

Initial treatment efficacy in Multiple Sclerosis at a Brazilian tertiary hospital

Eficácia no tratamento inicial da Esclerose Múltipla em um ambulatório de hospital terciário brasileiro

Eficacia del tratamiento inicial en la Esclerosis Múltiple en una clínica ambulatoria de hospital terciario brasileño

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Resumo

Introdução. A estratégia terapêutica inicial na esclerose múltipla (EM) influencia o prognóstico; evidências apontam melhor controle da doença com início precoce de terapias de alta eficácia (TAE) em comparação ao escalonamento com terapias de baixa a moderada eficácia (TBME). **Objetivo.** Avaliar o impacto do tratamento inicial com TAE versus TBME na progressão da incapacidade em pacientes com EM remitente-recorrente (EMRR) acompanhados em hospital público terciário no Brasil. **Método.** Estudo retrospectivo observacional com análise de prontuários eletrônicos de 35 pacientes com EMRR tratados entre dezembro de 2021 e dezembro de 2023, estratificados pela terapia inicial (TAE ou TBME). Foram coletados dados demográficos, topografia das lesões, tempo até o diagnóstico e até o início do tratamento, e variação da Escala Expandida do Estado de Incapacidade (EDSS) em 12 meses. As comparações e a estimativa do tamanho do efeito utilizaram testes apropriados. **Resultados.** O grupo TAE apresentou maior redução do EDSS em 12 meses ($-0,33 \pm 0,53$) do que o grupo TBME, que teve aumento do EDSS ($+0,50 \pm 1,10$; $p=0,00498$). Apesar de EDSS basal mais elevado no grupo TAE (4,08 vs. 1,50; $p=0,0002$), observou-se maior controle da progressão. Houve atrasos no diagnóstico (média 34,16 meses) e no início do tratamento (14,08 meses) em ambos os grupos, sugerindo barreiras estruturais no Sistema Único de Saúde (SUS). **Conclusão.** O início com TAE associou-se a melhores desfechos de incapacidade, mesmo em pacientes com maior gravidade inicial, reforçando a adoção precoce de terapias de alta eficácia e a necessidade de melhorias estruturais no cuidado da EM no SUS. **Unitermos.** Esclerose múltipla; Terapias modificadoras da doença; Avaliação da incapacidade

Abstract

Introduction. The initial therapeutic strategy in multiple sclerosis (MS) plays a crucial role in long-term prognosis. There is increasing evidence that initiating high-efficacy therapies (HET) early provides superior disease control compared to escalation approaches with low- to moderate-efficacy therapies (LMET). **Objective:** To evaluate the impact of initial treatment with HET versus LMET on disability progression in patients with relapsing-remitting MS (RRMS) followed in a Brazilian public tertiary hospital. **Methods:** A retrospective observational study

was conducted based on electronic medical records of 35 RRMS patients treated between December 2021 and December 2023. Patients were stratified by initial therapy into HET or LMET groups. Demographic data, lesion topography, time to diagnosis and treatment, and changes in the Expanded Disability Status Scale (EDSS) after one year were analyzed. **Results:** The HET group showed a significantly greater reduction in EDSS after one year (-0.33 ± 0.53) compared to an increase in the LMET group ($+0.5 \pm 1.1$; $p = 0.00498$). Despite having a higher baseline EDSS (4.08 vs. 1.5; $p = 0.0002$), the HET group demonstrated superior control of disease progression. Delays in diagnosis (mean 34.16 months) and treatment initiation (14.08 months) were observed in both groups, reflecting systemic barriers in the Brazilian Unified Health System (SUS). **Conclusion:** Early initiation of HET was associated with better disability outcomes, even in patients with more severe baseline presentations. These findings support the adoption of early, high-efficacy interventions and underscore the need for structural improvements in MS care within the SUS. **Keywords.** Multiple sclerosis; Disease-Modifying Therapies; Disability Evaluation

