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Long-Term Changes in the Expanded Disability Status Scale After Autologous Hematopoietic Stem Cell Transplantation in Patients with Multiple Sclerosis: A Single-Program Cohort of 1,657 Patients

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Abstract

Background

Autologous hematopoietic stem cell transplantation (AHSCT) is an immune-reconstitution strategy for selected patients with multiple sclerosis (MS). Large real-world studies with long-term disability assessments remain limited.

Objective

To evaluate longitudinal changes in Expanded Disability Status Scale (EDSS) scores after AHSCT and to determine the proportions of patients achieving clinically meaningful improvement, stability, or progression.

Materials and Methods

This retrospective longitudinal cohort included 1,657 patients with MS who underwent AHSCT within HSCT México, a single clinical program operating at sites in Puebla and Monterrey, Mexico, between November 2012 and July 2026. Baseline EDSS scores were assigned by a neurologist. At follow-up, EDSS scores were obtained from a neurologist assessment when available and when a neurologist-assigned EDSS was not available, the score was derived using a structured EDSS calculator during the scheduled follow-up assessment. Clinically meaningful improvement was defined as a decrease of at least 1.0 EDSS point, progression as an increase of at least 1.0 point, and stability as a change of less than 1.0 point in either direction. Outcomes were also examined according to relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS) phenotypes.

Results

Complete baseline–follow-up EDSS pairs were available for 675 patients at 3 months (40.7%), 549 at 6 months (33.1%), 578 at 12 months (34.9%), 350 at 18 months (21.1%), 361 at 24 months (21.8%), 245 at 36 months (14.8%), and 106 at 60 months (6.4%). Mean EDSS decreased significantly at 3 months (mean change, -0.18; 95% CI, -0.26 to -0.0; $p < 0.001$), 6 months (-0.16; 95% CI, -0.26 to -0.06; $p = 0.001$), 12 months (-0.36; 95% CI, -0.47 to -0.26; $p < 0.001$), 18 months (-0.24; 95% CI, -0.39 to -0.09; $p = 0.002$), and 24 months (-0.25; 95% CI, -0.40 to -0.10; $p = 0.001$). No significant differences from baseline were observed at 36 months (-0.13; 95% CI, -0.32 to 0.05; $p = 0.144$) or 60 months (0.02; 95% CI, -0.31 to 0.35; $p = 0.910$). Wilcoxon analyses yielded concordant findings, with the largest nonparametric effect observed at 12 months ($r = 0.334$). At 12 months, 27.2% of patients improved, 62.5% remained stable, and 10.4% progressed. At 60 months, 26.4% improved, 48.1% remained stable, and 25.5% progressed; thus, 74.5% of patients with long-term paired data have remained stable or improved.

Conclusions

AHSCT was associated with significant reductions in EDSS through 60 months, with the greatest improvement observed at 12 months; most patients with available long-term data remained stable or improved.

Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated disorder of the central nervous system characterized by inflammatory demyelination, axonal injury, and progressive neurodegeneration, ultimately leading to heterogeneous patterns of neurological disability. [1] The disease encompasses a spectrum of clinical phenotypes, ranging from relapsing-remitting MS (RRMS, to secondary progressive (SPMS) and primary progressive MS (PPMS), in which disability accumulates gradually over time. [1] Despite substantial advances in diagnostic criteria and the widespread availability of highly effective disease-modifying therapies (DMTs), long-term prevention of disability progression remains one of the principal unmet needs in MS management. [1, 2]

The Expanded Disability Status Scale (EDSS) remains the most widely used measure of neurological impairment and disability in both clinical practice and research settings [3]. By integrating functional system assessments and ambulatory performance into an ordinal scale ranging from 0 to 10, the EDSS provides a standardized framework for longitudinal evaluation and comparison across studies [3]. Nevertheless, the scale has recognized limitations, including its nonlinear structure, disproportionate weighting of ambulatory function at higher scores, and reduced sensitivity to cognitive impairment, fatigue, upper-extremity dysfunction, and other clinically meaningful aspects of disease burden. [4]

