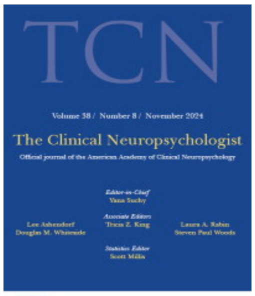

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Cognitive phenotypes in patients with relapsing-remitting multiple sclerosis with different disease duration, applying the international classification of cognitive disorders in MS (IC-CoDiMS)

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ABSTRACT

Objective: Cognitive impairment is experienced by 40–70% of multiple sclerosis patients, with information processing speed and memory most affected. Until now, cognitive results classified patients as impaired and not impaired. With this dichotomous approach, it is difficult to identify, in a heterogeneous group of patients with cognitive impairment, which cognitive domain(s) are most altered. This study aims to identify cognitive phenotypes in a clinical cohort of adult patients with Relapsing-Remitting Multiple Sclerosis (RRMS) using the International Classification of Cognitive Disorders in MS (IC-CoDiMS) and to characterize their clinical features. **Methods:** Three hundred patients with RRMS underwent neuropsychological assessment with the Brief Repeatable Battery of Neuropsychological Tests (BRBN-T) and the Brief International Cognitive Multiple Sclerosis (BICAMS). **Results:** In our cohort, the mean age was 41.38 [11.48 SD] years, and 205 [68.3%] were women. At the −1 SD threshold, 49% were cognitively intact, 25% had uni-domain impairment, 17% had bi-domain impairment, and 9% had multi-domain impairment. Processing speed was the most frequent single-domain impairment, followed by memory and verbal fluency. At the −1.5 SD threshold, 74.7% were cognitively intact, 17% had uni-domain impairment, 6% had bi-domain impairment, had bi-domain impairment, and 3.0% had multi-domain impairment. Memory was the most frequent single-domain impairment, followed by processing speed and verbal fluency. **Conclusions:** This study corroborates the importance of determining cognitive phenotypes through taxonomy (IC-CoDiMS). In addition, it contributes to improving the classification of cognitive phenotypes in patients with RRMS to enhance the development of more effective treatments and cognitive interventions.

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system that can impair bodily function, including cognition (Rao et al., 1991). Cognitive dysfunction affects 40 to 70% of patients (Benedict et al., 2020; Langdon, 2011; Meca-Lallana et al., 2021) and is increasingly among the most disabling symptoms (Chiaravalloti & DeLuca, 2008). This may occur at all stages of the disease, even at the early beginning (Amato et al., 2012; Zipoli et al., 2010) and it impacts the lives of MS patients and their families (Benedict et al., 2020; Kobelt et al., 2017; Sá et al., 2017), negatively affecting social and emotional functioning, employment and overall quality of life (Chiaravalloti & DeLuca, 2008). Marked cognitive dysfunction is more common in secondary progressive (SPMS) and primary progressive (PPMS) multiple sclerosis as compared to relapsing-remitting multiple sclerosis (RRMS) (Ruet et al., 2013; Sousa et al., 2021). Attention, information processing speed (IPS), memory, and executive functions are the most commonly affected cognitive domains (Chiaravalloti & DeLuca, 2008; Grzegorski & Losy, 2017). However, it is still challenging to know precisely how cognitive impairment is characterized in these patients because usually, after administering a neuropsychological battery, individuals are classified as having cognitive impairment or not according to various criteria (Amato et al., 2018). One of the first approaches to the study of cognitive phenotypes was introduced by Leavitt et al. (2018), identified cognitively homogeneous subgroups of MS patients that were defined as cognitive phenotypes: isolated memory impairment, isolated impairment of information processing speed and combined deficits in processing speed and memory. However, deficits in other cognitive domains have also been reported in MS (Chiaravalloti & DeLuca, 2008; Sousa et al., 2021), and that classification was based on the dichotomous definition of impairment for each domain, not considering patients with mild cognitive impairment (Amato et al., 2018). To classify and identify cognitive phenotypes in a clinical cohort of patients with MS, including the whole spectrum of disease subtypes, a recent study by De Meo et al. (2021) used Latent Profile Analysis (LPA) and found five cognitive phenotypes: preserved cognition; mild verbal memory/semantic fluency; mild multi-domains; severe executive/attention; and severe multi-domains. For this reason, a taxonomy that recognizes the predominant subtypes, called cognitive phenotypes, could lead to better knowledge about cognitive impairment and, therefore, contribute to effective personalized treatments and cognitive strategies. More recently, Hancock et al. (2023) advanced the taxonomy of cognitive phenotypes in MS and clarified the type and distribution of possible cognitive diagnoses, applying the International Classification of Cognitive Disorders in Epilepsy (IC-CoDE) to characterize the taxonomy of cognitive status in patients with MS (International Classification of Cognitive Disorders in MS; IC-CoDiMS; McDonald et al., 2022). The following phenotypic classifications were established: intact, single-domain impairment, bi-domain impairment, or multi-domain impairment (> three impaired domains).

However, there are some obstacles to this classification: Although some studies have analyzed the relationships between cognitive dysfunction and other variables such as depression, anxiety and EDSS (Nocentini et al., 2006; Wojcik et al., 2022), a few others focus only on cognitive dysfunction, without looking at clinical and emotional variables (Leavitt et al., 2018). In addition, samples are quite heterogeneous, and the cognitive tests used are not always part of the most recommended batteries for MS.

Our study aims to evaluate the possibility of defining cognitive phenotypes in a sample of patients with RRMS using only the ones with strong evidence of construct validity in Portuguese patients with MS.

Methods

Study design and participants

This cross-sectional study was designed to identify distinct and predominant cognitive phenotypes in a clinical cohort of Portuguese patients with RRMS applying two recommended cognitive batteries for MS: BRBN-T and BICAMS.

A group of 300 patients with RRMS diagnosed according to the McDonald criteria (Thompson et al., 2018) was acquired from a cohort of consecutive MS patients evaluated periodically in the MS consultation of the Neurology Department, Centro Hospitalar Universitário São João (CHUSJ). The cognitive assessment with the batteries mentioned above is part of the clinical routine. Inclusion criteria were: definitive diagnosis of MS, relapsing-remitting subtype, age above 18 years and fluency in European Portuguese as first language. Exclusion criteria were: current or past neurological disorder other than MS, presence of major psychiatric illness, history of learning disability, history of severe head trauma, presence of alcohol or drug abuse, relapse and corticosteroid use within four weeks preceding the neuropsychological assessment. For this study, the data was collected between 2020 and 2023.