Resumen

Introducción: La estrategia terapéutica inicial en la esclerosis múltiple (EM) condiciona el pronóstico; el inicio precoz de terapias de alta eficacia (TAE) podría superar el escalonamiento con terapias de baja a moderada eficacia (TBME). **Objetivo:** Evaluar el impacto de TAE versus TBME en la progresión de la discapacidad en esclerosis múltiple remitente-recurrente (EMRR) en un hospital terciario brasileño. **Métodos:** Estudio retrospectivo observacional de historias clínicas electrónicas (diciembre de 2021–diciembre de 2023) de 35 pacientes con EMRR, estratificados por terapia inicial (TAE o TBME). Se analizaron variables demográficas, topografía de las lesiones, tiempo hasta el diagnóstico e inicio del tratamiento, y el cambio en la Expanded Disability Status Scale (EDSS) a 12 meses. Se realizaron comparaciones estadísticas y estimación del tamaño del efecto con pruebas apropiadas. **Resultados:** El grupo TAE mostró mayor reducción del EDSS a 12 meses ($-0,33 \pm 0,53$) que el grupo TBME, que aumentó ($+0,50 \pm 1,10$; $p = 0,00498$). Aunque el EDSS basal fue más alto en TAE (4,08 vs 1,50; $p = 0,0002$), se observó mejor control de la progresión. Existieron retrasos en el diagnóstico (media 34,16 meses) y en el inicio del tratamiento (14,08 meses) en ambos grupos, compatibles con barreras estructurales del Sistema Único de Salud (SUS). **Conclusión:** El inicio con TAE se asoció con mejores desenlaces de discapacidad incluso con mayor gravedad inicial, apoyando su uso precoz y la necesidad de mejoras estructurales en la atención de la EM en el SUS. **Palabras clave.** Esclerosis múltiple; Terapias modificadoras de la enfermedad; Evaluación de la discapacidad

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INTRODUCTION

Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system, characterized by demyelination and progressive neurodegeneration. Affecting primarily young adults, it is one of the leading causes of non-traumatic neurological disability in economically active

populations¹. Globally, the prevalence of MS is estimated at approximately 2.8 million people, with significant regional variations. It is less prevalent in tropical regions near the equator and more frequent at higher latitudes, particularly in colder climates and populations with lower sun exposure². In Brazil, the estimated prevalence is around 15 cases per 100,000 inhabitants, highlighting it as a growing public health concern³.

The management of MS has evolved significantly with the advent of Disease-Modifying Therapies (DMTs), which are capable of altering the disease course by reducing the frequency of relapses and, to some extent, slowing the progression of disability⁴. DMTs can be classified into low/moderate-efficacy therapies (LMETs) and high-efficacy therapies (HETs), based on their potency profiles, safety, and clinical indications. LMETs, such as dimethyl fumarate, beta interferons, glatiramer acetate, and fingolimod, are traditionally used as first-line treatments due to their lower risk of adverse events. On the other hand, HETs - such as natalizumab and alemtuzumab, which are monoclonal antibodies - have greater capacity to suppress inflammatory activity and reduce disability progression, and are indicated in cases with higher disease burden or unfavorable prognostic factors⁵.

Despite these advances, the management of MS still faces significant challenges, particularly within public healthcare systems such as the Brazilian Unified Health System (SUS). Delays in diagnosis and treatment initiation

are common barriers, leading to irreversible accumulation of disability and worse functional outcomes. Studies suggest that the window of opportunity for effective interventions is limited, underscoring the importance of early identification of patients with poor prognostic factors and the prompt initiation of higher-efficacy treatments⁶. In the SUS, these barriers are further exacerbated by logistical and bureaucratic difficulties, as well as the limited availability of high-efficacy DMTs.

This study focused on evaluating the impact of initiating treatment with HET compared to LMET on disability progression in patients with MS. In addition, factors related to the time to diagnosis and treatment initiation were analyzed, as well as the relationship between baseline EDSS and the topography of demyelinating lesions. Considering the Brazilian context and the specific challenges of the SUS, this study aims to provide relevant data to support clinical decision-making and public health policy planning.

The primary objective of this study was to assess changes in EDSS scores among patients initially treated with HET or LMET. Secondary objectives included the analysis of delays in diagnosis and treatment initiation, as well as the exploration of prognostic factors such as baseline EDSS values and the topographic distribution of demyelinating lesions. The findings of this study aim not only to provide insights for clinical practice but also to stimulate discussion on structural improvements in MS management in Brazil.

To evaluate the impact of initial treatment with high-efficacy therapies versus low- to moderate-efficacy therapies on disability progression in patients with multiple sclerosis treated at a tertiary care hospital in the interior of the state of São Paulo, Brazil.

METHOD

Study Design

This is a retrospective and observational study based on the analysis of electronic medical records of patients followed at the Neuroimmunology Outpatient Clinic between December 2021 and December 2023. Patients with a confirmed diagnosis of relapsing-remitting multiple sclerosis (RRMS), according to the revised 2017 McDonald criteria, were included.

