The Prevalence of Comorbidities and Their Association With Disability Progression in Individuals With Multiple Sclerosis: A Study From Brazil

Marco Aurélio Gralha de Caneda, MD, MSc; Camila Batista Oliveira Silva PhD; and Maria Cecília Aragon de Vecino, MD

CE INFORMATION

ACTIVITY AVAILABLE ONLINE: To access the article and evaluation online, go to https://www.highmarksce.com/mscare.

TARGET AUDIENCE: The target audience for this activity is physicians, advanced practice clinicians, nursing professionals, and other health care providers involved in the management of patients with multiple sclerosis (MS).

LEARNING OBJECTIVES:

1. Recognize the importance of comorbidities in the progression of disability in patients with MS.
2. Apply evidence-based clinical strategies for managing comorbidities in patients with MS to improve clinical outcomes.

ACCREDITATION:

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ABSTRACT

BACKGROUND: Comorbidities negatively impact the course of multiple sclerosis (MS). Identifying them is essential, as they represent potentially modifiable prognostic factors that can adversely influence the disease course. However, comorbidity prevalence remains underexplored in certain populations, including in individuals in Brazil.

METHODS: In this cross-sectional study, we describe the frequency of comorbidities and their correlation with MS disability progression in a Brazilian population by reviewing the medical records of patients from a single MS center in Brazil. Preexisting comorbidities and those present at the time of MS diagnosis were screened. We assessed the prevalence of comorbidities, their prevalence ratios (PR) and the association between them, their number, and the confirmed disability worsening (CDW) that emerged during the follow-up visits.

RESULTS: Comorbidities were present in 68.9% of individuals. The most prevalent comorbidities included cardiovascular diseases (19.3%), migraine (13.3%), psychiatric disorders (12.4%), smoking (12.4%), autoimmune diseases (12.0%), respiratory diseases (10.3%), and neoplasms (5.6%). Patients with 1 comorbidity and those with multiple comorbidities (≥3) had a significant PR for CDW (2.67, $P = .01$; 1.25, $P = .03$, respectively). Cardiovascular and autoimmune diseases presented significant PR for CDW (2.28, $P = .03$; 4.2, $P = .004$, respectively).

CONCLUSIONS: Comorbidities are more prevalent among Brazilian individuals with MS than in the general population and are associated with disease progression. Identifying and managing them may mitigate their adverse effects on disease course.

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Multiple sclerosis (MS) is a chronic inflammatory and degenerative disease of the central nervous system that mainly affects young adults in the prime of their productive lives.[1,2] Although substantial progress has been made in understanding MS, its etiology and heterogeneous course remain incompletely understood.[3] Clinical, demographic, and psychosocial characteristics, along with individual genetic and epigenetic factors, are believed to influence disease onset and progression.[4-6]

Emerging evidence also suggests that comorbidities may play a significant role in the MS clinical course.[6-8] Comorbidities, chronic conditions distinct from the underlying disease, contribute to the overall burden of MS.[3,5,6,8,9] Complications directly derived from the underlying disease, such as bladder disturbances, or transient conditions, such as acute infections, are not considered comorbidities.[3,4] Regardless of disease phenotype, the most frequent MS comorbidities are depression, anxiety, hypertension, dyslipidemia, and chronic obstructive pulmonary disease (COPD), which are also highly prevalent even before MS diagnosis. The frequency does vary with age, highlighting the importance of monitoring these conditions across the entire population of individuals with MS.[4,6,10]

Studies have demonstrated an association between comorbidities and various negative outcomes in MS, including delays in diagnosis, increased hospitalizations and mortality rates, higher social and individual costs, and worsening disability progression and quality of life.[4,10,11] Additionally, comorbidities may influence the choice of disease-modifying drugs (DMDs) used for MS treatment, including switches between DMDs, since comorbidities may be associated with intolerance, worsening or onset of some pathologies, and adherence.[4,12,13]

Therefore, identifying comorbidities is crucial for reducing their negative impact on the MS course, as they are potentially modifiable prognostic factors.[4,8] Despite this, in many regions there is a paucity of research focusing on this aspect, particularly in Latin American countries, including Brazil.[5,9] In this study, we aim to address this gap by describing the frequency of comorbidities and their correlation with disease progression in a population of individuals with MS from Brazil.