Current disease-modifying therapies (DMTs) primarily target peripheral inflammatory mechanisms and have demonstrated substantial efficacy in reducing relapse frequency, magnetic resonance imaging (MRI) activity, and short-term disability progression, predominantly by compartmentalized inflammation and neurodegenerative processes, which may be less responsive to conventional systemic immunotherapies. [5, 6]

Autologous hematopoietic stem cell transplantation (AHSCT) has emerged as a highly effective immune-reconstitution strategy for selected patients with aggressive or treatment-refractory MS. The procedure combines profound immunosuppression followed by reinfusion of autologous hematopoietic progenitor cells, aiming to eliminate autoreactive immune populations and promote regeneration of a more tolerant immune repertoire. [7] Its therapeutic efficacy is attributed primarily to immune resetting rather than direct neural repair or replacement. [7, 8] Over the past two decades, accumulating evidence from prospective cohorts, registry analyses, meta-analyses, and randomized clinical trials has demonstrated that AHSCT can induce sustained suppression of inflammatory disease activity, particularly among younger patients with active RRMS, shorter disease duration, and suboptimal responses to DMTs. [9, 10] Notably, the MIST randomized clinical trial demonstrated a significantly longer time to disability

progression among patients undergoing non-myeloablative AHSCT compared with those receiving continued DMTs. [11]

The therapeutic landscape of AHSCT has evolved substantially over the past two decades owing to improvements in patient selection, conditioning regimens, infection prophylaxis, supportive care, and transplant-center expertise. These advances have resulted in marked reductions in treatment-related mortality and have contributed to the broader acceptance of AHSCT within contemporary MS treatment algorithms. [12–13]. Long-term real-world data are essential to better define the durability of clinical benefits following AHSCT and to characterize treatment responses across different MS phenotypes. HSCT México is a single clinical program operating at two sites, Puebla and Monterrey, Mexico, and has treated the largest cohort of patients with MS undergoing AHSCT ever reported. The expanded cohort analyzed in the present study includes 1,657 patients treated between November 2012 and July 2026, incorporating the cohorts in Puebla and Monterrey, with follow-up extending to 60 months and analyses across all types of MS.

The primary objective of this study was to evaluate changes in EDSS from baseline to prespecified follow-up visits after AHSCT. We estimated the proportions of patients demonstrating clinically meaningful improvement, stability, or progression; compared disability outcomes among RRMS, SPMS, and PPMS; and assessed the durability of disability changes through 60 months of follow-up.

Materials and Methods

Study design and setting

We conducted a retrospective, longitudinal, single-program, two-site observational cohort study of patients with MS who underwent AHSCT within HSCT México, a unified clinical program operating at sites in Puebla and Monterrey, Mexico, between November 2012 and July 2026. Clinical information was obtained from routinely recorded medical data generated during standard clinical care at the two sites. The manuscript was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. [14]

Participants

The study population consisted of 1,657 patients with MS who underwent AHSCT within the HSCT México program during the study period. The analytic cohort included 866 patients with RRMS, 433 with SPMS, and 358 with PPMS. The analytic cut-off was July 31, 2026; records with transplantation dates after this date were not included.

Among patients evaluated for transplantation, 19 (1.2%) did not proceed directly to transplantation. Temporary postponement occurred in 10 patients (0.63%) because of potentially reversible conditions, including infections, abnormal laboratory findings, inflammatory bowel disease activity,

hypergammaglobulinemia, and cardiopulmonary symptoms. All subsequently underwent transplantation and were included in the analytic cohort. Transplantation was permanently cancelled in 9 patients (0.57%) because of medical, infectious, oncological, psychiatric, or patient-related causes; these patients were not included in the analytic cohort.

The diagnosis of MS was established by treating neurologists according to the diagnostic criteria applicable at the time of evaluation. Clinical phenotype was classified as RRMS, SPMS, or PPMS based on the neurologist's assessment and disease course documented in the medical record.

No additional predefined inclusion or exclusion criteria for this study were applied beyond a diagnosis of MS, completion of AHSCT during the study period, documentation of an RRMS, SPMS, or PPMS phenotype, and availability of relevant clinical information. The cohort therefore represents a real-world population of consecutively treated patients within a specialized two-site referral program.

