consideration, resulted in most publications focusing on women with MS (Bove and Chitnis, 2013).

Though there are well defined sex differences, men have been scarcely considered when evaluating different MS aspects. It has been described that progressive onset of MS is more frequent in men and that the relapse rate in the relapsing phenotypes is lower in men compared to women (Compston et al., 2006; Tremlett et al., 2008).

Most available studies focus on biological factors (sex), disregarding social factors (gender). Therapy targets in current clinical practice are based on an individualized and precision approach; therefore, differences between sex and gender deserve much more attention (Houtches and Bove, 2018). Of concern, even though people of either sex are included in cohort studies, the data are seldom disaggregated by sex. Since the majority of the publications assess the overall MS population, the results may be markedly biased by the female predominance of the disease.

We aimed to study the clinical and the demographic characteristics of male MS patients included in the national registry –RelevarEM, to explore potential differences that could help us to better understand the disease behaviour and the outcomes for this minoritarian and underconsidered sub-population of patients.

2. Material and methods

2.1. Data source and variables

RelevarEM is a longitudinal, strictly observational MS registry in

Argentina (ClinicalTrials.gov Identifier: NCT03375177). Methodological aspects and characteristics have been described in a previous publication (Rojas et al., 2019). The registry is open to all practicing neurologists, MS specialists and their teams across the country. The objective is to follow up the outcomes of MS patients receiving care in routine clinical practice.

Data for the present study were obtained from the registry as of 04 April 2021. The variables used for analysis were:

Demographic: sex, health insurance type, province of residence, employment status, retirement, disability certificate, age at symptoms onset and at study inclusion, and

Clinical: comorbidities, MS phenotype (as defined by Lublin et al. 2014), date of first and second relapse, clinical presentation of first and second relapse (monosymptomatic or polysymptomatic), MRI characteristics at the time of diagnosis —i.e., number of lesions, contrast enhancement, presence or absence of spinal cord lesions and/or infratentorial lesions, time interval between first and second relapse, time period since disease clinical onset of MS, last Expanded Disability Status Scale (EDSS) assessment at the time of the present study and ongoing treatment for patients diagnosed with clinical isolated syndrome (CIS), relapsing-remitting MS (RRMS), secondary-progressive MS (SPMS) and primary-progressive MS (PPMS) (Lublin et al., 2014).

2.2. Operational definitions applied

2.2.1. The provinces of residence were grouped according to the statistical regions established by the Instituto Nacional de Estadísticas y Censos (INDEC) of Argentina (http://servicios.infoleg.gob.ar/infolegInternet/anexos/275000–279999/279545/norma.htm) as follows

- **Northwest Region**: Catamarca, Jujuy, La Rioja, Salta, Santiago del Estero y Tucumán.
- **Northeast Region**: Corrientes, Chaco, Formosa y Misiones.
- **Cuyo Region**: Mendoza, San Juan y San Luis.
- **Pampeana Region**: Buenos Aires, CABA, Córdoba, Entre Ríos, La Pampa y Santa Fe.
- **Patagonia Region**: Río Negro, Neuquén, Chubut, Santa Cruz y Tierra del Fuego

2.2.2.

The time period since disease clinical onset was calculated as the interval between the date of data collection in the registry and the first relapse date.

2.2.3. Treatments were grouped as follows

- No treatment.
- Injectable therapies (β interferon 1_a; β interferon 1_b; Glatiramer acetate).
- Oral therapies: Teriflunomide, fingolimod, dimethylfumarate
- Infusions: Natalizumab, alemtuzumab, ocrelizumab, rituximab.
- Oral Immunosuppressive: Cladribine, azathioprine, cyclophosphamide, mofetil mycophenolate.
- Other.
- Not specified.

2.2.4.

For all the variables, the "not specified" category was excluded when estimating the other categories' proportion and the statistical significance.

2.3. Statistical analysis

The analysis was performed using SPSS software version 21.0, SPSS Inc., Chicago-ILL, USA. All the patients' data were anonymized for the statistical analyses.

To explore for any sex difference, bivariate analyses were performed with the crude data and also after adjustment for the MS phenotype.

In the crude bivariate analysis, in order to assess the statistical significance of any potential difference between sexes, the z-Normal and the chi-square/Fisher tests were used as appropriate according to the qualitative or quantitative nature of the variables. For statistically significant differences, the odds ratio (OR) and its respective 95% confidence interval (95% CI) were estimated to quantify the difference magnitude.

In the adjusted bivariate analysis, and for the purposes of assessing MS phenotype as a confounder, the Mantel-Haenszel OR value was estimated and it was compared with the crude OR: any difference greater than 10% between the two estimators and/or the non-overlapping of the respective confidence intervals suggested the phenotype was a confounder. For the latter analysis, phenotype was categorised as progressive-onset MS (PoMS) including PPMS or relapsing-onset MS (RoMS), where CIS, RRMS and SPMS were included. A p value <0.05 was considered statistically significant.

3. Results

A total of 3099 patients with MS diagnosis were included, 1074 (34.7%) of whom were men and 2025 (65.3%) women.