METHODS

This cross-sectional study was conducted at the Multiple Sclerosis and Other Demyelinating Disorders Unit of Hospital Moinhos de Vento in Porto Alegre, Rio Grande do Sul. The local health department authority provides MS treatment, and according to information from this agency, 1944 individuals were undergoing treatment in the state of Rio Grande do Sul at the end of 2020.

The medical records of patients who received a diagnosis of MS from January 2, 1991, to December 30, 2020, designated as the prevalence day (PD; ie, the proportion of a population that has a specific characteristic in a given time period), were retrospectively reviewed. These were captured through coding, and MS diagnoses were confirmed by medical progress notes or laboratory test results. The comorbidities screened in the study were selected according to literature data and included both preexisting conditions and those present at the time of MS diagnosis.[9,10] No particular scale was used for screening comorbidities. Instead, comorbidities were identified based on documentation in the medical records by health care providers. They encompassed cardiovascular diseases (hypertension, dyslipidemia, ischemic and other heart diseases, stroke, obesity, and type 2 diabetes mellitus); respiratory pathologies (COPD, asthma, and chronic bronchitis); neoplasms; autoimmune diseases (thyropathies, inflammatory bowel diseases, rheumatologic and dermatologic pathologies); liver diseases; epilepsy; migraine; smoking; and psychiatric disorders.

Demographic (sex and age) and clinical (phenotype and DMD treatment at the PD) data were extracted from the medical records. The initial Expanded Disability Status Scale (EDSS)

From the Multiple Sclerosis and Demyelinating Disorders Unit, Department of Neurology, Hospital Moinhos de Vento, Porto Alegre, Rio Grande do Sul, Brazil (MAGC); Vecino Medical Center, Porto Alegre, Rio Grande do Sul, Brazil (CBOS); Multiple Sclerosis and Demyelinating Disorders Unit, Department of Neurology, Hospital Moinhos de Vento, Porto Alegre, Rio Grande do Sul, Brazil (MCAV). *Correspondence*: Marco Aurélio Gralha de Caneda, MD, Desing Office Center, 630; Ramiro Barcelos St, 5th floor, CEP 90660-020; *email*: mcaneda@terra.com.br; magdecaneda@gmail.com.

score at the time of MS diagnosis (EDSSi), the final EDSS score on the PD (EDSSf), and the time elapsed between them (Δt-EDSSif) were recorded. All EDSS scores considered were at least 2 months apart from MS relapses. Confirmed disability worsening (CDW) was defined by an increase in the scale score of 1 point if the EDSSi was less than 5.5, or 0.5 points if it was greater than or equal to 5.5,[14] and documented in at least 2 consecutive records before the PD.

The variables were described using means, with their respective standard deviations, or as percentages. Differences between groups of patients with vs without comorbidities, and with vs without CDW, were assessed using Student *t*, Mann-Whitney *U*, or χ^2 tests. The Shapiro-Wilk test was employed to check for normal distribution. The prevalence of each comorbidity was calculated as the proportion of individuals with a specific condition among the total number of patients with MS on the PD. The prevalence ratios (PR) of the comorbidities, along with 95% CIs, were calculated by a generalized linear model (GLM) stepwise regression analysis. The GLM was based on a log-binomial distribution for the outcome, with a test for collinearity and adjustment by the Hosmer-Lemeshow test. Additionally, the association of the presence and number of comorbidities with CDW was assessed. The significance level was set at $P < .05$, and the results were calculated using SPSS Version 25.0 software. This study was conducted with authorization from the research ethics committee of the Hospital Moinhos de Vento.