AHSCT procedure

AHSCT was performed using the non-myeloablative "Mexican Method," consisting of peripheral-blood stem-cell mobilization and collection, conditioning based on cyclophosphamide and rituximab, and reinfusion of noncryopreserved autologous hematopoietic progenitor cells, as previously described by Ruiz-Argüelles and colleagues. [12]

Outcome measures and data sources

The primary outcome was change in EDSS score from baseline to 3, 6, 12, 18, 24, 36, and 60 months after AHSCT. Secondary outcomes included the proportion of patients classified as improved, stable, or progressed, both overall and according to MS phenotype.

Clinical improvement was defined as a decrease of at least 1.0 EDSS point from baseline, disease progression as an increase of at least 1.0 EDSS point, and stability as a change of less than 1.0 point in either direction. A 1.0-point EDSS change has been considered clinically meaningful in MS outcome assessment, and a 1.0-point decrease has been used to define neurological improvement in longitudinal clinical studies [15,16]. In the present retrospective analysis, these categories were assigned independently at each prespecified follow-up visit relative to the baseline EDSS and were not required to be confirmed at a subsequent visit. The three categories were mutually exclusive.

Clinical and longitudinal follow-up information was obtained from the institutional databases of the HSCT México program. Baseline EDSS scores were assigned by a neurologist during the pre-transplant neurological evaluation. Follow-up EDSS scores were obtained from a neurologist when a recent neurological consultation was available. When a recent neurologist-assigned EDSS was not available, the follow-up EDSS was derived using a structured EDSS calculator based on the neurological symptoms, functional-system findings, and ambulatory status documented during the encounter. Because most

patients resided outside Mexico, follow-up was frequently conducted by telemedicine when in-person assessment was not feasible. The present patient-level analysis evaluated the 3, 6, 12, 18, 24, 36, and 60-month time points. Neurological symptoms, medications, adverse events, hospitalizations, MRI findings, laboratory results, ambulatory support, and EDSS scores were recorded during follow-up encounters.

Statistical analysis

Continuous variables are summarized using means and standard deviations (SD) or medians and interquartile ranges (IQR), as appropriate, whereas categorical variables are summarized as frequencies and percentages. Follow-up availability was calculated relative to the full cohort of 1,657 patients.

Changes in EDSS from baseline to each follow-up visit were analyzed using two-sided paired Student t-tests, with mean differences and 95% confidence intervals. Because EDSS is ordinal and the paired-change distributions contained numerous tied values, complementary two-sided Wilcoxon signed-rank tests were performed. Analyses used complete baseline-follow-up pairs only, and missing EDSS values were not imputed.

For Wilcoxon analyses, the paired difference was defined as follow-up EDSS minus baseline EDSS. Differences equal to zero were retained in descriptive summaries as ties but excluded from signed-rank calculations according to the conventional Wilcoxon zero-difference method. Numeric EDSS values of 0 were retained because 0 is a valid clinical score; a sensitivity analysis excluding isolated, uncorroborated follow-up zeros and one exact duplicate patient did not change the overall significance pattern. Wilcoxon p values were obtained using the asymptotic normal approximation with tie adjustment and without continuity correction. Effect size was calculated as $r=|z|/\sqrt{n}$, where n represented the number of nonzero paired differences. Data management was performed in Microsoft Excel and GraphPad Prism version 10.0; final patient-level analyses were conducted using Python version 3.13.5 with SciPy version 1.17.0 and NumPy version 2.3.5. Two-sided p values <0.05 were considered statistically significant.

Results

Cohort and follow-up

Complete baseline–follow-up EDSS pairs were available for 675 patients at 3 months (40.7%), 549 at 6 months (33.1%), 578 at 12 months (34.9%), 350 at 18 months (21.1%), 361 at 24 months (21.8%), 245 at 36 months (14.8%), and 106 at 60 months (6.4%).