3.1. Relationship between clinical phenotype and lesion topography in MRI

The relationship between phenotype and lesion topography in MRI performed at the time of diagnosis was evaluated in 2364 of 3099 MS cases. Lesion sites were classified as: infratentorial without spinal cord involvement (IT), spinal cord without infratentorial involvement (SC), and infratentorial plus spinal cord involvement (IT+SC).

The evidence showed that lesions had significantly uneven localisation patterns according to phenotype ($P \cong 0$ for chi-square test) (Fig. 1). In CIS patients, SC lesions were slightly more frequent than the IT ones, with borderline significance: OR 1.8 [95% confidence interval (CI): 1.0 - 2.4]; $P = 0.04$. The probability for each lesion allocation according to the MS phenotype was measured excluding CIS patients from the analysis.

3.1.1. IT±SC lesions

SPMS patients had almost twice the risk of this lesion location compared to those with PPMS: OR 1.9 (95% CI: 1.4–2.8); $P < 0.001$, and the difference showed borderline significance compared to the RRMS group: OR 1.6 (1.0 - 2.5); $P = 0.04$. The risk of these lesion location was similar between PPMS and RRMS phenotypes ($P = 0.20$).

3.1.2. IT lesions

RRMS patients had almost 4 times the risk of this lesion topography compared to PPMS patients and twice the risk than SPMS patients: OR 3.7 (2.2–6.2; $P = 0.0001$) and OR 1.7 (1.1–2.6; $P = 0.02$), respectively. In turn, SPMS patients had a 2-fold higher risk of showing IT lesions than PPMS patients: OR 2.2 (1.1–4.3); $P = 0.02$.

3.1.3. SC lesions

PPMS patients had 3- and 2-times higher risk of showing this type of lesions than SPMS and RRMS patients: OR 3.1 (1.8–5.3) and OR 1.9 (1.4–2.6), respectively; $P = 0.0001$ for both comparisons. RRMS patients had a 1.6 times higher risk of showing SC lesions than SPMS patients, with borderline statistical significance: OR 1.6 (1.0–2.6); $P = 0.04$.

On the other hand, when categorisation according to disease onset phenotype was considered, patients with PoMS had almost twice the risk of SC lesions than those with RoMS: OR 1.8 (1.3–2.4); $P = 0.0003$. The risk of IT+SC lesions was similar ($P < 0.13$) (Fig. 2).

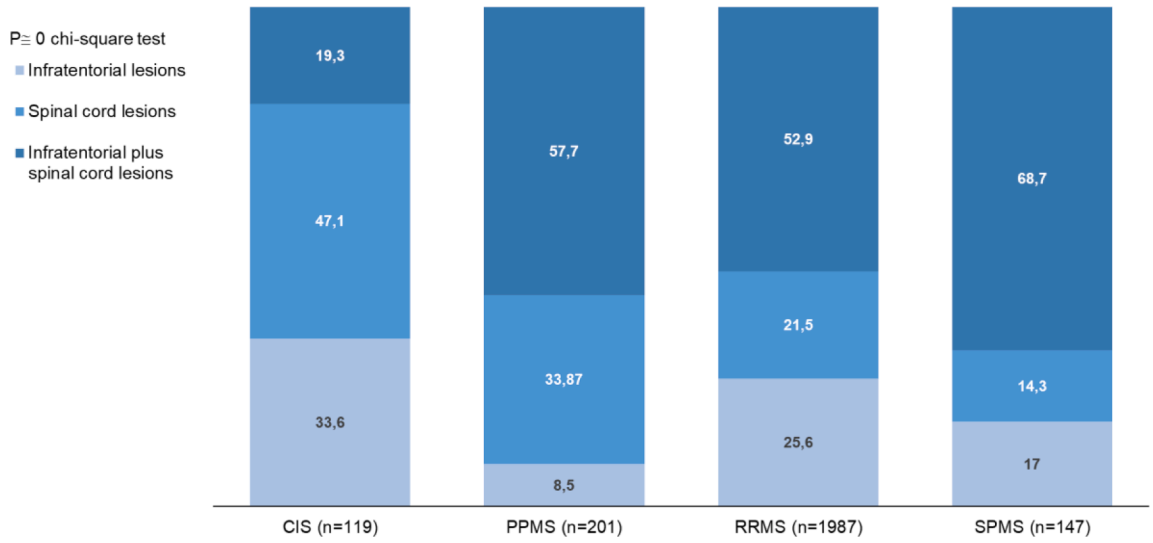

Fig. 1. Distribution of lesions seen on MRI at the time of diagnosis by MS phenotype.