RESULTS

A total of 232 individuals with MS were included, with a mean age of 45.2 ± 12.9 years, 178 (76.7%) women, and 212 (91.4%) with the relapsing-remitting phenotype. Comorbidities were present in 160 (68.9%) individuals, with an average of 1.5 comorbidities per patient. The mean EDSSi was 1.6 ± 1.5; the mean EDSSf was 2.5 ± 1.8; the Δt-EDSSif was 6.4 ± 6 years. On the PD, 180 (77.6%) patients were receiving some DMD; however, no statistically significant difference was identified between patients with and without MS CDW (**TABLE S1**). The most prevalent comorbidities were cardiovascular diseases (19.3%; 95% CI, 14.4%-25%), migraine (13.3%; 95% CI, 9.2%-18.3%), psychiatric disorders (12.4%; 95% CI, 8.5%-17.3%), smoking (12.4%; 95% CI, 8.5%-17.3%), autoimmune diseases (12%; 95% CI, 8.1%-17%), respiratory diseases (10.3%; 95% CI, 6.7%-15%), and neoplasms (5.6%; 95% CI, 3%-9.3%), as shown in **TABLE 1**.

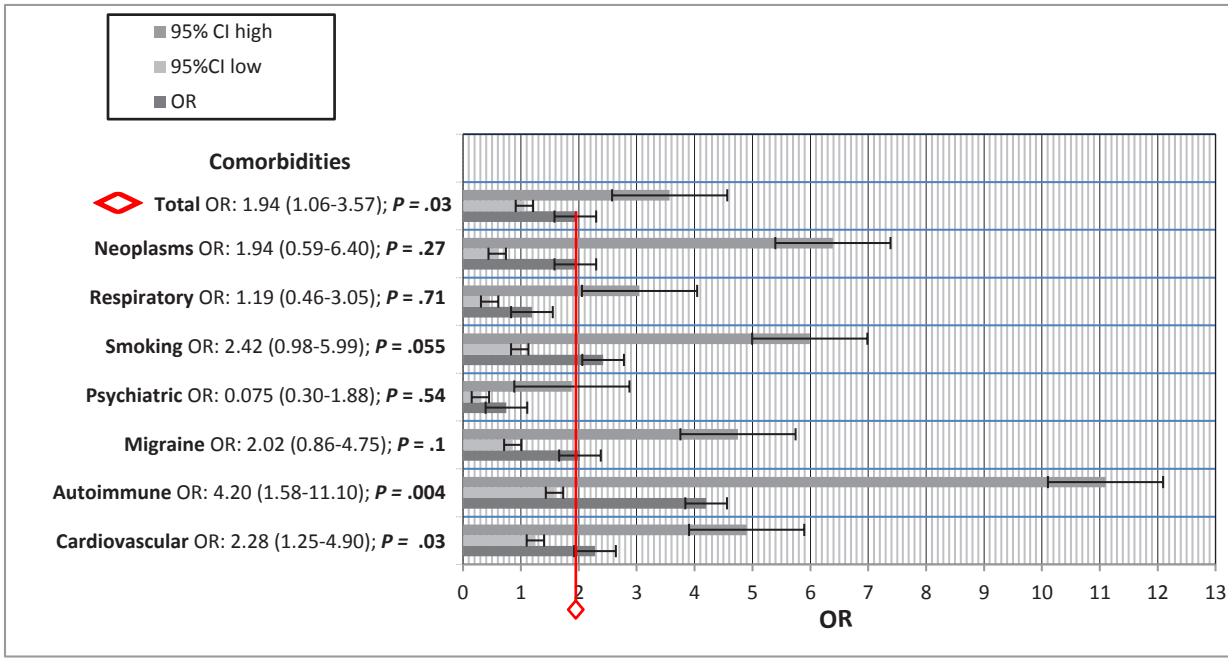
There were no differences between patients with vs without comorbidities in the proportion of sex, MS phenotypes, EDSSi and EDSSf scores, and of Δt-EDSSif (**TABLE S2**). A significant difference was found between these groups in age ($P = .008$), with a higher average age in patients with comorbidities (46.7 ± 12.5 vs 41.9 ± 13.3 years), and in the number of patients with CDW ($P = .04$). There were 54 individuals with 1 comorbidity (33.7%), with 34 (63.0%) with CDW; 54 patients had 2 comorbidities, with 22 (40.7%) with CDW; 52 (32.5%) patients had multiple comorbidities (≥ 3 conditions), with 27 (51.9%) with CDW. Patients with 1 comorbidity were younger, with a higher number of individuals 45 years or younger (66.6%, $P = .005$), whereas patients with 2 or more comorbidities were more likely to be older than 45 years (71.7%, $P = .005$).