The Ethics Committee of the CHUSJ approved the study protocol (CE-390-19), and written informed consent was obtained from all patients before their inclusion in the study, by the Revised Declaration of Helsinki.

Procedures

An initial demographic interview was conducted. This was based on a standard script that included a demographic questionnaire (i.e. age, education level), medical history, drinking and drug habits, and current health. The MS data, such as type, disease duration, degree of disability and severity by the Expanded Disability Status Scale (EDSS; Kurtzke, 1983), was assessed by a neurologist and obtained in the clinical protocols.

Cognitive assessment

Participants underwent the Brief Repeatable Battery of Neuropsychological Tests (BRBN-T) and the Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS). Both evaluate the most frequently impaired cognitive domains in MS and are adapted and validated for European Portuguese (Sousa et al., 2018, 2021). We maintained our typical clinical routine, and the two neuropsychological batteries were administered on the same day. The BRBN-T was administered before the medical consultation, and the BICAMS was administered after the medical consultation.

The tests that are part of each battery are described in Table 1.

Impairment assessed by the BRBN-T was defined as impairment in at least two cognitive domains. For the BICAMS, cognitive impairment was defined as impairment in at least one of the cognitive domains evaluated by the battery. To determine the cognitive phenotypes, we used an existing taxonomy of cognitive phenotypes in neurological diseases (IC-CoDiMS), as recently proposed by Handcock and colleagues (2023). By prior research (Hancock et al., 2023; Jak et al., 2009), we used cutoffs of −1.0 and −1.5 SD to define cognitive impairment. However, in this study, it was essential to adjust the framework of this taxonomy because BRBN-T and BICAMS do not have two separate tests that assess executive function and language. Therefore, our methodology generated four cognitive domains: verbal memory, visuo-spatial memory, information processing speed and verbal fluency (as shown in Table 2). Phenotypes were classified as intact, uni-domain (i.e. only one domain impaired), bi-domain (i.e. two domains impaired) and multi-domain (i.e. three or more domains impaired). A domain was considered impaired if scores on two tests within the domain fell below one of the two thresholds of interest (−1.0 and −1.5 SD below the mean). Since the sample only included the RRMS subtype, we also classified all patients according to the disease duration, as early (duration ≤10 years) or late (duration > 10 years) groups. Studies indicate that in the first ten years, there is a lower risk of disability progression (Beckerman et al., 2013; Kerbrat et al., 2014).

Table 1. The neuropsychological tests and corresponding cognitive domains measured by the Brief Repeatable Battery Neuropsychology Test (BRBN-T) and Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS).

Test – BRBN-T	Domain
Selective Reminding Test - SRT	Verbal learning and memory
10/36 Spatial Recall Test - SPART	Visuo-spatial learning and memory
Symbol Digit Modalities Test - SDMT	Sustained attention, information processing speed, working memory
Paced Auditory Serial Addition Test - PASAT	Sustained attention, information processing speed, working memory
Controlled Oral Words Auditory Test-COWAT	Phonemic and semantic verbal fluency
Test - BICAMS	Domain
California Verbal Learning Test- CVLT-2	Verbal learning and memory
Brief Visual Memory Test-revised – BVMT-R	Visuo-spatial learning and memory
Symbol Digit Modalities Test - SDMT	Sustained attention, information processing speed, working memory

Table 2. Neuropsychological measures by domain.

Cognitive domains	Test
Attention and information processing speed	Processing speed with no motor component: SDMT (oral version); PASAT
Verbal fluency	Phonemic Fluency (COWAT- letter PFS); semantic fluency (WLG-category:Animals)
Visuospatial Memory	Visuospatial memory by reproducing BVMT-R; SPART 10/36 recall test
Verbal Memory	List-learning/memory: SRT; CVLT-II

Note: CLTR: consistent long term retrieval; SPART: 10/36 spatial recall test; PASAT: paced auditory serial addition test (PASAT); SDMT: symbol digit modalities test; CLVT-II: California verbal learning test; BVMT-R: brief visuospatial memory test.

Fatigue, depression, and anxiety assessment

Patients were tested using the Hospital Anxiety and Depression Scale (HADS), a self-assessed questionnaire consisting of 14 items (0–3 Likert scale) assessing symptoms of depression (HADS-D subscale) and anxiety (HADS-A subscale). A threshold score of 8 or above was found to be an accurate indicator for both depression and anxiety symptoms. The HADS is widely used in clinical practice and has been validated in the MS population (da Silva et al., 2011; Honarmand & Feinstein, 2009). In the present study, we used a cut-off point of 11 to differentiate between MS patients with and without anxiety/depression (Pais-Ribeiro et al., 2018). Fatigue was assessed using the Modified Fatigue Impact Scale (MFIS), with a score range of 0–84 for each item, with the highest score indicating greater fatigue severity (Gomes, 2011; Larson, 2013).

Statistical analysis

Estimates of sample size were deemed appropriate by a post-hoc analysis in G*Power 3.1 (Faul et al., 2009), as a sample size of 300 participants was estimated to achieve .95 power (f = .25). Statistical analysis was conducted using SPSS Statistics (version 29). Descriptive results are expressed as frequency (percentages), mean ± SD or range. Descriptive statistics and between-group differences for age, sex, EDSS, duration of disease, education, HADS, MFIS, treatment with DMD's, CLTR, SPART, PASAT, SDMT, COWAT, CLTR-II, BVMT-R, and WLG, were conducted using an independent samples *t*-test (with a duration of disease as a between-subject factor). Descriptive statistics and between group differences for age, sex, EDSS, duration of disease, education, HADS, MFIS, treatment with DMD's, CLTR, SPART, PASAT, SDMT, COWAT, CLTR-II, BVMT-R, and WLG were conducted using an one-way ANOVA (with cognitive phenotype as a between subject factor). Correlation statistics were done using Pearson's correlation. Statistical analyses were performed with the α threshold of .05.