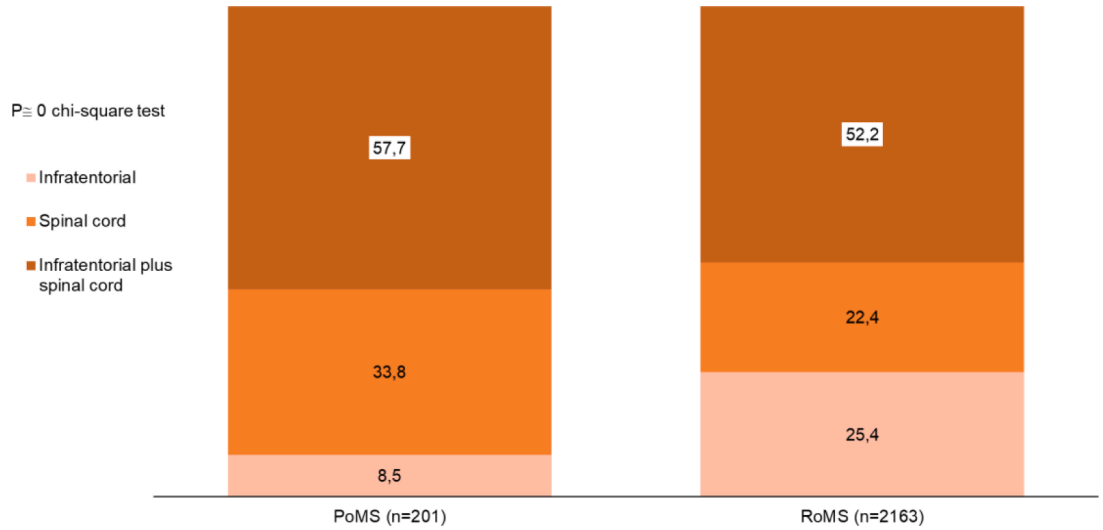

Fig. 2. Distribution of lesions in MRI at time of diagnosis by type of MS onset (progressive or relapsing).

3.2. Relationship between phenotype of MS onset and age at symptoms onset

Disease symptoms started at significantly later age in patients with PoMS than with other phenotypes (Table 1).

Table 1
Age at disease onset and EDSS score according to progressive or remitting MS phenotypes.

	PoMS (n = 233)	RoMS (n = 2866)
Age at disease onset (years)		
Mean ± SD	41.8 ± 11.0*	32.4 ± 10.3*
Median (min-max)	42 (17-71)	31 (2-79)
95% CI	40.4 to 43.2	32.0 to 32.8
EDSS score (last measured)		
0-3.5	42 (18.1%)	2,142 (74.4%)
4.0-5.5	51 (21.9%)	342 (11.9%)
6.0-6.5	73 (31.3%)	231 (8.1%)
7.0-8.5	62 (26.6%)	149 (5.2%)
9-9.5	5 (2.1%)	12 (0.4%)

* Differences: −9.4 (−10.8 to −8.0), (P < 0.0001 for z-Normal test).

3.3. Relationship of phenotype and patient's most recent EDSS score

The latest EDSS score showed to be strongly associated with the phenotype at disease onset. Evidence suggested that patients with PoMS have worse scores than other phenotypes (P ≅ 0) (Table 1).

3.4. Bivariate analysis accounting for biological sex (Table 2)

3.4.1. Clinical phenotype

Males had predominantly PPMS (♂11.7% vs. ♀5.3%) and females RRMS or CIS (♀88.8% vs. ♂82.4%), while SPMS phenotype showed similar proportion in both sexes (5.9%) ($P = 1.3 \times 10^{-7}$).

3.4.2. MRI lesion sites

Evidence supported a relationship between sex and MRI lesion location ($p = 0.001$). In males, IT lesions were more frequent [OR 1.43 (95% CI: 1.18–1.73); $P = 0.0002$], while IT+SC lesions were slightly more usual in females [OR 0.85 (0.72–1.01); $P = 0.06$]. SC involvement was comparable in both sexes [OR 0.86 (0.70–1.04); $P = 0.133$].