In a comparison of patients with vs without CDW, a significant difference in sex was observed, with a lower number of male patients among individuals with CDW ($P = .01$) and in the number of patients with comorbidities ($P = .04$). There was no significant difference in age, MS phenotype, or in the Δt-EDSSif. There was a highly significant difference in EDSSi ($P < .0001$), with patients without CDW presenting a higher average score. EDSSf was also significantly higher in patients

TABLE 1. Comorbidity Frequency in Individuals With Multiple Sclerosis (N=232)

Disease group	Comorbidity	n	Prevalence (95% CI)
Vascular			19.3% (14.4%-25.0%)
	Hypertension	24	10.3% (6.2%-13.8%)
	Hyperlipidemia	15	6.4% (3.3%-9.5%)
	Diabetes	3	1.3% (−0.1% to 2.7%)
	Obesity	3	1.3% (−0.1% to 2.7%)
	Congestive failure and ischemic cardiopathy	1	0.43% (−0.05% to 0.69%)
Autoimmune			12% (8.1%-17.0%)
	Thyropathies	18	7.7% (3.7%-10.3%)
	Rheumatologic disease	6	2.5% (0.5%-4.5%)
	Psoriasis	3	1.3% (−0.1% to 2.7%)
	Crohn disease	1	0.43% (−0.05% to 0.69%)
Respiratory		24	10.3% (6.7%-15.0%)
	Asthma	16	6.9% (3.6%-10.0%)
	Chronic obstructive pulmonary disease	8	3.4% (0.8%-5.6%)
Neoplasms			5.6% (3.0%-9.3%)
	Breast	4	1.7% (0.1%-3.3%)
	Gynecologic	2	0.86% (−0.25% to 2.0%)
	Thyroid	2	0.86% (−0.25% to 2.0%)
	Skin	2	0.86% (−0.25% to 2.0%)
	Hepatic	2	0.86% (−0.25% to 2.0%)
	Central nervous system	1	0.43% (−0.05% to 0.69%)
Psychiatric			12.4% (8.5%-17.3%)
	Depression	22	9.4% (5.7%-13.4%)
	Anxiety	7	3% (0.9%-5.2%)
Other			
	Smoking	29	12.4% (8.5%-17.3%)
	Migraine	31	13.3% (9.2%-18.3%)
	Liver diseases	10	4,3% (1.7%-6.9%)
	Cholelithiasis	5	2.1% (0.3%-3.9%)
	Epilepsy	3	1.3% (−0.1% to 2.7%)
	Anemia	3	1.3% (−0.1% to 2.7%)
	Glaucoma	2	0.86% (−0.25% to 2.0%)
	Gastritis	1	0.43% (−0.05% to 0.69%)
	Obstructive apnea	1	0.43% (−0.05% to 0.69%)
	Polycystic ovarian	1	0.43% (−0.05% to 0.69%)
	Osteoporosis	1	0.43% (−0.05% to 0.69%)
	Herniated disc	1	0.43% (−0.05% to 0.69%)
	Hiatus hernia	1	0.43% (−0.05% to 0.69%)
Accumulated comorbidities	1	54	23.3%
	2	54	23.3%
	3	34	14.6%
	4	11	4.7%
	5	4	1.7%
	6	3	1.3%

FIGURE. Comorbidity Prevalence Ratios



with CDW ($P < .0001$). Among the 108 (46.5%) individuals with CDW, 83 (76.8%) had comorbidities. In turn, among patients without comorbidities, 77 (62.1%) did not have CDW (**TABLE S3**).