Results

Demographics and clinical characteristics of the sample

The study sample included only the RRMS subtype, totalling three hundred patients (age 41.38 [11.48 SD] years; 205 women [68.3%]). Of those 300 patients, 161 had been diagnosed less than ten years, and 139 more than 10 years before participation in the study. For the total sample, the average anxiety score was 8.13, and the average depression score was 5.48, as measured by HADS. When divided by years of diagnoses, those diagnosed less than ten years prior, had a score of 8.24 in the anxiety scale and 5.83 in the depression scale. For those with a diagnosis of more than ten years, anxiety scores averaged at 8 and depression scores at 5.08. There were significant differences between the two groups in terms of age, with the group diagnosed more than 10 years prior being significantly older. Table 3 summarizes the patients' main demographic characteristics and clinical features and cognitive impairment in the sample for all patients and divided by duration of MS.

Table 3. Demographic, clinical characteristics and cognitive impairment in the whole sample and also divided by duration of MS ($N = 300$).

	All participants	10 years or less	More than 10 years	*t*	*p*
Participants, n	300	161	139		
Age, y (range)	41.38 (18–72)	36.70 (18–63)	46.80 (23–72)	−8.45	**<.001***
Sex				−1.00	.160
Female, *N* %	205 (68.3%)	106 (65.8%)	99 (71.2%)		
Male, *N* %	95 (31.7%)	55 (34.2%)	40 (28.8%)		
EDSS, median (range)	1.5 (0–6)	1.5 (0–5)	1.5 (0–6)		
EDSS, mean	1.63	1.49	1.79	−2.49	**.007***
Disease duration, y, mean (range)	10.16 (0–38)	3.76 (0–10)	17.58 (6–38)	−27.83	**<.001***
Education, y, mean (sd)	13.16 (4.14)	13.58 (3.79)	12.68 (4.47)	1.88	**.031***
HADS – Anxiety, mean (SD)	8.13 (4.42)	8.24 (4.51)	8.00 (4.34)	.45	.326
HADS – Depression, mean (SD)	5.48 (4.18)	5.83 (4.26)	5.08 (4.08)	1.46	.073
Treatment with DMD's, n (%)	257 (86.8%)	132 (83%)	125 (91.2%)	−2.14	**.017***
MFIS, mean (SD)	33.87 (20.12)	35.33 (19.83)	32.22 (20.40)	1.26	.104
BRBN-T, n (% deficit)	101 (33.7%)	53 (32.9%)	48 (34.5%)	−.29	.385
BICAMS, n (% deficit)	103 (34.3%)	55 (34.2%)	48 (34.5%)	−.07	.473

Note. EDSS: Expanded Disability Status Scale; MFIS: modified fatigue impact scale; HADS: Hospital Anxiety and depression scale; BICAMS: Brief International Cognitive Assessment for MS; BRBN-T: brief repeatable battery of neuropsychological tests; t denotes values for in between-group comparisons; p denotes statistical significance; Sample consisted of 300 participants. Significant values in bold.

Cognitive impairment

Using a taxonomic dichotomy approach where failure was defined as a score equal to or below the 5th percentile, according to age, sex, education and adjusted to Portuguese norms (Langdon et al., 2012; Sousa et al., 2018, 2021), the prevalence of cognitive impairment (CI) in the sample was 33.7% when measured by the BRBN-T and 34.3% when measured by the BICAMS.

However, when using cutoffs of −1.0 and −1.5 SD to describe cognitive impairment, the prevalence in the sample was 85% when using −1.0 SD when measured by the BRBN-T and 58.3% when measured by BICAMS. When using −1.5 SD, cognitive impairment was 65.7% when measured by the BRBN-T and 36.3% when measured by the BICAMS. For each cognitive phenotype, when measured using −1.0 SD, impairment in BRBN-T was 18% for uni-domain impairment, 22.3% for bi-domain impairment and 45% for multidomain. For BICAMS, prevalence was 35% for uni-domain impairment, 15.7% for bi-domain impairment and 8.3% for multidomain impairment. When measured using −1.5 SD, impairment in BRBN-T was 25% for uni-domain impairment, 15% for bi-domain impairment and 15.7% for multidomain. For BICAMS, prevalence was 22.7% for uni-domain impairment, 9.3% for bi-domain impairment and 4.7% for multidomain impairment. Figure 1 summarizes base rates of test impairment using both cutoffs. The most frequent impairments involved CLTR, where deficits occurred in 51.6 and 38.3% of the sample, respectively (**–**1.0 SD or −1.5 SD). Similarly, 52.6 and 19.7% represent the impairment on the CVLT, 43.7 and 26% on SPART, 29.4 and 23.7% on the SDMT and 50 and 30.7% on the verbal fluency test.

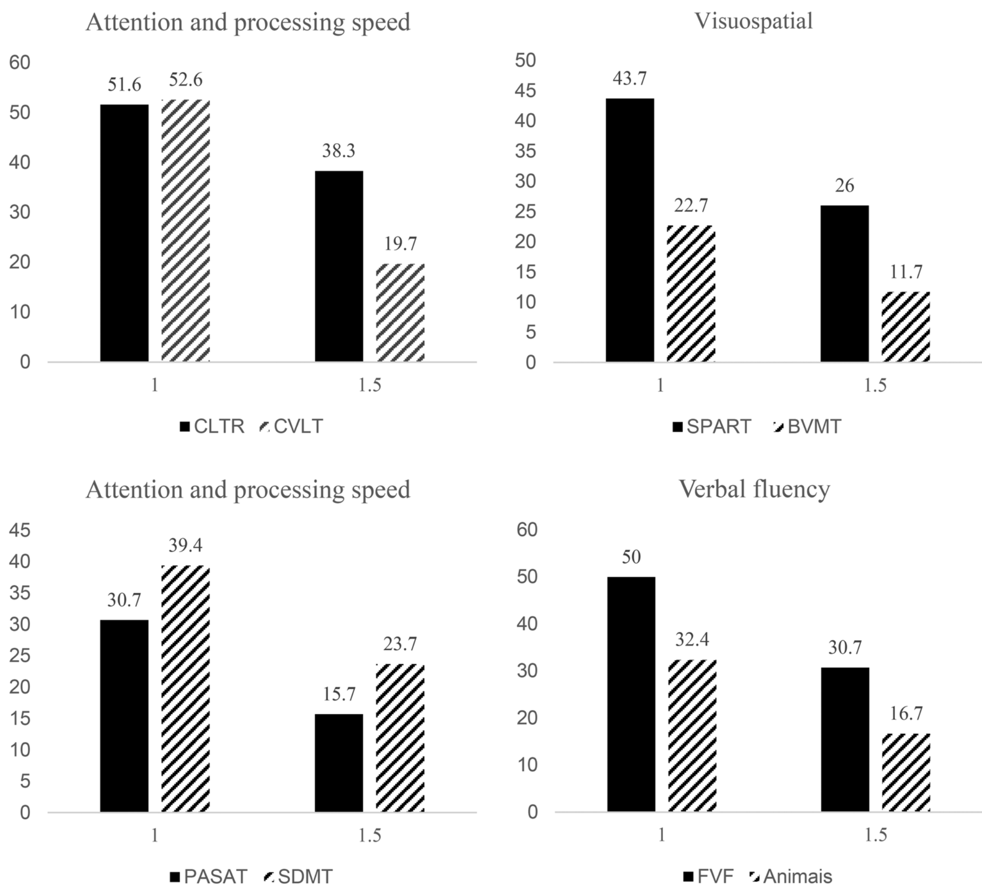

Figure 1. Rates of single-test impairment, comparing 1.0 SD and 1.5 SD ($N = 300$).