Table 2

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Demographic and clinical variables	Male (n=1074)	Female (n=2025)	P*
Current age	(n=1069)	(n=2021)	
Median (max-min)	43 (7 to 80)	43 (7 to 80)	*NS*
CI 95%	42.4 to 43.9	43.6 to 44.7	
Health insurance			
Public	114 (10.6%)	187 (9.2%)	
Provincial health organization	127 (11.8%)	262 (12.9%)	
Social Security	435 (40.5%)	777 (38.4%)	P= 0.26 (NS)
Pre-Paid	250 (23.3%)	533 (26.3%)	
National (PAMI)	71 (6.6%)	116 (5.7%)	
Other	77 (7.2%)	150 (7.4%)	
Region of residence			
Northeast	83 (7.7%)	173 (8.5%)	
Northwest	28 (2.6%)	44 (2.2%)	P= 0.41 (NS)
Cuyo	55 (5.1%)	100 (4.9%)	
Pampeana	877 (81.7%)	1626 (80.3%)	
Patagonia	31 (2.9%)	82 (4.0%)	
Employment			
Employed	732 (68.2%)	1323 (65.3%)	P= 0.11 (NS)
Unemployed	342 (31.8%)	702 (34.7%)	
Retired			
No	926 (86.2%)	1741 (86.0%)	P= 0.85 (NS)
Yes	148 (13.8%)	284 (14%)	
Disability certificate			
No	605 (56.3%)	1197 (59.1%)	P= 0.14 (NS)
Yes	469 (43.7%)	828 (40.9%)	
Comorbidities (Charlson index)			
0	935 (87.1%)	1772 (87.5%)	P= 0.72 (NS)
≥1	139 (12.9%)	253 (12.5%)	
1	107 (10.0%)	198 (9.8%)	
2	26 (2.4%)	49 (2.4%)	
3	3 (0.3%)	4 (0.2%)	P= 0.67 (NS)
4	2 (0.2%)	1 (0.0%)	
5	-	-	
6	1 (0.1%)	-	
8	-	1 (0.0%)	
MS onset – First relapse			
Age at symptom onset (years)	(n=1068)	(n=2017)	*Difference: 0.60 (-0.18 to 1.38)*
Mean ± SD	32.7 ± 10.7	33.3 ± 10.5	
Median (min-max)	32 (2 to 69)	32 (2 to 79)	P= 0.13 (NS)
CI 95%	32.1 to 33.3	32.8 to 33.8	
MS Phenotype			
Clinical Isolated Syndrome	53 (4.9%)	134 (6.6%)	
Relapsing-remitting MS	832 (77.5%)	1665 (82.2%)	P= 1.3 x 10^{-7}
Secondary-progressive MS	63 (5.9%)	119 (5.9%)	
Primary-progressive MS	126 (11.7%)	107 (5.3%)	
Clinical presentation of first relapse			
Monosymptomatic	833 (78.1%)	1591 (79.2%)	
Polysymptomatic	233 (21.9%)	417 (20.8%)	P= 0.51 (NS)
Not specified	8	17	
MRI. n° of gadolinium enhancing lesions			
0	485 (50%)	829 (46.9%)	P=0.13 (NS)
≥1	485 (50%)	936 (53.1%)	
0	485 (50.0%)	829 (46.9%)	
1	143 (14.7%)	301 (17.1%)	
2	98 (10.1%)	178 (10.1%)	P= 0.38 (NS)
3	51 (5.3%)	70 (3.9%)	
4	26 (2.6%)	57 (3.2%)	
5	18 (1.9%)	43 (2.4%)	
6	18 (1.9%)	36 (2.0%)	
>6	131 (13.5%)	251 (14.2%)	
Not specified	104	260	
Only infratentorial lesions	255 (28.1%)	312 (21.4%)	
Only spinal cord lesions	197 (21.7%)	355 (24.4%)	P= 0.001
Infratentorial and spinal cord lesions	456 (50.2%)	789 (54.2%)	
Not specified	166	569	
	-	-	
Second Relapse			
n° of cases that had a second relapse	699/1074 (65.1%)	1399/2025 (69.1%)	P= 0.02
Clinical presentation of second relapse			
Monosymptomatic	511 (73.6%)	1046 (75.6%)	
Polysymptomatic	183 (26.3%)	337 (27.2%)	P= 0.32 (NS)
Not specified	5	16	
Time between first and second relapse (years)			
≤1	350 (50.3%)	670 (48.6%)	
2 - 5	239 (34.4%)	487 (35.3%)	
6 - 10	67 (9.6%)	143 (10.4%)	
11 - 15	28 (4.0%)	48 (3.5%)	
16 - 20	6 (0.9%)	22 (1.6%)	P= 0.94 (NS)
21 - 25	1 (0.1%)	5 (0.4%)	
26 - 30	2 (0.2%)	2 (0.1%)	
>30	2 (0.2%)	3 (0.2%)	
Not specified	4	19	
Mean ± SD (years)	2.9 ± 4.2	3.0 ± 0.7	*Difference: 0.10 (-0.27 to 0.47)*
Median (min-max)	1 (<1 to 40)	2.0 (<1 to 45)	*P= 0.60 (NS)*
CI 95%	2.6 to 3.2	2.96 to 3.04	
Treatment and Follow-up			
Time course of MS (years)	(n=1074)	(n=2024)	
Mean ± SD	11.6 ± 8.2	11.9 ± 8.9	*Difference: 0.30 (-0.34 to 0.94)*
Median (min-max)	9.8 (0.5 to 54.4)	9.6 (0.3 to 62.4)	P= 0.36 (NS)
CI 95%	11.1 to 12.1	11.5 to 12.3	
Current EDDS			
0 - 3.5	701 (65.2%)	1473 (72.7%)	
4.0 - 5.5	157 (14.6%)	236 (11.6%)	P= 0.0002
6.0 - 6.5	119 (11.1%)	185 (9.1%)	
7.0 - 8.5	93 (8.7%)	118 (5.8%)	
9.0 - 9.5	4 (0.4%)	13 (0.7%)	
Mean ± SD	3.1 ± 2.3	2.8 ± 2.2	*Difference: -0.30 (-0.46 to -0.13)*
Median (min-max)	2.0 (0.0 a 9.5)	2.0 (0.0 a 9.5)	*P= 0.0004*
CI 95%	2.96 a 3.24	2.70 a 2.89	
Ongoing treatment			
No treatment	232 (21.6%)	389 (19.2%)	
Injectables	233 (21.7%)	448 (22.1%)	
Oral	450 (41.8%)	888 (43.9%)	P= 0.31 (NS)
Infusion	121 (11.3%)	204 (10.1%)	
Oral immunosuppressor	35 (3.3%)	89 (4.4%)	
Other (Siponimod, homeopathy, clinical trials)	3 (0.3%)	7 (0.3%)	

Table 2 (*continued*)

* Chi-square or z-Normal, according to the variable (discrete or continuous). In cases with statistical significance, magnitude of the difference between groups and its significance are described.