Patients with a confirmed diagnosis of RRMS who initiated treatment with any disease-modifying therapy (DMT) during the study period were included. Patients were excluded if they had insufficient data regarding treatment initiation, a diagnosis of primary progressive MS, or incomplete information regarding the outcomes analyzed.

This study was conducted at a tertiary care hospital located in the interior of the state of São Paulo, Brazil, and was approved by the local Research Ethics Committee (protocol number 116156/2024). All patients included in the study provided written informed consent in accordance with the ethical guidelines set forth in the Declaration of Helsinki.

Procedure

Data were collected from electronic medical records after informed consent was obtained. The variables analyzed included age, sex, lesion topography during the first demyelinating event (infratentorial; optic neuritis; myelitis; or other), time to diagnosis, time to treatment initiation, and Expanded Disability Status Scale (EDSS) scores, including the change in EDSS after one year of treatment.

The EDSS is the international reference instrument for assessing neurological disability in patients with multiple sclerosis⁷. It is a standardized ordinal scale ranging from 0 to 10 points, in 0.5-point increments, where 0 indicates a normal neurological examination and 10 represents death due to multiple sclerosis. The score is determined based on the evaluation of eight functional systems — pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral (mental), and other functions — reflecting the degree of impairment in each domain. The final score is strongly influenced by ambulation capacity and is widely used in clinical trials and observational studies as the gold standard for quantifying disability progression in multiple sclerosis.

In cases where EDSS was not directly recorded in the medical records, it was retrospectively estimated based on the neurological and cognitive examinations described, following the official EDSS scoring protocol, which is widely validated in the scientific literature.

Clinical outcomes and disease-control definition

Disease control was operationalized using the EDSS-based minimal clinically important difference (MCID)⁸. For each patient, the EDSS change at 12 months was calculated as follow-up minus baseline. We classified outcomes as: improved (EDSS decrease ≥ 1.0 point when baseline EDSS < 5.5 , or ≥ 0.5 point when baseline EDSS ≥ 5.5), worsened (EDSS increase meeting the same MCID thresholds), or stable (absolute change $< \text{MCID}$). For descriptive analyses, we aggregated improved + stable as "improvement or disease control." When multiple EDSS measurements were available between 9 and 15 months, the value closest to 12 months was used. Whenever feasible based on chart documentation, EDSS determinations within 30 days of an acute relapse were avoided to minimize relapse-related transient fluctuations.

Statistical Analysis

Data were analyzed using Bioestat version 5.3. Continuous variables were expressed as mean $\pm$ standard deviation, while categorical variables were reported as percentages. For comparisons between the two groups, the unpaired t-test was used for normally distributed continuous variables, and the Mann–Whitney test was applied for non-normally distributed data. For categorical variables, the chi-square test or Fisher's exact test was used, as appropriate.

The primary outcome was defined as the change in EDSS after one year of treatment initiation. Based on the

observed results, effect size (Cohen's d) was calculated using the difference in mean EDSS variation between groups and the pooled standard deviation. The statistical power of the study was estimated at approximately 80%, assuming a significance level of 5% ($p < 0.05$) and a total sample size of 35 patients.

For the categorical outcome (improved + stable vs worsened), between-group comparisons were performed using Fisher's exact test. Results are reported as proportions and p -values.

The estimated effect size, calculated based on the mean difference and pooled variability between the two groups, was used to determine the statistical power of the study. Although the estimated power was acceptable, we acknowledge that the limited sample size may have affected the ability to detect smaller differences between groups, representing a limitation of this study.

A limitation in data collection was identified, as some medical records did not contain direct EDSS documentation. To minimize this bias, EDSS scores were retrospectively estimated based on the available clinical data, following the official scoring criteria. Additionally, although the sample size was adequate for preliminary analysis, it may limit the generalizability of the findings.

RESULTS

Population Characteristics

The total sample included 35 patients diagnosed with relapsing-remitting multiple sclerosis (RRMS), with 12 patients in the high-efficacy therapy (HET) group and 23 in the low- to moderate-efficacy therapy (LMET) group. The mean age was 38.75 ± 14.42 years in the HET group and 39.56 ± 12.48 years in the LMET group ($p=0.332$). Regarding sex distribution, the HET group consisted of 33.33% males and 66.67% females, while the LMET group had 26.09% males and 73.91% females ($p=0.4703$; Table 1).