Cognitive phenotypes

Impairment was defined using cutoffs of −1.0 and −1.5 SD. Tables 4 and 5 present the complete characteristics of the patients by cognitive phenotype using a − 1.0 SD and −1.5 SD cut-offs. Using the −1.0 SD cut-off, for the entire sample, 49% were considered to have no impairment, 25% had a uni-domain impairment, 17% had bi-domain impairment, and 9% had multi-domain impairment (Figure 2). For the uni-domain impairment, the most impaired domain was processing speed at 9%. Processing speed and verbal fluency were the most impaired domains for the bi-domain impairment, 4%. Finally, the most impaired domains for the multi-domain impairment were verbal memory, visual-spatial memory, processing speed and verbal fluency impairment (Figure 3). Using the −1.5 SD cut-off, for the sample, 74% were cognitively intact, 17% had uni-domain impairment, 6% had bi-domain impairment, and 3% had multi-domain impairment (Figure 2). For the uni-domain impairment, the most impaired domain was memory at 6.3%. For the bi-domain impairment, the most impaired domains were verbal memory and verbal fluency impairment, at 1.7%. Finally, the most impaired domains for multi-domain impairment were visual-spatial memory, verbal memory, and verbal fluency impairment, at 2% (Figure 3).

Table 4. Cognitive impairment in each test for each cognitive phenotype as determined by −1.5SD cut-off. ($N = 300$).

	Intact Cognition	Uni-domain	Bi domain	Multidomain	*F*	*p*
Characteristic						
Participants, n	224	50	17	9		
Age, y (range)	40.53 (18–71)	44.32 (22–68)	43.65 (29–72)	42.00 (30–61)	1.75	.157
Sex					.950	.417
Female, N %	157 (70.1%)	34 (68%)	21 (47.1%)	5 (55.6%)		
Male, N %	67 (29.9%)	16 (32%)	9 (52.9%)	4 (44.4%)		
EDSS, median (range)	1.5 (0–6)	1.5 (1–4)	2 (0–5.5)	2 (1–3.5)		
EDSS, mean	1.50	1.88	2.09	2.5	5.66	**<.001***
Disease duration, y, mean (range)	9.88 (0–38)	10.10 (0–35)	11.76 (0–26)	14.44 (0–23)	1.15	.331
Education, y, mean (sd)	13.44 (3.91)	12.68 (4.69)	11.94 (4.58)	11.22 (5.04)	1.73	.160
Treatment with DMD's, n (%)	191 (86.4%)	44 (89.8%)	14 (82.4%)	8 (88.9%)	.244	.866
HADS – Anxiety, mean (SD)	8.45 (4.44)	7.48 (4.34)	6.79 (4.64)	6.44 (3.71)	1.56	.199
HADS – Depression, mean (SD)	5.82 (4.21)	4.85 (4.31)	4.00 (2.99)	3.44 (3.57)	2.11	.099
MFIS, mean (SD)	35.23 (20.04)	33.43 (20.64)	28.00 (16.97)	14.56 (12.98)	3.54	**.015***
CLTR (SD)	42.49 (73.04)	17.53 (26.44)	10.28 (23.79)	.52 (.84)	3.91	**.009***
SPART (SD)	35.02 (28.12)	19.46 (22.09)	18.18 (20.23)	3.18 (4.92)	9.53	**<.001***
PASAT (SD)	44.86 (29.97)	22.64 (24.19)	9.57 (11.61)	12.19 (18.63)	17.29	**<.001***
SDMT (SD)	41.95 (29.88)	16.28 (20.34)	5.40 (6.70)	3.66 (5.94)	23.28	**<.001***
COWAT (SD)	32.05 (27.48)	13.07 (18.91)	11.18 (19.69)	5.57 (11.84)	12.15	**<.001***
CVLT-II (SD)	54.89 (30.26)	28.23 (31.32)	15.65 (28.13)	.66 (.65)	25.17	**<.001***
BVMT-R (SD)	63.91 (30.12)	41.54 (32.65)	21.72 (27.66)	2.14 (2.11)	26.08	**<.001***
WLG (SD)	10.84 (2.73)	8.54 (2.48)	7.56 (2.87)	5.62 (1.51)	23.59	**<.001***

Note. MFIS: modified fatigue impact scale; HADS: Hospital Anxiety and depression scale; t denotes values for in between-group comparisons; BRBN-T: brief repeatable battery of neuropsychological tests; LTS: long term storage; CLTR: consistent long term retrieval; SPART: 10/36 spatial recall test; PASAT: paced auditory serial addition test (PASAT); SDMT: symbol digit modalities test; COWAT: controlled oral word association test; WLG: word list generation, BICAMS: Brief International Cognitive Assessment for MS; CLVT-II: California verbal learning test; BVMT-R: brief visuospatial memory test; *F* denotes values for in between-group comparisons; *p* denotes statistical significance. Significant values in bold.

Cognitive phenotypes and duration of disease

To obtain the prevalence of patients diagnosed ten years ago or less and those diagnosed over ten years ago, we divided the sample into two groups, assessed by −1.0 and −1.5 SD cut-off.