Table 3
Clinical and demographic characteristics of each sex adjusted by MS onset phenotype.

Clinical and demographic variables	PoMS: Primary progressive MS (n = 233)		RoMS: Other MS phenotypes (CIS, RRMS, SPMS) (n = 2,866)	
	Males (n= 126)	Females (n= 107)	Males (n= 948)	Females (n= 1,918)
	MS onset - First relapse			
Age at symptom onset (years)			(n=942)	(n=1,910)
Mean ± SD	41.5 ± 10.7	42.3 ± 11.4	31.5 ± 10.2	32.8 ± 10.3
Median (min-max)	41 (17 - 69)	44 (17 - 71)	31 (2 - 69)	32 (2 - 79)
95% CI	39.6 - 43.4	40.1 - 44.5	30.8 - 32.2	32.3 - 33.3
Crude analysis	*Difference: 0.80 (-2.06 to 3.66)*		*Difference: 1.3 (0.50 to 2.09)*	
*Difference: 0.60 (-0.18 to 1.38)***	*P = 0.58 (NS)*		*P = 0.001*	
P = 0.13 (NS)				
Clinical presentation of first relapse				
Monosymptomatic	105 (86.1%)	84 (80.8%)	728 (77.1%)	1,507 (79.1%)
Polysymptomatic	17 (13.9%)	20 (19.2%)	216 (22.9%)	397 (20.9%)
Not specified	4	3	4	14
*Crude analysis: OR = 0.94 (0.78 to 1.12); P= 0.51 (NS)***	*OR_{MH} = 0.92 (0.68 to 1.24)*			
MRI enhancing lesions				
Yes	99 (86.1%)	69 (79.3%)	386 (45.1%)	760 (45.3%)
No	16 (13.9%)	18 (20.7%)	469 (54.9%)	918 (54.7%)
Not specified	11	20	93	240
*Crude analysis: OR = 1.13 (0.97 to 1.32); P = 0.13 (NS)***	*OR_{MH} = 1.02 (0.74 to 1.41)*			
Only infratentorial lesions	10 (9%)	7 (7.8%)	245 (30.7%)	305 (22.3%)
Only spinal cord lesions	39 (35.1%)	29 (32.2%)	158 (19.8%)	326 (23.9%)
Infratentorial plus spinal cord lesions	62 (55.9%)	54 (60%)	394 (49.5%)	735 (53.8%)
Not specified	15	17	151	552
*Crude analysis: P = 0.001***	*P = 0.83 (NS)*		*P = 0.00006*	
	Second Relapse			
n° of cases	16/126 (12.7%)	14/107 (13.1%)	683/948 (72.0%)	1,385/1918 (72.2%)
*Crude analysis: OR = 1.2 (1.0 to 1.4); P = 0.02***	*OR_{MH} = 0.99 (0.48 to 2.04)*			
Clinical presentation of second relapse				
Monosymptomatic				
Polysymptomatic	14 (87.5%)	11 (78.6%)	497 (73.3%)	1,035 (75.6%)
Not specified	2 (12.5%)	3 (21.4%)	181 (26.7%)	334 (24.4%)
	-	-	5	16
*Crude analysis: OR = 0.90 (0.73 to 1.11); P= 0.32 (NS)***	*OR_{MH} = 0.89 (0.39 to 2.01)*			
Time between first and second relapses (years)				
≤1				
2 - 5	8 (50%)	2 (15.4%)	342 (50.5%)	668 (48.9%)
6 - 10	3 (18.7%)	7 (53.8%)	234 (34.6%)	480 (35.1%)
11 - 15	4 (25%)	4 (30.8%)	63 (9.3%)	139 (10.2%)
16 - 20	1 (6.3%)	-	27 (3.9%)	48 (3.5%)
21 - 25	-	-	6 (0.9%)	22 (1.6%)
26 - 30	-	-	1 (0.1%)	5 (0.4%)
>30	-	-	2 (0.3%)	2 (0.1%)
Not specified	-	-	2 (0.3%)	3 (0.2%)
	-	1	1	18
Crude analysis: P = 0.94 (NS)	*P = 0.35 (NS)*		*P = 0.96 (NS)*	
Mean ± SD (years)	4.1 ± 4.3	3.8 ± 2.5	2.9 ± 4.2	3.0 ± 4.1
Median (min-max)	1.5 (0 - 15)	3.0 (1 - 8)	1 (0 - 40)	2.0 (0 - 45)
95% CI	1.8 - 6.4	2.4 - 5.2	2.6 - 3.2	2.8 - 3.2
Crude analysis: Difference: 0.10 (-0.27 to 0.47)	*Difference: -0.30 (-1.22 to 0.63)*		*Difference: 0.10 (-0.22 to 0.42)*	
*P = 0.60 (NS)***	*P = 0.52 (NS)*		*P = 0.54 (NS)*	
Treatment and follow up				
MS duration (years)				(n=1,917)
Mean ± SD	12.1 ± 7.8	14.1 ± 8.5	11.5 ± 8.2	11.8 ± 8.9
Median (min-max)	11 (0.8 - 47)	12.3 (1.3 - 42)	9.6 (0.5 - 54.4)	9.4 (0.3 - 62.4)
95% CI	10.7 - 13.5	12.5 - 15.7	10.9 - 12.0	11.4 - 12.2
Crude analysis: Difference: 0.30 (-0.34 to 0.94)	*Difference: 2.0 (-0.11 to 4.11)*		*Difference: 0.30 (-0.37 to 0.97)*	
*P = 0.36 (NS)***	*P = 0.06 (borderline)*		*P = 0.38 (NS)*	
Current EDSS				
0 - 3.5	21 (16.7%)	21 (19.6%)	680 (71.7%)	1,452 (75.7%)
4.0 - 5.5	35 (27.8%)	16 (14.9%)	122 (12.9%)	220 (11.5%)
6.0 - 6.5	36 (28.6%)	37 (34.6%)	83 (8.8%)	148 (7.7%)
7.0 - 8.5	32 (25.4%)	30 (28.0%)	61 (6.4%)	88 (4.6%)
9.0 - 9.5	2 (1.6%)	3 (2.8%)	2 (0.2%)	10 (0.5%)
Crude analysis P = 0.0002	*P = 0.21 (NS)*		*P = 0.06 (borderline)*	
Mean ± SD	5.5 ± 1.9	5.7 ± 1.8	2.8 ± 2.2	2.6 ± 2.1
Median (min-max)	6 (0 - 9.5)	6 (1 - 9.5)	2 (0 - 9.5)	2 (0 - 9.5)
95% CI	5.2 - 5.8	5.4 - 6.0	2.7 - 2.9	2.5 - 2.7
Crude analysis: Difference: -0.30 (-0.46 to -013)	*Difference: 0.20 (-0.28 to 0.68)*		*Difference: -0.20 (-0.37 to -0.03)*	
*P = 0.0004***	*P = 0.41 (NS)*		*P = 0.02*	