After controlling for age, sex, MS phenotype, and Δt-EDSSif, the regression analysis showed a higher probability of CDW among patients with comorbidities vs patients without comorbidities, with a PR of 1.94 (95% CI, 1.06-3.57; $P = .03$). Patients with 1 comorbidity had a significant PR of 2.67 (95% CI, 1.25-5.71; $P = .01$), those with 2 comorbidities had a PR of 1.15 (95% CI, 0.78-1.68, $P = .48$), and individuals with multiple comorbidities had a PR of 1.25 (95% CI, 1.01-1.55; $P = .03$) for CDW. In addition, the GLM estimated that for every comorbidity, there was a mean increase of 1.15 points in the EDSS score (95% CI, 0.87-1.43). Regarding specific comorbidities, patients with cardiovascular diseases had a significantly higher probability of CDW vs patients without comorbidities, with a PR of 2.28 (95% CI, 1.25-4.9; $P = .03$). Patients with autoimmune diseases also had a high probability, with a PR of 4.2 (95% CI, 1.58-11.1; $P = .004$). Those who smoked were more likely to have CDW, with a PR of 2.42 (95% CI, 0.98-5.99; $P = .055$); however, that was not statistically significant (**FIGURE**).

DISCUSSION

Many of the findings of this study may seem intuitive, but they reaffirm that screening for comorbidities should be routine in MS care.[3,4] This practice can establish expectations about the presence of specific pathologies, helping to identify at-risk patients and choose the best treatment. The identification of preexisting comorbidities at the time of MS diagnosis is crucial not only for managing the comorbidity itself, but also for reducing its impact on the course of MS. Assessing the impact of comorbidities on the progression of MS improves the quality of care and directly results in a better quality of life for patients.[4]

In countries with significant economic limitations, such as Brazil, optimizing the treatment of high-cost conditions like MS, which is fully funded by the state, becomes crucial for more efficient resource allocation. It is important to note that demographic characteristics are likely associated with specific comorbidities and can be very heterogeneous, partly explaining the heterogeneity of the MS course.[2,5] Therefore, it is essential to identify pathologies commonly present in specific populations. Local environmental factors such as dietary and hygiene habits, sun exposure, vaccination policies, access to the health care system, and population concentration in urban areas also can increase or reduce the risk of additional pathologies that may influence the prognosis of MS. This study, which, to the best of our knowledge is the first on the subject from Brazil, may contribute to the proper management of MS and promote research on the topic in different regions of the country.

Individuals with MS exhibit a higher prevalence of preexisting comorbidities compared with age-, sex-, and geographic-matched population controls.[15,16] Therefore, it is not surprising to observe a comorbidity rate of 69.0% in our sample because 52% of the Brazilian population as a whole has a disorder.[17] This rate is consistent with that in some previous studies, where it ranged from 65.3% to 73.2%.[18,19] Another study, however, indicated that at least 1 comorbidity of those listed in the Charlson Comorbidity Index (CCI) was present in just 22.7% of the individuals up to 10 years prior to receiving their MS diagnosis.[15] Based on self-reported information, other studies have found that the prevalence of preexisting comorbidities is quite a bit

lower than prevalence at the time of MS diagnosis.[3] These data suggest that instruments designed for the general population, such as the CCI or self-report methods, may not perform as well as previously reported for individuals with MS.[3,20]