Overall EDSS outcomes

At 3 months, mean EDSS decreased from 4.69 ± 1.95 at baseline to 4.52 ± 2.05, corresponding to a mean change of -0.18 points (95% CI, -0.26 to -0.09; t[674]=-4.17; p<0.001). At 6 months, mean EDSS

decreased from 4.66 ± 1.98 to 4.50 ± 2.06, with a mean change of -0.16 points (95% CI, -0.26 to -0.06; t[548]=-3.20; p=0.001). At 12 months, mean EDSS decreased from 4.77 ± 1.92 to 4.41 ± 2.17, representing a mean change of -0.36 points (95% CI, -0.47 to -0.26; t[577]=-6.61; p<0.001). At 18 months, mean EDSS decreased from 4.73 ± 1.98 to 4.49 ± 2.22, with a mean change of -0.24 points (95% CI, -0.39 to -0.09; t[349]=-3.12; p=0.002). At 24 months, mean EDSS decreased from 4.66 ± 1.95 to 4.41 ± 2.30, with a mean change of -0.25 points (95% CI, -0.40 to -0.10; t[360]=-3.27; p=0.001).

At longer follow-up, mean EDSS decreased from 4.66 ± 1.93 at baseline to 4.52 ± 2.42 at 36 months, corresponding to a mean change of -0.13 points (95% CI, -0.32 to 0.05; t[244]=-1.47; p=0.144). At 60 months, mean EDSS changed from 4.72 ± 1.79 to 4.74 ± 2.35, with a mean difference of 0.02 points (95% CI, -0.31 to 0.35; t[105]=0.11; p=0.910). Therefore, paired Student t-tests demonstrated statistically significant reductions in EDSS at 3, 6, 12, 18, and 24 months, whereas no statistically significant differences from baseline were observed at 36 or 60 months. Mean changes were calculated as follow-up EDSS minus baseline EDSS, and all reported p values were two-sided and unadjusted. **Figure 1.**

Wilcoxon signed-rank analysis

Wilcoxon signed-rank analyses were concordant with the paired Student t-tests. At 3 months, the median EDSS was 5.0 (IQR, 3.0–6.5) at baseline and 5.0 (IQR, 3.0–6.5) at follow-up. Among 675 paired observations, 322 were ties and 353 contributed to the signed-rank calculation; EDSS was significantly lower than baseline (W=23,232.0; p<0.001; r=0.225). At 6 months, median EDSS was 5.0 (IQR, 3.0–6.5) at baseline and 5.0 (IQR, 3.0–6.5) at follow-up. Of 549 paired observations, 212 were ties and 337 were ranked, demonstrating a statistically significant reduction (W=22,248.0; p<0.001; r=0.193). At 12 months, the median EDSS decreased from 5.5 (IQR, 3.0–6.5) to 5.0 (IQR, 2.5–6.5). Among 578 paired observations, 199 were ties and 379 contributed to the rank analysis; the reduction was statistically significant (W=22,276.5; p<0.001) and showed the largest nonparametric effect size (r=0.334). At 18 months, median EDSS decreased from 5.5 (IQR, 3.0–6.5) to 5.0 (IQR, 3.0–6.5); 107 of 350 observations were ties and 243 were ranked (W=11,791.5; p=0.005; r=0.179).

At 24 months, the median EDSS decreased from 5.0 (IQR, 3.0–6.5) at baseline to 4.5 (IQR, 2.5–6.5) at follow-up. Of 361 paired observations, 101 were ties and 260 were ranked, with a statistically significant reduction in EDSS (W=13,262.0; p=0.002; r=0.191). At longer follow-up, no statistically significant differences were identified. At 36 months, median EDSS was 5.0 (IQR, 3.0–6.0) at baseline and 5.0 (IQR, 2.5–6.5) at follow-up; among 245 paired observations, 54 were ties and 191 were ranked (W=8,266.5; p=0.234; r=0.086). At 60 months, median EDSS changed from 5.0 (IQR, 3.5–6.0) to 6.0 (IQR, 2.6–6.5); of 106 paired observations, 25 were ties and 81 contributed to the signed-rank calculation (W=1,594.0; p=0.753; r=0.035).