* P from chi-square test or z-Normal as appropriate. NS: without statistical significance.
** Full details of bivariate (not adjusted) analyses are in Table 2.

3.4.3. Second relapses

While assessed at similar time interval from disease clinical onset in both sexes, women showed 1.2 times higher risk of second relapses than men: OR 1.2 (1.0–1.4); $P = 0.02$.

Of note, although the P value is significant, the confidence interval of the OR includes the value 1.0, suggesting caution when interpreting this finding.

3.4.4. Current EDSS score

Even though both men and women had a similar disease duration (*P*

= 0.36, NS), men showed a significantly higher mean EDSS score than women ($P = 0.0004$), from EDSS scores ≥ 4.0.

Since EDSS scores are strongly related to phenotype, it was considered to be necessary to adjust the bivariate analysis for the phenotype of disease onset -PoMS or RoMS.

No evidence was found to support any relationship between sex and health insurance type, region of residence, occupation, retirement, disability certificate, Charlson comorbidity index, age of symptom onset, symptoms at first relapse, MRI lesion enhancement, occurrence of second relapse, time interval between first and second relapses, or current treatment (P = NS).

3.5. Bivariate analysis adjusted by phenotype of disease onset (PoMS or RoMS) (Table 3.)

3.5.1. Age at symptom onset

In the crude analysis, the age at symptom onset was similar for both sexes ($P = 0.13$). After adjusting for phenotype of MS onset, RoMS cases showed symptoms 9.4 years earlier than PoMS cases.

Furthermore, males with RoMS phenotype showed onset of symptoms 1.3 years earlier than females ($P = 0.001$).

3.5.3. MRI lesion sites

In the crude analysis, the evidence showed different lesion location patterns between male and female patients ($P = 0.001$).

After adjusting for phenotype of disease onset, such differences were only observed in patients with RoMS, where male patients had significantly more IT lesions than females ($P = 0.00006$).

3.5.4. Second relapses

In the crude analysis, women showed 1.2 times higher risk of second relapses than men, though with borderline significance because the confidence interval included the OR value 1.

When adjusting for onset phenotypes, no association of sex with second relapses was evident.

3.5.5. EDSS score

After adjusting for sex, men showed a significantly higher mean EDSS score than women, though both had comparable disease duration ($P = 0.0004$); such difference was observed from EDSS scores ≥ 4.0.