As expected, there was a significant correlation between age and comorbidity prevalence, given the greater risk of emergence with aging.[6,10] The accumulation of comorbidities as individuals with MS age appears to surpass what would be expected from natural aging, exceeding the prevalence observed in the matched general population.[5,18] This overaccumulation may be attributed to DMDs, which are associated with an increased risk of developing pathologies, and to the potential sharing of risk factors of MS and specific pathologies.[12,18,19] Conversely, our findings do not support an association between aging and CDW, since the group of individuals with 1 comorbidity, which had a significantly higher number of younger individuals, showed higher probability of CDW. This result is in line with recent studies, which found higher rates of disease activity and subsequent risk of disability worsening among younger individuals with MS.[20-22] However, prominent disease activity may justify the predominance of women with CDW. This is aligned with a recent publication that described higher inflammatory activity in women compared with men, especially before 50 years of age, suggesting sex hormones play a role in this outcome.[23] Considering the averages of 6.4 years for Δt-EDSSif and a 1.15-point increase in EDSS scores for the entire cohort, our results indicate an average annual rise of 0.18 points in EDSS scores for each comorbidity. This is in line with results from previous studies that have consistently reported an association between the presence of comorbidities and CDW, with rates ranging between 0.18 and 0.28.[3,4,8]

Previous literature has systematically identified cardiovascular comorbidities as among the most frequent in individuals with MS, even before diagnosis.[5,6,10,15,16,18-20] The prevalence of 19.3% found in our study was higher than the 12.9% described in a study performed at diagnosis; however, the study excluded patients with hyperlipidemia.[15] Hypertension was found to be the most frequent cardiovascular comorbidity in our study, with a prevalence of 10.3%, which was slightly higher than previous publications, which reported rates from 7.4% to 8.8%.[8,15,18] Notably, Marrie et al reported a prevalence of 15.2% at the time of MS diagnosis, attributing this to disproportionately higher rates of hypertension in men compared with matched controls.[16] We found a hyperlipidemia prevalence of 6.4%, which is in line with the literature, which ranges from 6.9% to 7.2%.[16,18] Our data showed that patients with vascular comorbidities are 1.28 times more likely to have CDW, which is in agreement with findings reported in several previous publications.[3,8,20-24]

Migraine is twice as common in individuals with MS compared with the general population,[5,6] possibly resulting from chronic inflammatory mechanisms. A previous study identified migraine as the second most common comorbidity prior to MS diagnosis, although the reported prevalence of 20.2% was higher than the 13.3% we found.[18] In a Brazilian publication, a significantly higher prevalence of migraine (approximately 54.0%) was reported. However, 55.4% of patients attributed the headache onset to MS treatment, which may be a common adverse effect of DMDs.[25]

Smoking seems to have a dose-dependent duration and intensity correlation with MS, is a contributing factor to the negative effects of other comorbidities on the MS course, and is associated with a higher risk of other autoimmune diseases.[26] The 12.4% prevalence of smokers in our study was practically the same as the 12.6% reported for the general Brazilian population.[27] It was lower than the 20.7% and 22% at the time of MS diagnosis, as reported in 2 previous studies.[28,29] This lower rate may be attributed to the intense Brazilian government control policies implemented in recent decades.

The 12.4% prevalence of psychiatric disorders observed in our study aligns with the rate of 11.8% reported in a Swedish study on comorbidities present before MS diagnosis.[30] In contrast, a study from Australia reported a rate of 32.5%, and a Danish study found a prevalence of 5.1%.[17,31] This wide range could be attributed to the insidious nature of psychiatric conditions, which may be secondary to pathological mechanisms present before the MS onset and that may emerge independently of the disease stage.[5,6,18,20,21,30,31] Depression was the most common psychiatric pathology in our sample, with a prevalence of 9.4%, an intermediate rate between the 6.5% and 15.8% reported by previous publications.[26,30] In previous Brazilian studies, the prevalence of depression ranged from 18.3% to 34%, however these described the depression as emerging after diagnosis.[32] Likewise, another Latin study found a higher rate of 40.0% throughout the disease course.[33] Early detection of psychiatric comorbidities may be a viable strategy to reduce the severity of so-called invisible MS symptoms,

PRACTICE POINTS

The presence of comorbidities is common in individuals with multiple sclerosis (MS), and they have an impact on disease prognosis, which partly explains disease course heterogeneity.

Comorbidity management is crucial, as comorbidities are associated with worsening disability.