For the group with the maximum of 10 years of diagnosis, with a −1.5SD cut-off, we found that 75% had no impairment, 19% had uni-domain impairment, 4% bi-domain impairment and 2% multi-domain impairment (Figure 4). For the uni-domain impairment, the most impaired domain was memory at 9.3%. For the bi-domain impairment, verbal memory and verbal fluency had the most impairment at 2.5%. For the multi-domain, visual memory, verbal memory, and verbal fluency impairment were the most impaired at 1.2% (Figure 5). For the same group of patients but assessed by −1.0SD, we found that 51% did not have any impairment, 25% had uni-domain impairment, 16% had bi-domain impairment and 8% had multi-domain impairment (Figure 4). The most impaired domain for the uni-domain was processing speed at 10.5%. For the bi-domain, verbal memory and verbal fluency had the most impairment at 4.3%. For the multi-domain, visual memory, verbal

Table 5. Cognitive impairment in each test for each cognitive phenotype as determined by −1.0SD cut-off ($N = 300$).

	Intact cognition	Uni-domain	Bi domain	Multidomain	*F*	*p*
Characteristic						
Participants, *n*	148	74	50	28		
Age, y (range)	40.50 (19–71)	40.89 (18–64)	44.26 (20–72)	42.18 (27–62)	1.44	.232
Sex					.644	.587
Female, *N* %	106 (71.6%)	50 (67.6%)	32 (64%)	17 (60.7%)		
Male, *N* %	42 (28.4%)	24 (32.4%)	18 (36%)	11 (39.3%)		
EDSS, median (range)	1.5 (0–4)	1.5 (0–6)	1.5 (0–5.5)	2 (0–5)		
EDSS, mean	1.41	1.64	1.85	2.24	7.85	**<.001***
Disease duration, y, mean (range)	9.55 (0–38)	9.72 (0–26)	11.22 (0–35)	12.71 (0–31)	1.57	.196
Education, y, mean (sd)	14.01 (3.68)	13.46 (3.90)	11.28 (4.52)	11.29 (4.83)	8.09	**<.001***
HADS – Anxiety, mean (SD)	8.16 (4.53)	8.76 (4.53)	7.57 (3.75)	7.50 (4.77)	.84	.472
HADS – Depression, mean (SD)	5.38 (4.07)	6.49 (4.29)	5.17 (4.33)	4.12 (3.89)	2.25	.083
Treatment with DMD's, n (%)	130 (87.8%)	61 (85.9%)	41 (83.7%)	25 (89.3%)	.250	.861
MFIS, mean (SD)	32.94 (20.27)	39.44 (19.32)	32.96 (20.07)	26.92 (19.22)	2.80	**.041***
CLTR (SD)	50.89 (86.01)	29.55 (33.29)	14.02 (21.61)	5.52 (13.01)	7.09	**<.001***
SPART (SD)	38.49 (29.05)	30.52 (26.33)	19.82 (20.13)	7.54 (9.68)	14.98	**<.001***
PASAT (SD)	52.51 (28.73)	34.45 (28.78)	16.94 (17.16)	11.17 (14.16)	35.82	**<.001***
SDMT (SD)	46.56 (28.86)	34.19 (30.66)	15.58 (18.28)	4.88 (5.99)	30.28	**<.001***
COWAT (SD)	35.90 (27.54)	25.46 (26.04)	13.57 (30.32)	7.01 (11.80)	17.12	**<.001***
CVLT-II (SD)	63.92 (25.79)	41.34 (30.77)	26.60 (31.33)	4.66 (8.14)	52.66	**<.001***
BVMT-R (SD)	71.47 (25.30)	57.38 (31.14)	32.06 (30.63)	12.66 (18.98)	52.24	**<.001***
WLG (SD)	11.45 (2.34)	10.01 (2.76)	8.02 (2.72)	7.12 (2.61)	37.04	**<.001***

Note. MFIS: modified fatigue impact scale; HADS: Hospital Anxiety and depression scale; t denotes values for in between-group comparisons; BRBN-T: brief repeatable battery of neuropsychological tests; LTS: long term storage; CLTR: consistent long term retrieval; SPART: 10/36 spatial recall test; PASAT: paced auditory serial addition test (PASAT); SDMT: symbol digit modalities test; COWAT: controlled oral word association test, WLG word list generation; BICAMS: Brief International Cognitive Assessment for MS; CLVT-II: California verbal learning test; BVMT-R: brief visuospatial memory test; *F* denotes values for in between-group comparisons; *p* denotes statistical significance. Significant values in bold.

memory, processing speed, and verbal fluency were the most impaired at 3.7% (Figure 5).

In the group with more than ten years of diagnosis, assessed using a −1.5 SD cut-off, 75% did not have any impairment, 14% had uni-domain impairment, 7% had bi-domain impairment and 4% had multi-domain impairment (Figure 4). For the uni-domain impairment, processing speed impairment had 5.8% impairment, being the most impaired domain. Processing speed and verbal fluency impairment were the most prevalent for the bi-domain impairment at 2.2%. For multi-domain impairment, visual memory, verbal memory and verbal fluency impairment were the most prevalent at 2.9% (Figure 4). In the same group of patients assessed using a −1.0 SD cut-off, 47% did not have any impairment, 25% had uni-domain impairment, 17% had bi-domain impairment and 11% had multi-domain impairment (Figure 4). For the uni-domain impairment, memory impairment was at 10.1%, which was the most impaired domain. For the bi-domain impairment, processing speed and verbal fluency impairment were the most prevalent at 4.3%, along with processing speed and verbal memory. For multi-domain impairment, visual memory, verbal memory,