Table 1. Baseline demographic and lesion topography characteristics of the study population. This table summarizes the demographic characteristics and lesion topography observed at the time of the first demyelinating event in patients treated with either HET or LMET. Although proportional differences were observed between the groups, no significant differences were found in sex, age, or lesion distribution.

Category	HET Group	LMET Group
Age (mean $\pm$ SD)	38.75 ± 14.42	39.56 ± 12.48
Male (%)	33.33	26.09
Female (%)	66.67	73.91
Infratentorial (%)	75	52.17
Optic Neuritis (%)	16.67	43.48
Myelitis (%)	8.33	0
Other Topographies (%)	0	4.35

HET = High-efficacy therapies; LMET = Low- to moderate-efficacy therapies; SD = Standard deviation.

Regarding lesion topography during the initial demyelinating event, the groups showed proportional

differences, with a predominance of infratentorial (IT) lesions in the HET group (75%) compared to the LMET group (52.17%). Optic neuritis (ON) was more prevalent in the LMET group (43.48%) than in the HET group (16.67%). However, these differences did not reach significance ($p=0.1889$).

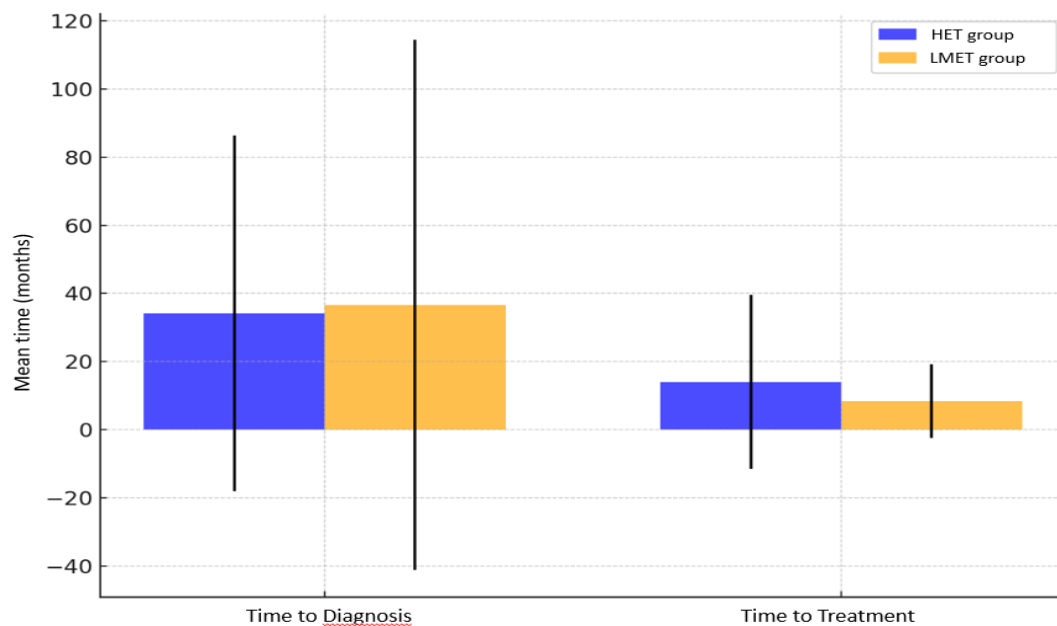
Temporal Parameters

The mean time between the first demyelinating episode and diagnosis (time to diagnosis) was 34.16 ± 52.17 months in the HET group and 36.60 ± 77.74 months in the LMET group ($p=0.3772$). The mean interval between diagnosis and treatment initiation (time to treatment initiation) was longer in the HET group (14.08 ± 25.51 months) compared to the LMET group (8.43 ± 10.86 months), although this difference was also not significant ($p=0.2171$; Figure 1).

Expanded Disability Status Scale (EDSS)

Baseline EDSS was significantly higher in the HET group (4.08 ± 1.89) compared to the LMET group (1.5 ± 1.5 ; $p=0.0002$). After one year of treatment, the mean EDSS was 3.75 ± 1.09 in the HET group and 2.06 ± 1.81 in the LMET group, with a significant difference between groups ($p=0.0053$).

Figure 1. Mean intervals and standard deviations for time to diagnosis and time to treatment initiation.



The analysis of EDSS variation over one year revealed a mean reduction in the HET group (-0.33 ± 0.53), while the LMET group showed a mean increase ($+0.5 \pm 1.1$). This difference was significant ($\tau = -3.01$; $p = 0.00498$; Figures 2 and 3).