When adjusting for phenotype of MS onset, sex differences were found in the RoMS group ($p = 0{,}02$), while in the PoMS group, the EDSS scores were comparable between male and female patients.

No evidence was found to support that MS onset phenotype is associated with any sex difference in the following variables: health insurance, region of residence, occupation, retirement, disability certificate, Charlson comorbidity index, symptoms of the first relapse, lesion enhancement in MRI, occurrence of second relapse, symptoms of the second relapse, time interval between first and second relapses, treatment received and MS duration (P = NS).

4. Discussion

There are well-established sex differences in MS risk and course. The female to male ratio has been markedly increasing in most parts of the world over the last decades (Cristiano et al., 2016; Makhani et al., 2014; Kingwell et al., 2015).

Our results show that men present as double the frequency of PPMS than women (11% vs. 5%, $p = 0.00000013$). We found a female to male ratio of 2:1 for the relapsing phenotypes and an almost levelled sex ratio (1:1.2) for the progressive phenotypes. The average age at MS onset was almost a decade later for PoMS (41.8 years) than for RoMS (32.4 years). These results are in accordance with the literature, where the age at disease onset is 33.2 years for men and women with relapsing disease and approximately 42 years for patients (both sexes) with progressive disease from onset (Miller et al., 2007; Reich et al., 2018; Rommer et al., 2020).

To account for potential confounders, we analysed the crude sex ratio for clinical and demographic characteristics and then we applied an adjustment by disease onset phenotype –either PoMS or RoMS. The sex ratio was balanced for patients with PoMS, an observation also informed in a recently published German study (Rommer et al., 2020).

An interesting observation from our study is that MRI lesion distribution at the time of diagnosis was significantly unequal ($p \cong 0$). In a first analysis, we found that patients with SPMS showed predominantly IT+SC lesions, while patients with RRMS had IT lesions with more frequency, and in patients with progressive disease onset, the SC location was the most found. The differences in lesion topography frequency were statistically significant. When we stratified the analysis by sex, we found that the presence of IT lesions without SC involvement was more frequent in males than in females ($p = 0.0002$). After adjusting by MS onset phenotypes, such predominance was only present in males with RoMS ($p = 0.00006$). We found no differences in lesion location between males and females with PoMS and neither between the two sexes in the number of gadolinium enhanced lesions at the time of diagnosis.

In the initial analysis of our study, higher EDSS scores were strongly associated with PoMS ($p = 0$), while the sex stratified analysis found higher EDSS scores in men (0.0004) from ≥ 4 points. Such sex difference disappeared when the analysis was adjusted by MS onset phenotype, where higher EDSS scores in men were only observed in the RoMS group ($p = 0.02$). This finding is in line with other studies (Koch et al., 2010; Bove et al., 2012; Ribbons et al., 2015). Moreover, it has been described that men and women tend to reach similar disability scores at overall similar age (Bove et al., 2016; Tremlett et al., 2006).

In our study we were not able to find any other statistically significant clinical or demographic difference between sexes when we accounted for the disease phenotype.

As stated in a recent publication, if phenotype is not considered in MS studies, then the age at onset and the tendency for men to reach higher EDSS scores faster could be wrongly attributed to differences because of sex, when it is really the result of their tendency to exhibit progressive MS (Houtchens et al., 2018).

There are differences in clinical features between men and women independently from phenotype. Men with RoMS have more cerebellar, motor and sexual disfunction, while women show higher prevalence of visual and sensitive symptoms as well as cognitive impairment, pain, depression, fatigue and psychological manifestations (Bove et al., 2016; Carnero Contentti et al., 2019; Grech et al., 2021; Rommer et al., 2020). In our study, these individual clinical symptoms (and many other variables of potential interest), could not be analysed because such information was not available; however, the number of symptoms at the first clinical presentation (polysymptomatic or monosymptomatic) was the same for men and women.

Regarding MRI parameters, we evaluated only the topography and the contrast enhancement of the lesions. Data on other variables such as brain atrophy or other specific MRI measurements, were not available for analysis and were out of the scopes of the present study.

The limitations of this study include its observational nature and retrospective design. The data source has its own drawbacks, which are common to all registries -e.g., register bias, selection bias, data not being collected systematically as in clinical trials, limitations to analyse certain parameters not included in the registry (such as detailed symptom information, cognitive and psychologic manifestations or some MRI parameters). Nevertheless, all the data for this study were assessed by neurologists with experience in MS and reflect the “real world”. Another limitation is that we did not analyse follow-up information about disease progression and the variables collected at disease onset and study inclusion were descriptive; however, the main objective of this study was to explore any clinical and demographic difference between sexes in phenotype-stratified MS patients.

As has been previously described, differences between sexes may lie on the fact that men have more prevalence of PPMS than women and this

could be the reason determining their divergence in prognosis. Our results support a similar observation communicated in the recent publication from the German MS Registry group, which authors concluded that clinical and demographic data differ between men and women mostly due to the disease course than to the biological sex (Rommer et al., 2020).