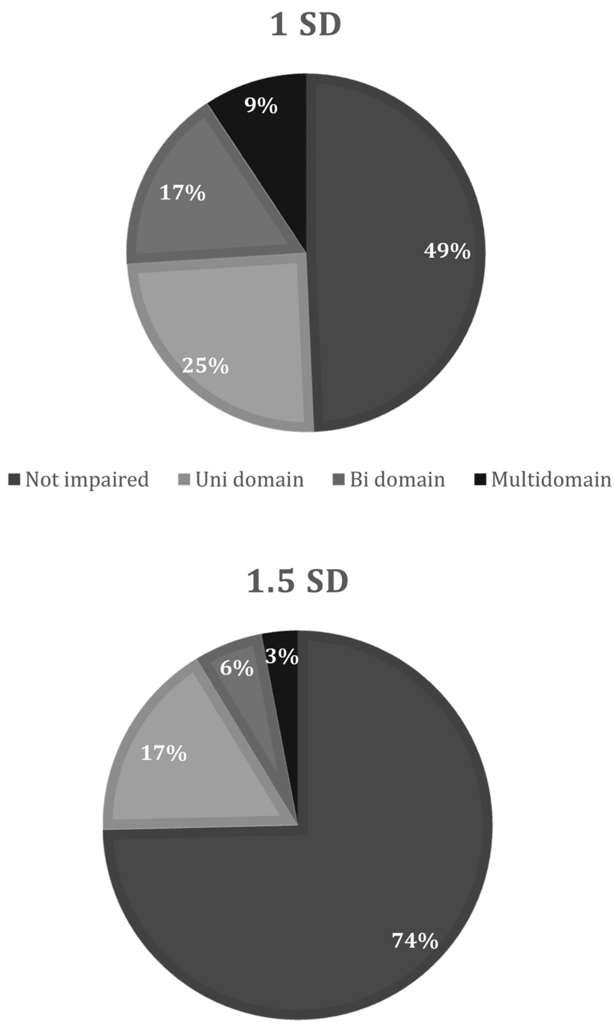

Figure 2. Cognitive impairment in each test for each taxonomic classification with −1.0 SD and −1.5SD cut-offs ($N = 300$).

processing speed and verbal fluency impairment were the most prevalent at 5.1% (Figure 5).

Cognitive phenotypes and depression and anxiety

Our sample had a prevalence of 30.6% of patients with anxiety and 12.3% with depression. Our results reveal that depression and anxiety were not significantly correlated with any of the cognitive functions. Anxiety and depression were also not correlated with cognitive phenotypes at the 1.0 SD cut-off. There was, however, a low significant negative correlation between depression ($r = -0.152$) and anxiety ($r = -0.130$) and cognitive phenotypes, when using −1.5 SD. Therefore, increased deficit in multiple domains was correlated with decreased depression and anxiety. However, there were

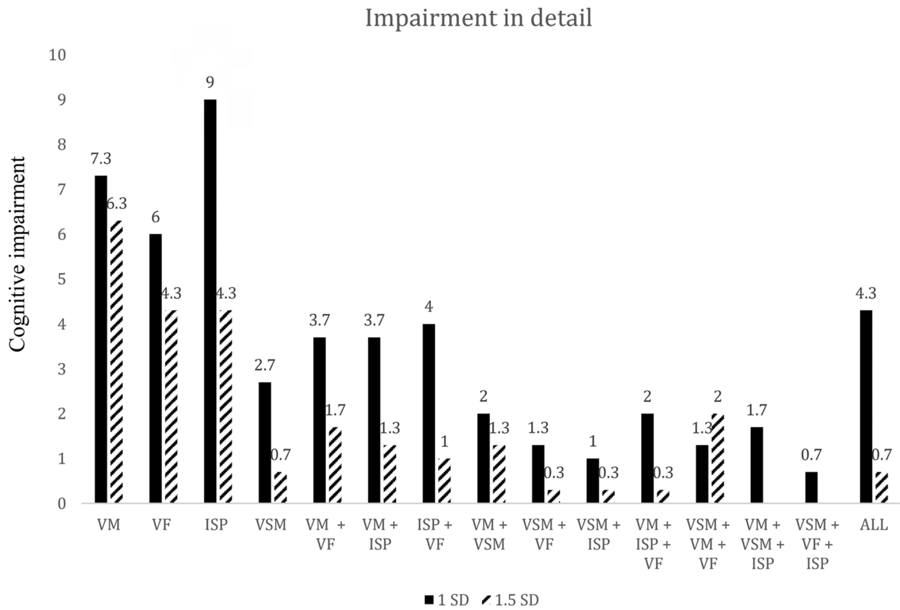

Figure 3. Cognitive impairment in each test for each taxonomic classification is detailed with −1.0SD and −1.5SD cut-offs. (N = 300). Note. VM = Verbal memory; VSM = Visual-spatial memory; IPS = information processing speed; VF = verbal fluency.

no differences between cognitive phenotypes for anxiety or depression (see Tables 4 and 5).

Discussion

In this cross-sectional study, we used a classification of four cognitive phenotypes across two batteries and different cutoffs to understand the neuropsychological profiles of patients with MS. We adapted a framework of The International Classification of Cognitive Disorders in MS (IC-CoDiMS), which has recently been used and tested by Hancock et al. (2023), to the neuropsychological data from a large cohort of patients with RRMS.

We emphasize that the patient's cognitive performance was evaluated using two neuropsychological batteries, explicitly developed for the disease (BRBN-T and BICAMS), which have validation standards for Portuguese patients. As far as we know, this double assessment has not yet been done in other studies.

The prevalence of cognitive impairment found in our study was 33.7% (assessed by BRBN-T) and 34.3% (assessed by BICAMS), values that are in line with those reported in the literature (Chiaravalloti & DeLuca, 2008; Maubeuge et al., 2021; Skorve et al., 2019; Sousa et al., 2022; Walker et al., 2016). In a recent study of our group (Sousa et al., 2022), in which MS patients with various subtypes of disease were evaluated, we found that BRBN-T and BICAMS showed approximately the exact prevalence of cognitive impairment, a finding corroborated in the present study, in which only patients with RRMS were included.