Differences equal to zero were retained as ties in the descriptive analyses but excluded from the signed-rank calculations. Two-sided p values were obtained using the asymptotic normal approximation with

adjustment for tied ranks and without continuity correction. Overall, the effect sizes were small to moderate, with the greatest effect observed at 12 months.

Clinically meaningful EDSS outcomes

Using the prespecified clinical thresholds, 119 of 675 evaluable patients (17.6%) improved by at least 1.0 EDSS point at 3 months, 484 (71.7%) remained stable, and 72 (10.7%) progressed by at least 1.0 point. At 6 months, improvement was observed in 109 of 549 patients (19.9%), stability in 376 (68.5%), and progression in 64 (11.7%). At 12 months, 157 of 578 patients (27.2%) improved, 361 (62.5%) remained stable, and 60 (10.4%) progressed. At 18 months, 83 of 350 patients (23.7%) improved, 211 (60.3%) remained stable, and 56 (16.0%) progressed. At 24 months, 104 of 361 patients (28.8%) improved, 189 (52.4%) remained stable, and 68 (18.8%) progressed.

At longer follow-up, 64 of 245 patients (26.1%) improved at 36 months, 130 (53.1%) remained stable, and 51 (20.8%) progressed. At 60 months, 28 of 106 patients (26.4%) improved, 51 (48.1%) remained stable, and 27 (25.5%) progressed. Therefore, 79 of 106 patients with 60-month paired data (74.5%) remained stable or improved, which may represent a clinically meaningful outcome given the progressive nature of disability accumulation in a substantial proportion of the cohort.

Twelve-month outcomes by phenotype

In exploratory phenotype-specific analyses, 281 patients with RRMS, 121 with PPMS, and 176 with SPMS had complete 12-month pairs. Mean EDSS changed from 3.74 to 3.32 in RRMS, from 5.41 to 5.17 in PPMS, and from 5.98 to 5.62 in SPMS. Improvement by at least 1.0 point occurred in 32.0%, 20.7%, and 23.9%, respectively; 54.8%, 71.9%, and 68.2% remained stable; and 13.2%, 7.4%, and 8.0% progressed by at least 1.0 point.

Sixty-month outcomes by phenotype

At 60 months, complete phenotype-specific pairs were available for 48 patients with RRMS, 20 with PPMS, and 38 with SPMS. Mean EDSS changed from 3.74 to 3.71 **Figure 2**; in RRMS, from 4.97 to 5.15 **Figure 3**; in PPMS, and from 5.83 to 5.83 in SPMS. **Figure 4**. The proportions classified as stable were 37.5%, 55.0%, and 57.9%, respectively. No phenotype demonstrated a statistically significant mean EDSS change at 60 months, supporting the interpretation that later outcomes were characterized principally by stabilization rather than continued improvement.

Discussion

In this large single-program, two-site real-world cohort, paired Student t-tests and Wilcoxon signed-rank tests demonstrated concordant reductions in EDSS at 3, 6, 12, 18, and 24 months after AHSCT. The

greatest mean reduction and nonparametric effect size were observed at 12 months. No statistically significant paired difference was demonstrated at 36 or 60 months, suggesting that stabilization rather than continued neurological improvement may better characterize later outcomes. At 60 months, 48% of evaluable patients remained stable and 27% improved by at least 1.0 EDSS point, whereas 25% progressed, resulting in a positive response rate (improvement or stabilization) of 75%.

The early reduction in disability is biologically plausible because AHSCT rapidly suppresses inflammatory activity and permits immune reconstitution. Improvement is most likely when baseline disability includes a reversible component related to recent relapses or active inflammation rather than fixed neuroaxonal loss. [5, 7, 8] This interpretation is consistent with the stronger and more durable improvement observed in RRMS and with contemporary recommendations that favor younger patients with active relapsing disease, shorter disease duration, and lower baseline disability. [5, 7, 13]

The magnitude and temporal pattern of disability change observed in the present cohort are broadly consistent with previous AHSCT studies, although direct comparisons are limited by differences in patient selection, baseline disability, disease phenotype, outcome definitions, and follow-up duration. The MIST trial demonstrated a longer time to disability progression with nonmyeloablative AHSCT than with continued DMT in RRMS. [11] Comparative-effectiveness analyses have also reported favorable disease-control outcomes with AHSCT compared with fingolimod, natalizumab, and, depending on follow-up duration and endpoint selection, ocrelizumab in highly active RRMS. [17] More recent single-center data similarly supports durable disease control after AHSCT compared with alemtuzumab and ocrelizumab. [18] Because the present study was not designed as a comparative trial, these findings provide contextual evidence rather than a direct estimate of comparative treatment efficacy.