In summary, we did not find any other significant difference except those described (higher EDSS scores and higher MRI IT lesion location in males with RoMS) in either the clinical or the demographic aspects assessed between sexes when the progressive or remitting MS presentation was specifically considered, although differences between phenotypes were confirmed. This information is important to understand the behaviour of the disease in relation to sex as well as the role of certain social and hormonal factors in explaining the findings –either if any difference is present or not. Moreover, there are a number of additional aspects related to gender that impact on social issues as, for example, it is well described how differently men experience many features of the disease from women (Bove et al. 2016; Carnero Contentti et al., 2019; Dastoorpoor et al., 2021; Grech et al., 2021; Mayo et al., 2021). This knowledge can help individualize each patient's risk and select the most appropriate care.

To our knowledge, there are no published data focusing on this subject -sex differences, in MS patients from South America.

In a previous publication, we described the clinical and the demographic characteristics of PPMS of patients included in the RelevarEM registry (Alonso et al., 2020). Even though it is not the objective of the present study, our results update and aggregate new detailed and stratified information to that publication.

The present study adds to the evidence that there are no significant differences in either the clinical or the demographic characteristics that disfavour men once the phenotype is accounted for. Moreover, our findings warn about the crucial importance of including stratified analysis by sex and phenotype when designing MS studies.

CRediT authorship contribution statement

Geraldine G. Luetic: Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration. **María Laura Menichini:** Investigation, Data curation, Writing – review & editing. **Carlos Vrech:** Resources, Data curation. **Agustín Pappolla:** Resources, Data curation. **Liliana Patrucco:** Resources, Data curation. **Edgardo Cristiano:** Resources, Data curation. **Mariano Marrodán:** Resources, Data curation. **María C. Ysrraelit:** Resources, Data curation. **Marcela Fiol:** Resources, Data curation. **Jorge Correale:** Resources, Data curation. **Leila Cohen:** Resources, Data curation. **Ricardo Alonso:** Resources, Data curation. **Berenice Silva:** Resources, Data curation. **Magdalena Casas:** Resources, Data curation. **Orlando Garcea:** Resources, Data curation. **Norma Deri:** Resources, Data curation. **Marcos Burgos:** Resources, Data curation. **Susana Liwacki:** Resources, Data curation. **Verónica Tkachuk:** Resources, Data curation. **Andrés Barboza:** Resources, Data curation. **Raúl Piedrabuena:** Resources, Data curation. **Patricio Blaya:** Resources, Data curation. **Judith Steinberg:** Resources, Data curation. **Alejandra Martínez:** Resources, Data curation. **Adriana Carrá:** Resources, Data curation. **Darío Tavolini:** Resources, Data curation. **Pablo López:** Resources, Data curation. **Eduardo Knorre:** Resources, Data curation. **Pedro Nofal:** Resources, Data curation. **Gabriel Volman:** Resources, Data curation. **Edgar Carnero Contentti:** Resources, Data curation. **Amelia Alves Pinheiro:** Resources, Data curation. **Felisa Leguizamon:** Resources, Data curation. **Emanuel Silva:** Resources, Data curation. **Javier Hryb:** Resources, Data curation. **María Eugenia Balbuena:** Resources, Data curation. **Gisela Zanga:** Resources, Data curation. **Matías Kohler:** Resources, Data curation. **Aníbal Chertcoff:** Resources, Data curation. **Luciana Lazaro:** Resources, Data curation. **Santiago Tizio:** Resources, Data curation. **Carolina Mainela:** Resources, Data curation. **Edgardo Reich:** Resources, Data curation. **Luciano Recchia:** Resources, Data curation. **Jorge Blanche:** Resources, Data curation. **Marcela Parada Marcilla:** Resources, Data curation. **María Eugenia Fracaro:** Resources, Data curation. **Gustavo Sgrilli:** Resources, Data curation. **Pablo Divi:** Resources, Data curation. **Miguel Jacobo:** Resources, Data curation. **Mariela Cabrera:** Resources, Data curation. **Fátima Pagani Cassara:** Resources, Data curation. **Vladimiro Sinay:** Resources, Data curation. **Celeste Curbelo:** Resources, Data curation. **Jimena Míguez:** Resources, Data curation. **Mariano Coppola:** Resources, Data curation. **Nora Fernández Liguori:** Resources, Data curation. **Iván Martos:** Resources, Data curation. **Juan Pablo Pettinicchi:** Resources, Data curation. **Juan Pablo Viglione:** Resources, Data curation. **Gustavo José:** Resources, Data curation. **Santiago Bestoso:** Resources, Data curation. **Rubén Manzi:** Resources, Data curation. **Guido Vázquez:** Resources, Data curation. **Débora Nadur:** Resources, Data curation. **Carlos Martínez:** Resources, Data curation. **Marina Alonso Serena:** Resources, Data curation. **Juan I. Rojas:** Methodology, Investigation, Resources, Data curation, Writing – review & editing, Visualization.

Declaration of Competing Interest

Authors declare no potential conflicts of interest regarding this research, authorship and/or publication of this article.

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