Health care professionals should establish routine practices to identify comorbidities at the time of diagnosis and implement models of care to treat and prevent them, leading to better outcomes for patients. ■

thereby enhancing quality of life for individuals with MS. Moreover, it may mitigate the higher risk of suicide during the diagnostic process and early stages of the disease.[6,31,32]

Autoimmune diseases had a prevalence of 12.0%, which was higher than previous studies (range, 6.1%-8.4%).[24,34] In fact, a systematic review found rates that varied from 3.0% to 26.0%, with these discrepancies attributable to the methodological heterogeneity.[10] Thyropathies were the most common autoimmune comorbidities in our study, with a prevalence of 7.7%, higher than the rates reported at the time of MS diagnosis (range, 3.3%-4.5%).[15,18] Another Latin American study reported a 15.7% prevalence of thyropathies, but this was throughout the MS course.[33] Few studies have evaluated the impact of autoimmune diseases on MS course. Our results indicate that individuals with these comorbidities are 3.2 times more likely to have CDW, which is in line with a previous publication that found risk increased by 3.02 times in individuals with rheumatoid arthritis.[7]

Respiratory pathologies had a prevalence of 10.3%, which is close to a previously reported 12.0% rate at the time of MS diagnosis.[16] Asthma was the most frequent respiratory pathology, with a prevalence of 6.9%, which is similar to the 7.6% reported in a study that assessed patients up to 1 year before the MS diagnosis.[8] In contrast, some studies reported asthma prevalence ranging from 16.5% to 18.7%.[7,34,35] The prevalence of asthma in the Brazilian population ranges from 7.7% to 9.3%, whereas in the locations where these studies were conducted, it ranges from 14.0% to 21.0%. Conversely, some studies have indicated lower occurrence of asthma in individuals with MS, with a prevalence as low as 3.2%, which may be explained by genetic and environmental factors.[30]

The prevalence of neoplasms in our study was 5.6%, which was higher than in previous studies, where it ranged from 2.0% to 3.6%.[10,15,18,20-22,36,37] Our higher rate may be attributed to breast neoplasms, which accounted for 30% of cases and is highly prevalent in the Brazilian population, especially among young women. A study from Belgrade, Serbia, reported a breast cancer prevalence of 0.95%, whereas in our patients it was about 80% higher, and another, from Sweden, showed a prevalence of 0.7%, which was 140% lower than ours.[24,30] Women with MS have a 28% increased risk of mortality from breast cancer compared with the general population.[37] Therefore, along with assessing personal and family histories, considering the possible effects of some DMDs on the occurrence of specific malignancies and their differential effects according to sex is advisable.

This study has several limitations. First, its retrospective design may restrict the generalizability of the findings. Second, the sample was selected from a tertiary center dedicated to demyelinating diseases, which may have led to earlier and more frequent comorbidity diagnoses compared with the general population due to the higher frequency of health care use. Despite the relatively small sample size, the study cohort accounts for approximately 12% of the population of patients with MS registered in the state at the end of 2020, according to data from the local health department authority. We believe this sample size is sufficient to obtain reliable data on the prevalence of MS comorbidities within the local community. Third, variables that could be related to both the presence of comorbidities and CDW, such as socioeconomic status, physical activity, alcohol and drug consumption, diet, and the continuous use of medications other than DMDs, were not assessed.

CONCLUSIONS

The presence of comorbidities further complicates the complex management of MS. Our data emphasize the importance of early treatment of these conditions to avoid a worse prognosis. Health care professionals should establish expectations and routine practices regarding the presence of specific comorbidities at the time of MS diagnosis and implement care models for their prevention and treatment. Our results show a significant association between comorbidities and disability progression, highlighting the need for further research to determine whether early treatment of comorbidities can effectively reduce disability progression and improve clinical outcomes for individuals with MS. ■

CONFLICTS OF INTEREST: The authors declare no conflicts of interest.