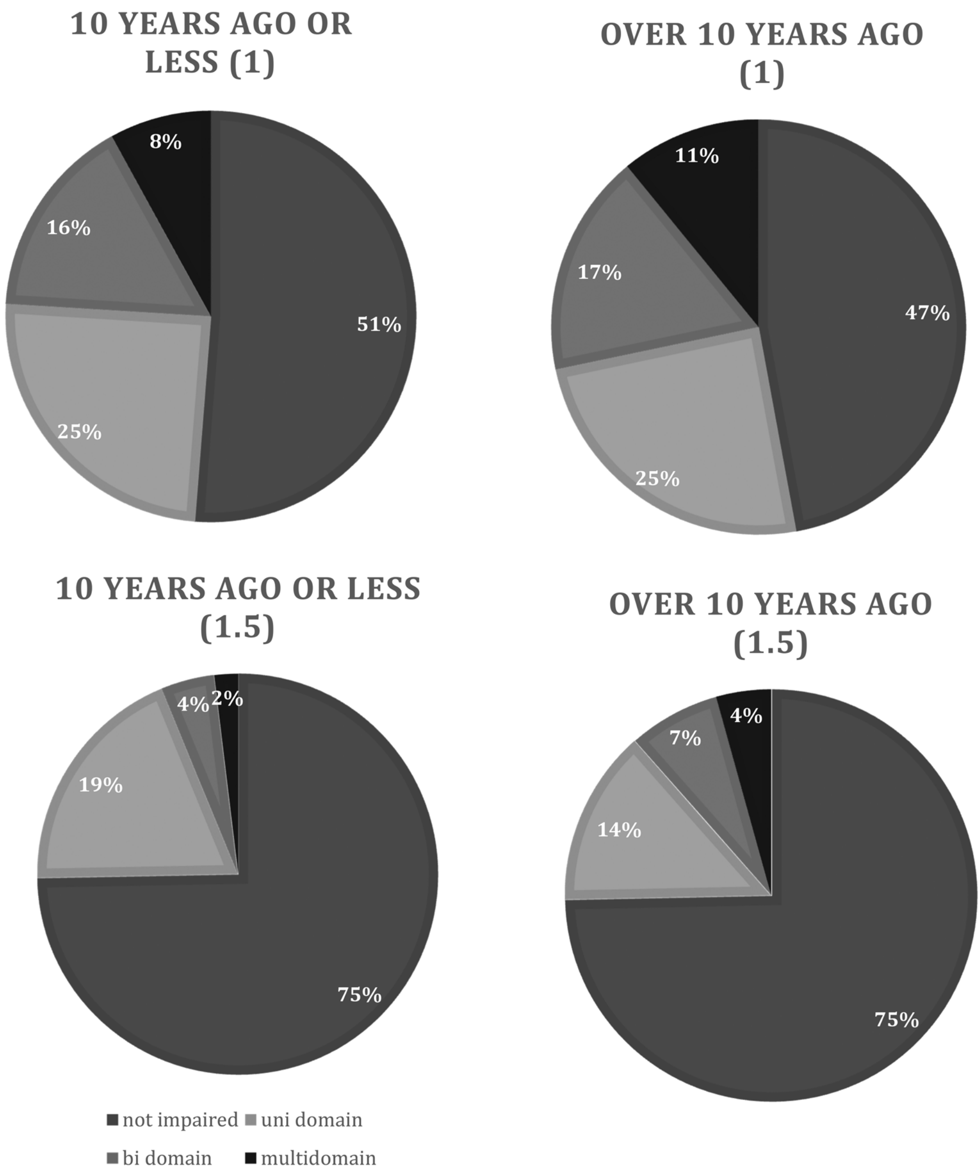

Figure 4. Cognitive results considering disease duration ≤ 10 years or > than 10 years, using cutoffs −1.0 and −1.5SD. (N = 300).

Both batteries have demonstrated good accuracy, but separately they only give us information about the presence or absence of cognitive impairment. Most studies have used a more conservative z-score of −1.5, while clinical trials in MS in which cognition is evaluated vary in the cutoff points specified for inclusion criteria (Benedict et al., 2008; Krupp et al., 2004; Morrow et al., 2009). Yet, in general, there needs to be more clear consensus regarding the most appropriate criteria. Because of this, we analyzed all results using both cut-offs of −1.0 and −1.5 SD. We found a higher percentage of cognitive impairment, which can demonstrate and confirm that the use of −1.0 SD and −1.5 SD may be more sensitive and enlightening about patients'

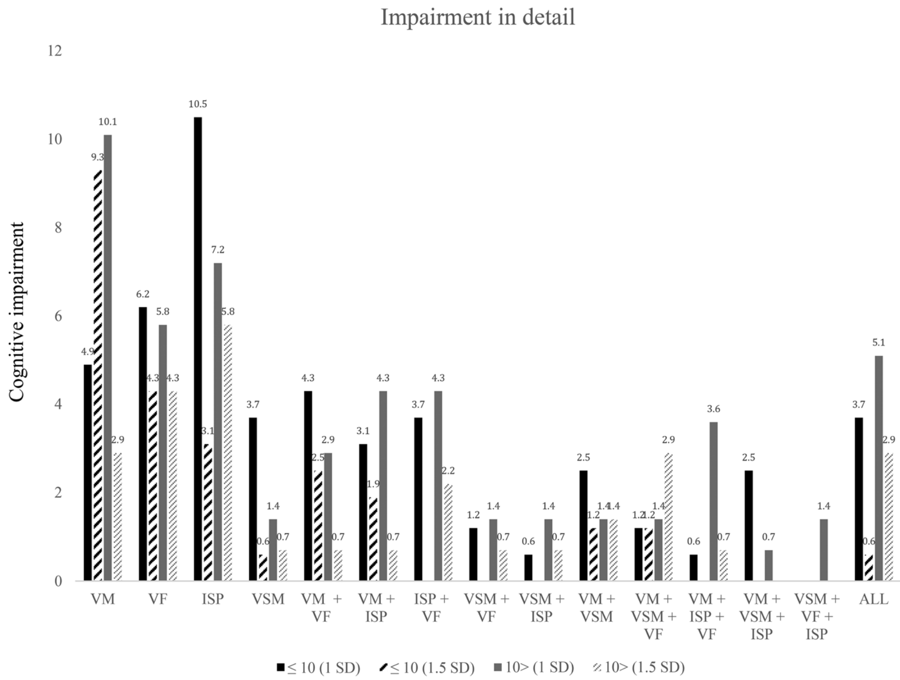

Figure 5. Cognitive impairment in each test for each taxonomic classification in detail, for −1.0SD and −1.5SD cut-offs, for those diagnosed ≤10 years and > 10 years of disease (*N* = 300). Note. VM = Verbal memory; VSM = Visual-spatial memory; ISP = information processing speed; VF = verbal fluency.

cognitive changes. Adapting and following the assumptions of IC-CoDiMS, we classified cognitive phenotypes using BRBN-T and BICAMS for the assessment. Unlike previous studies, this evaluation focuses on the four cognitive domains we can extract from these two cognitive batteries through the same normative source and using the same neuropsychological protocol most used in this population.

In addition to defining whether a patient with MS has a cognitive impairment, it has increasingly become essential to identify the performance pattern and which specific areas are most altered in the individual. It is also important to understand the longitudinal trajectory of this cognitive pattern to detect moments of disease progression possibly. This study, when adapting the framework and reproducing the same previously defined model, demonstrated that with a different cohort and methodology, there are similarities in cognitive phenotypes, which supports that this model has evidence of construct validity and may be useful in other clinical settings.