Outcomes Related to Disease Control

Applying the prespecified EDSS MCID-based classification, 11/12 (91.7%) patients in the HET group achieved improvement or disease control (improved or stable), whereas 1/12 (8.3%) worsened. In the LMET group, 16/23 (69.6%) achieved improvement or disease control and 7/23 (30.4%) worsened. Although the distribution favored HET, the difference did not reach significance ($p = 0.216$,

Fisher's exact test). These categorical findings are directionally consistent with the continuous EDSS analyses (greater mean reduction in HET and increase in LMET).

Figure 2. Scatter plot (left) of initial EDSS values and those after 1 year of treatment, showing a tendency toward EDSS reduction in the HET group and increase in the LMET group. The boxplot (right) similarly illustrates a downward trend in EDSS in the HET group and an upward trend in the LMET group.

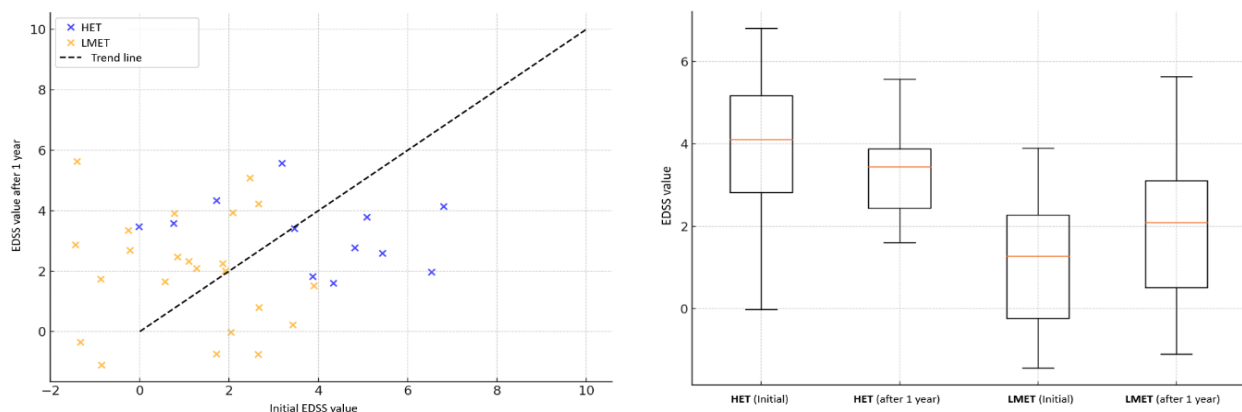
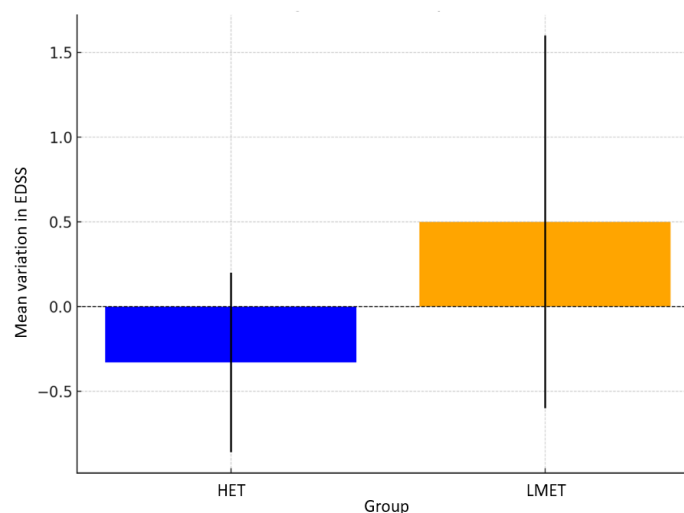


Figure 3. Bar graph showing EDSS variation after 1 year of treatment. A statistically significant difference was observed between the groups: the HET group showed a decrease in EDSS values, while the LMET group exhibited an increase, indicating a better prognosis in patients treated with HET.