An important consideration when interpreting the present results is the heterogeneity of conditioning regimens used across AHSCT programs. Earlier multicenter cohorts included patients treated with conditioning regimens of different intensities, making direct comparisons of long-term outcomes difficult because conditioning intensity was closely intertwined with disease phenotype, baseline disability, and treatment era. In the large multicenter cohort reported by Muraro et al., which included 281 patients with a median follow-up of 6.6 years, conditioning intensity was among the treatment-related variables evaluated, although disease subtype and baseline disability remained important determinants of long-term outcome. [9] Current ECTRIMS/EBMT recommendations recognize cyclophosphamide–ATG and BEAM–ATG among the principal conditioning approaches used in contemporary AHSCT programs. [5] More recently, a retrospective EBMT analysis of 1,114 patients directly compared BEAM/ATG with cyclophosphamide/ATG and found no statistically significant difference in NEDA failure after adjustment for MS phenotype, baseline disability, and year of transplantation, suggesting that differences in long-term disease control cannot be attributed solely to conditioning regimen. [28] The present cohort was treated using the HSCT México “Mexican Method,” a cyclophosphamide- and rituximab-based approach that differs from the BEAM/ATG and cyclophosphamide/ATG regimens commonly reported in contemporary European transplant cohorts. Therefore, the disability trajectory observed in our study extends real-world evidence on AHSCT to a large population treated with a distinct conditioning strategy.

Nevertheless, differences in conditioning regimen, patient selection, MS phenotype, baseline EDSS, disease duration, and prior treatment exposure should be considered when comparing outcomes across cohorts.

Large national and multicenter cohorts further support the durability of disease control in routine practice. The Swedish observational cohort reported sustained no-evidence-of-disease-activity outcomes in a substantial proportion of treated patients, and Norwegian long-term follow-up similarly documented durable clinical benefit. [19, 20] A real-world series of 507 patients demonstrated the feasibility of nonmyeloablative AHSCT outside randomized trials. [21] Most recently, a multicenter UK cohort reported durable remission of inflammatory activity and stabilization or improvement of neurological disability, particularly in RRMS, across a clinically heterogeneous population. [22] Differences in conditioning regimens, baseline disability, prior treatment exposure, and follow-up methods should nevertheless be considered when comparing these cohorts with the present study.

The smaller magnitude of improvement in progressive forms of MS should not be interpreted as absence of clinical value. Progressive MS is characterized by gradual accumulation of disability, often driven by compartmentalized inflammation, neuroaxonal loss, and limited capacity for neurological recovery. Consequently, preventing or delaying further worsening may represent a meaningful therapeutic outcome even when EDSS improvement is not observed. This interpretation is consistent with pivotal trials in primary and secondary progressive MS, in which treatment benefit was demonstrated principally by reducing the risk of confirmed disability progression rather than by requiring neurological improvement. [23, 24] In the ORATORIO trial, ocrelizumab reduced the risk of confirmed disability progression in PPMS, and in the EXPAND trial, siponimod reduced confirmed disability progression in SPMS. [23, 24] Therefore, the stability observed in the present progressive subgroups is clinically relevant, although it cannot be attributed causally to AHSCT in the absence of a contemporaneous comparator. The systematic review by Braun and colleagues found heterogeneous outcomes in progressive disease, with more favorable results when inflammatory activity remained evident. [6] Studies in SPMS have suggested that AHSCT may influence disability accumulation and neurodegenerative biomarkers in selected patients, but benefit appears less consistent once progression is predominantly non-inflammatory. [25] A matched comparison of AHSCT and natalizumab in progressive MS did not demonstrate a clear disability advantage, reinforcing the need for cautious patient selection and appropriate expectations. [26]