The definition of cognitive impairment was rigorous; the individual had to have two scores within the same domain below the cutoff for it to be considered altered. Compared with other studies, which detected that 72.9% (Hancock et al., 2023) and 56.7% (Leavitt et al., 2018) of the sample was cognitively intact, we found a very similar percentage in our cohort (74.7%). When the patients were divided by the duration of the disease (≤10 years and >10 years), we found the same percentages (75% without cognitive impairment).

Cognitive phenotypes can provide broader information about the cognitive deficit in these patients and thus be helpful in intervention decisions. For example, memory was the most frequently altered domain in this sample using the highest cutoffs. Also, knowing that the use of the SDMT is a recommendation for regular screening assessments, there will likely be patients whose impairment will go unnoticed. In our study, in both measures that assess verbal memory (CLTR and CVLT-II), deficits occurred in 51.6 and 38.3% of the sample, respectively (–1.0 SD or −1.5 SD), and 52.6 and 19.7% were impaired on the CVLT. This difference occurs equally in visual memory, processing speed and verbal fluency. This suggests that the best cutoff will probably be the lowest (–1.0 SD) to detect possible cognitive impairment.

We identified a first phenotype, preserved cognition, characterized by preserved functioning in all cognitive tests. This phenotype, similar to another study (De Meo et al., 2021), prevails in the early stages of the disease, including patients with shorter disease duration and less disability compared with other phenotypes.

A second phenotype, uni-domain, was identified (i.e. decreased performance in SRT and CVLT-II). As reported in another study (Leavitt et al., 2018), we found that the most common cognitive phenotype is the uni-domain (17%), more specifically the amnesic uni-domain (memory: 6.3%). Memory was the most impaired cognitive domain in our study. This differs from the findings of Hancock et al., who found that processing speed and executive function were the most impaired domains. This difference may be associated with heterogeneity across samples, the tests used, or differences in the statistical approach. Another explanation is that some tests do not measure just one aspect of cognitive functioning; for example, phonemic verbal fluency measures both processing speed and cognitive flexibility. In our study, verbal fluency was also the most impaired domain. Therefore, this result may point to a deficit in executive functions and thus corroborate the study's results by Hancock et al.

A third phenotype, bi-domain, was characterized by decreased performance in two cognitive domains (i.e. verbal memory/processing speed; decreased performance in SRT and CVLT-II and PASAT and SDMT). These are similar results to previous research. In contrast, since we found that information processing speed and verbal fluency were the most impaired within the bi-domain phenotype (using −1.0 SD), while Hancock and colleagues found that it was processing speed and executive function. This is so since, as mentioned previously, psychometric tests do not measure just one aspect of cognitive functioning; for instance, verbal fluency tasks are frequently used to measure executive function. Regardless of the duration of the disease, the most altered bi-domain impairment is memory and verbal fluency. The absence of a significant effect of disease duration on the cognitive phenotypes and domains affected is another finding from this study that is also evidenced in other studies (Ruano et al., 2017).

The fourth phenotype, multidomain impairment, is more frequent and increases in RRMS patients with more years of MS diagnosis, similar to what was observed in previous research (De Meo et al., 2021).

Our results reinforce the importance of evaluating at least the four cognitive domains presented to reduce the number of cognitive deficits that go unnoticed and not just recommend the use of SDMT as a screening test for MS.

In our sample, the psycho-emotional aspects (depression and anxiety) were not significantly correlated with any of the cognitive functions, and patients with more severe cognitive phenotypes revealed less depression and anxiety. One recent study revealed the opposite results in epilepsy patients. Patients with elevated depressive symptoms were more likely to demonstrate more severe cognitive phenotypes than patients without depression (Bingaman et al., 2023). In these patients, the relationship between depression and cognitive function is not clear. In studies with MS patients' referrals, it is not easy to determine the direction of the causality regarding cognitive functioning and depression. Depression can influence cognitive performance, but the awareness of cognitive deficits can also be an essential reason for a depressive reaction (Nocentini et al., 2006). An additional hypothesis is that more years of illness can help the patient achieve better adaptation and integration of the disease over time, and thus depressive and anxiety symptoms can decrease.

There are several limitations to consider in the present study. Firstly, only patients with RRMS were included. Patterns of cognitive impairment in progressive forms of MS are qualitatively and quantitatively distinct from those of RRMS (Langdon et al., 2012; Rao, 1990). Thus, future work that examines cognitive phenotypes in these patients is warranted. The second limitation is that we did not correlate cognitive phenotypes with other clinical data, such as neuroimaging. Recognizing cognitive phenotypes may facilitate the development of effective targeted treatments for cognition in MS by enabling future neuroimaging work to identify precise neural correlates of processing speed and memory impairment. Furthermore, our sample was not assessed regarding pre-morbid capacity and cognitive reserve. Finally, we did not use a test that separately measures executive functions and language. Future studies should consider adding instruments that assess these two domains. Also, it is essential to highlight that when adapting this taxonomy with the batteries used, the focus was on four domains (verbal memory, visuospatial memory, attention/processing speed and verbal fluency) instead of five domains as done in previous studies (McDonald et al., 2022). This is an important challenge for future longitudinal studies.

Conclusion

Our study strengthens the taxonomic classification in four cognitive phenotypes (intact, uni-domain, bi-domain and multidomain). The most common are uni-domain impairments with a predominance of memory, verbal fluency, and information processing speed impairment. This classification and cognitive predominance remain similar regardless of disease duration. Thus, it seems relevant to classify patients according to this new taxonomy and evaluate them longitudinally to understand the evolution of cognitive phenotypes. It will also be important to conduct the same study with progressive forms of the disease. According to the consensus statement of research priorities (Sumowski et al., 2018), the study of cognitive phenotypes can advance the composition and development of treatments aimed at cognition and the most effective planning of non-pharmacological treatments such as cognitive stimulation and rehabilitation in patients with MS.

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Authors' contributions

Claudia Sousa: contributed to study concept and design, drafting and revising the manuscript, and acquiring and interpreting data. Teresa Jacques: drafting and revising the manuscript in acquiring and interpreting data and statistical analysis. Marcia França: drafting and revising the manuscript and in the acquisition and interpretation of data Patricia Campos: drafting and revising the manuscript and in the acquisition and interpretation of data Maria José Sá: contributed to study concept and design, drafting and revising the manuscript, in the analysis and interpretation of data and study supervision Rui Alves: contributed to study concept and design, drafting and revising the manuscript, in the analysis and interpretation of data and study supervision. All authors read and approved the final manuscript.

Disclosure statement

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