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TABLE S1. Disease-Modifying Drugs: Patients Without CDW vs With CDW

Drug	Without CDW (n = 124)	With CDW (n = 108)	P*
Interferon beta	33 (26.6%)	20 (18.5%)	.14
Glatiramer acetate	16 (12.9%)	10 (9.2%)	.38
Teriflunomide	12 (9.6%)	12 (11.1%)	.72
Dimethyl fumarate	19 (15.3%)	16 (14.8%)	.91
Fingolimod	7 (5.6%)	10 (9.2%)	.29
Cladribine	1 (0.8%)	1 (0.9%)	.92
Natalizumab	7 (5.6%)	11 (10.2%)	.19
Ocrelizumab	0	2 (1.8%)	-
Alemtuzumab	1 (0.8%)	2 (1.8%)	.48
No treatment	28 (22.5%)	24 (22.2%)	.94

CDW, confirmed disability worsening.
*χ^2 test.

TABLE S2. Demographic and Clinical Data: Individuals With Multiple Sclerosis Without vs With Comorbidities

	Individuals with MS N = 232	Without comorbidity n = 72	With comorbidity n = 160	P
Age, mean (SD)[a]	45.2 (12.9)	41.9 (13.3)	46.7 (12.5)	.008
Sex,[b] n (%)	178 F (76.7%) 54 M (23.3%)	53 F (73.6%) 19 M (26.4%)	125 F (78.1%) 35 M (21.9%)	.45
RRMS,[b] n (%)	212 (91.4%)	67 (93%)	145 (90.6%)	.54
EDSSi,[c] n (SD)	1.6 (1.5)	1.5 (1.5)	1.9 (1.5)	.16
EDSSf,[c] n (SD)	2.5 (1.8)	2.6 (1.8)	2.4 (1.7)	.34
Δt-EDSSif,[c] n (SD)	6.4 (6)	6.6 (6.6)	6.3 (5.8)	.94
EDSS worsening,[b] n (%)	108 (46.5%)	27 (37.5%)	83 (51.9%)	.04

Δt-EDSSif, elapsed time in years between Expanded Disability Status Scale initial and Expanded Disability Status Scale final; EDSS, Expanded Disability Status Scale; EDSSf, Expanded Disability Status Scale final; EDSSi, Expanded Disability Status Scale initial; F, female; M, male; RRMS, relapsing-remitting multiple sclerosis.
[a]*T* test.
[b]χ^2 test.
[c]Mann-Whitney *U* test.

TABLE S3. Demographic and Clinical Data: Individuals With Multiple Sclerosis Without vs With CDW

	Individuals with MS N = 232	Without CDW n = 124	With CDW n = 108	P
Age, mean (SD)[a]	45.2 (12.9)	46.4 (13.2)	43.9 (12.6)	.13
Sex,[b] n (%)	178 F (76.7%) 54 M (23.3%)	87 F (70.2%) 37 M (29.8%)	91 F (84.3%) 17 M (15.7%)	.01
RRMS,[b] n (%)	212 (91.4%)	107 (86.3%)	101 (93.5%)	.27
EDSSi,[c] n (SD)	1.6 (1.5)	2.7 (1.5)	1.2 (1.2)	< .00001
EDSSf,[c] n (SD)	2.5 (1.8)	1.7 (1.2)	3.6 (1.9)	< .00001
Δt-EDSSif,[c] n (SD)	6.4 (6)	6.3 (6.5)	6.5 (5.5)	.33
With comorbidity,[b] n (%)	160 (68.9%)	77 (62.1%)	83 (76.8%)	.04

Δt-EDSSif, elapsed time in years between Expanded Disability Status Scale initial and Expanded Disability Status Scale final; CDW, confirmed disability worsening; EDSS, Expanded Disability Status Scale; EDSSf, Expanded Disability Status Scale final; EDSSi, Expanded Disability Status Scale initial; F, female; M, male; RRMS, relapsing-remitting multiple sclerosis.
[a]*T* test.
[b]χ^2 test.
[c]Mann-Whitney *U* test.