Recent work on prognostic factors also emphasizes that outcomes after AHSCT are not uniform. Analyses from the Swedish AutoMS cohort identified baseline and treatment-related characteristics associated with subsequent inflammatory activity and disability outcomes. [27] These observations reinforce the importance of age, phenotype, inflammatory activity, disease duration, prior treatment exposure, and baseline disability when interpreting aggregate EDSS trajectories. They also support the development of standardized selection criteria and prospective registries capable of separating treatment effect from differences in baseline risk.

The principal limitation of this study is the incomplete availability of longitudinal follow-up, particularly at later time points. Because the cohort included an international referral population, geographic distance and logistical barriers may have limited patients' ability to return for in-person neurological assessments. Differential follow-up may introduce selection, reporting, and ascertainment bias, particularly if patients with different disability trajectories were differentially likely to remain in contact with the program. The outcomes of patients without available follow-up therefore cannot be assumed, and the long-term estimates should be interpreted as outcomes among patients with available paired assessments rather than as complete population-level estimates. Importantly, loss to follow-up was not passive. The clinical team made repeated and exhaustive efforts to maintain contact and encourage longitudinal assessment, including repeated e-mail communications and telephone calls to patients who had not returned for scheduled follow-up. Despite these efforts, some patients did not respond or could not be re-engaged. This limitation is particularly relevant to the 36- and 60-month analyses and should be considered when interpreting the long-term distribution of improvement, stability, and progression.

The major strength of this study is its size and the breadth of longitudinal real-world experience. With 1,657 patients treated within a single clinical program operating at two sites, the cohort includes 866 patients with RRMS, 433 with SPMS, and 358 with PPMS and reflects routine practice in an international referral population across the Puebla and Monterrey sites of HSCT México. The availability of follow-up data through 60 months provides information beyond the early post-transplant period, while the predefined categories of improvement, stability, and progression facilitate clinical interpretation of EDSS trajectories. Importantly, the cohort also provides long-term real-world data from a program using the Mexican Method, thereby complementing evidence generated from centers using other conditioning strategies. Taken together, these findings provide clinically relevant information on both early neurological improvement and longer-term disability stabilization after AHSCT across different MS phenotypes.

Conclusion

In this large real-world cohort of 1,657 patients with multiple sclerosis treated within the HSCT México program, AHSCT was associated with significant reductions in EDSS during the first 24 months after transplantation, with the greatest improvement observed at 12 months. At 36 and 60 months, mean EDSS remained comparable to baseline; however, among patients with available paired assessments at 60 months, 27% experienced a clinically meaningful improvement of at least 1.0 EDSS point and 48% remained stable, while 25% experienced progression. Thus, 75% of patients with available long-term paired data showed either improvement or stabilization.

The observed trajectory was characterized by early neurological improvement followed by longer-term stabilization, with more pronounced improvement in relapsing disease and a clinically relevant pattern of stabilization in progressive MS. These findings complement existing real-world evidence across different AHSCT conditioning strategies and support the importance of patient selection and long-term monitoring. However, the retrospective design, absence of a contemporaneous comparator, incomplete

long-term follow-up, and potential variability in EDSS assessment limit causal inference. Prospective comparative studies with standardized neurological and MRI assessments and more complete longitudinal follow-up are needed to further define the long-term effects of AHSCT across MS phenotypes.

Declarations

Ethical considerations

This retrospective study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the applicable provisions of the Mexican General Health Law on Health Research. Under Article 17, Section I, the study was classified as research without risk because it involved retrospective review of existing clinical records without direct intervention or modification of biological, psychological, or social variables.

The study protocol was reviewed and approved by the Institutional Review Board of Clínica Ruiz (approval number CEI-10-03-24-02) and was registered at ClinicalTrials.gov (Identifier: NCT02674217). Written informed consent was obtained from all patients before treatment, including authorization for the collection, storage, and research use of their clinical information. All data were deidentified before analysis, and access to the study database was restricted to authorized investigators.