DISCUSSION

The results of this study highlight the superiority of high-efficacy therapies (HET) in the management of multiple sclerosis (MS) with regard to controlling functional disability. Patients initially treated with HET showed a mean EDSS reduction of -0.33 ± 0.53 , whereas those treated with low- to moderate-efficacy therapies (LMET) exhibited a mean increase of $+0.5 \pm 1.1$, with a significant difference between the groups ($p=0.00498$). These findings are consistent with robust evidence in the literature suggesting that early therapeutic interventions with HET not only stabilize disease activity but may also reverse some degree of accumulated disability^{5,9}. Studies such as OPERA I/II, which evaluated the impact of ocrelizumab, demonstrated consistent reductions in disability progression compared to traditional first-line therapies, reinforcing the importance of initiating HET in patients at high risk of progression⁵. Likewise, the CAMMS223 trial, published in 2020, showed that early use of alemtuzumab was associated with a lower annualized relapse rate and greater stabilization of EDSS, particularly in patients who presented with severe initial relapses¹⁰.

Moreover, the baseline EDSS difference between groups -4.08 ± 1.89 in the HET group versus 1.5 ± 1.5 in the LMET group - reflects a selection bias based on initial clinical severity, which is well supported in the literature. Previous studies have suggested that patients presenting with infratentorial lesions or myelitis are more likely to receive more aggressive therapies due to the higher likelihood of

permanent functional disability⁶. Nevertheless, our data indicate that even among patients with higher baseline EDSS scores, treatment with HET was able to mitigate disease progression, suggesting substantial benefits for individuals with more severe clinical presentations.

The results of this study reinforce the growing body of evidence suggesting that early initiation of high-efficacy therapies (HET) in patients with multiple sclerosis (MS) is associated with better clinical outcomes. Recent international studies have challenged the traditional escalation approach, which begins with lower-efficacy treatments and progresses to more potent options as the disease advances. For example, a recent cohort published in the *Journal of Neurology*¹¹ emphasized that patients who start treatment with HET experience a more significant reduction in both disability progression and disease activity compared to those who follow the escalation strategy.

Furthermore, a retrospective cohort study¹² demonstrated that patients who initiated treatment with HET had a significantly higher likelihood of achieving no evidence of disease activity (NEDA) during the first and second years of treatment compared to those who started with moderate-efficacy therapies. These findings suggest that the initial choice of HET may be crucial for optimizing long-term outcomes in patients with MS.

Early identification and prompt initiation of treatment in MS are crucial for improving patient prognosis. Delays in diagnosis and in the initiation of disease-modifying therapy

can lead to greater accumulation of disability and a decline in quality of life¹³. In the Brazilian context, the Unified Health System (SUS) faces challenges that contribute to these delays: the complexity of diagnostic criteria, the requirement for multiple complementary tests, and the overload of public healthcare services can prolong the time between symptom onset and diagnostic confirmation. Moreover, the incorporation of new therapies into the SUS can be slow, further delaying patient access to more effective treatments. These delays have socioeconomic implications, increasing long-term healthcare costs and negatively affecting patient productivity and quality of life¹³. Therefore, it is imperative that public policies be implemented to accelerate the diagnosis and initiation of MS treatment in Brazil, ensuring timely and equitable access to DMTs and, consequently, improving clinical outcomes and quality of life for patients.

This study has some limitations inherent to its retrospective design and small sample size. The retrospective nature of the analysis may introduce selection biases, potentially affecting the accuracy of the collected data. Additionally, the need to retrospectively estimate EDSS in some cases may compromise the precision of disability assessment. The limited sample size also restricts the generalizability of the results to broader populations. In future research, to mitigate these limitations, prospective studies with larger samples and rigorous data collection standardization are recommended to ensure greater validity and reliability of the findings.

These findings reinforce the importance of initiating high-efficacy therapies early in patients with multiple sclerosis, particularly those with unfavorable prognostic factors such as high EDSS scores and infratentorial lesions. Within the context of the Brazilian Unified Health System (SUS), it is crucial to improve access to timely diagnosis and effective treatments, reducing delays that can negatively impact patient prognosis. Future research should focus on prospective and multicenter study designs, exploring not only clinical outcomes but also patient quality of life and cost-effectiveness analyses of therapeutic interventions, with the aim of optimizing disease management across different socioeconomic settings.

CONCLUSION

The findings of this study suggest that the initiation of high-efficacy therapies may provide better control of disability progression in patients with relapsing-remitting multiple sclerosis, including those presenting with greater baseline severity. These therapies appear to represent an important option for reducing functional decline when considered as part of initial treatment strategies.

The results also indicate substantial delays in both diagnosis and treatment initiation within the public healthcare setting, highlighting structural barriers that may compromise outcomes. Expanding timely access to high-efficacy therapies and improving early recognition of high-risk patients could contribute to more favorable prognoses

and enhanced quality of life for individuals living with multiple sclerosis.

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