Conflict of interest

The authors declare no conflicts of interest.

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Figures

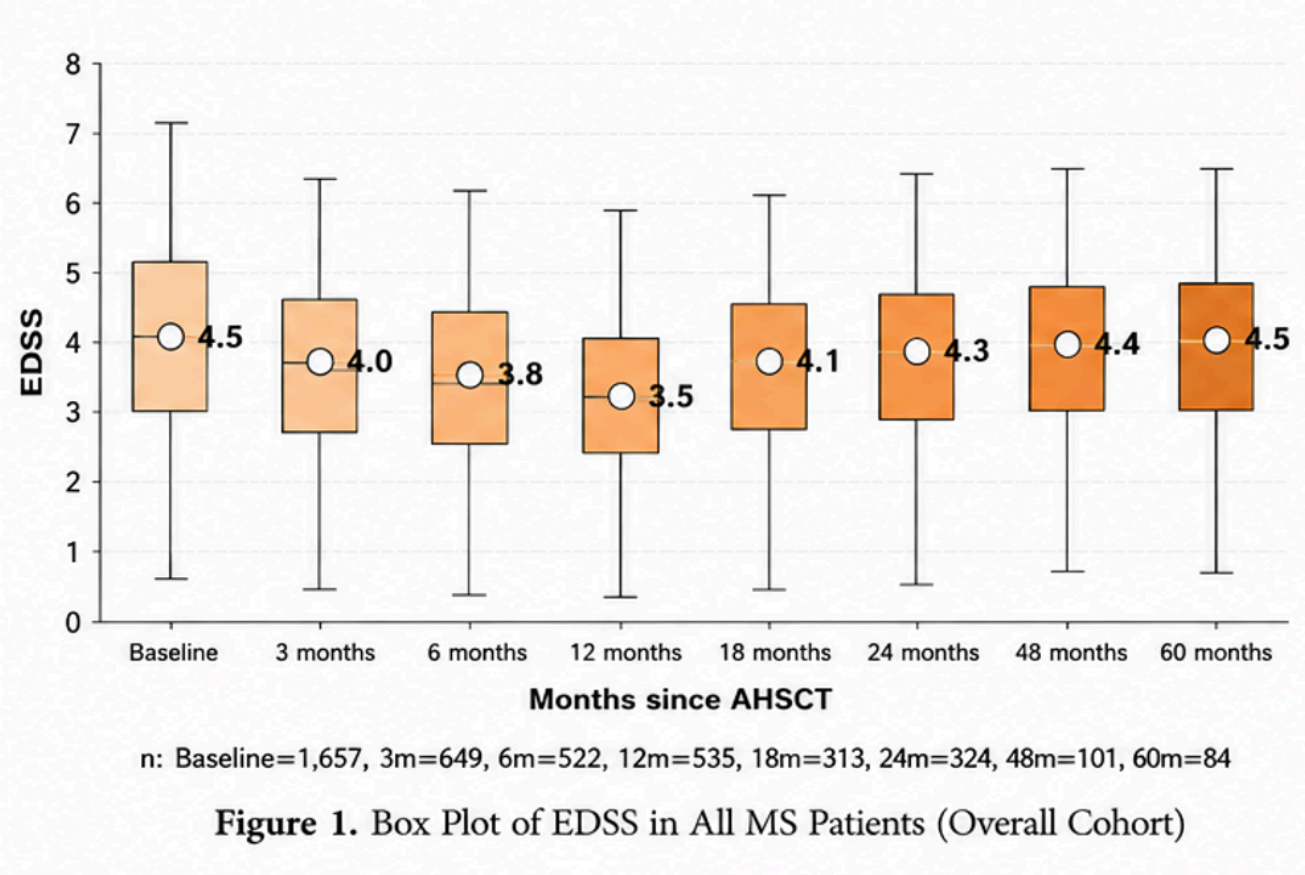


Figure 1. Box Plot of EDSS in All MS Patients (Overall Cohort)

Figure 1

See image above for figure legend.

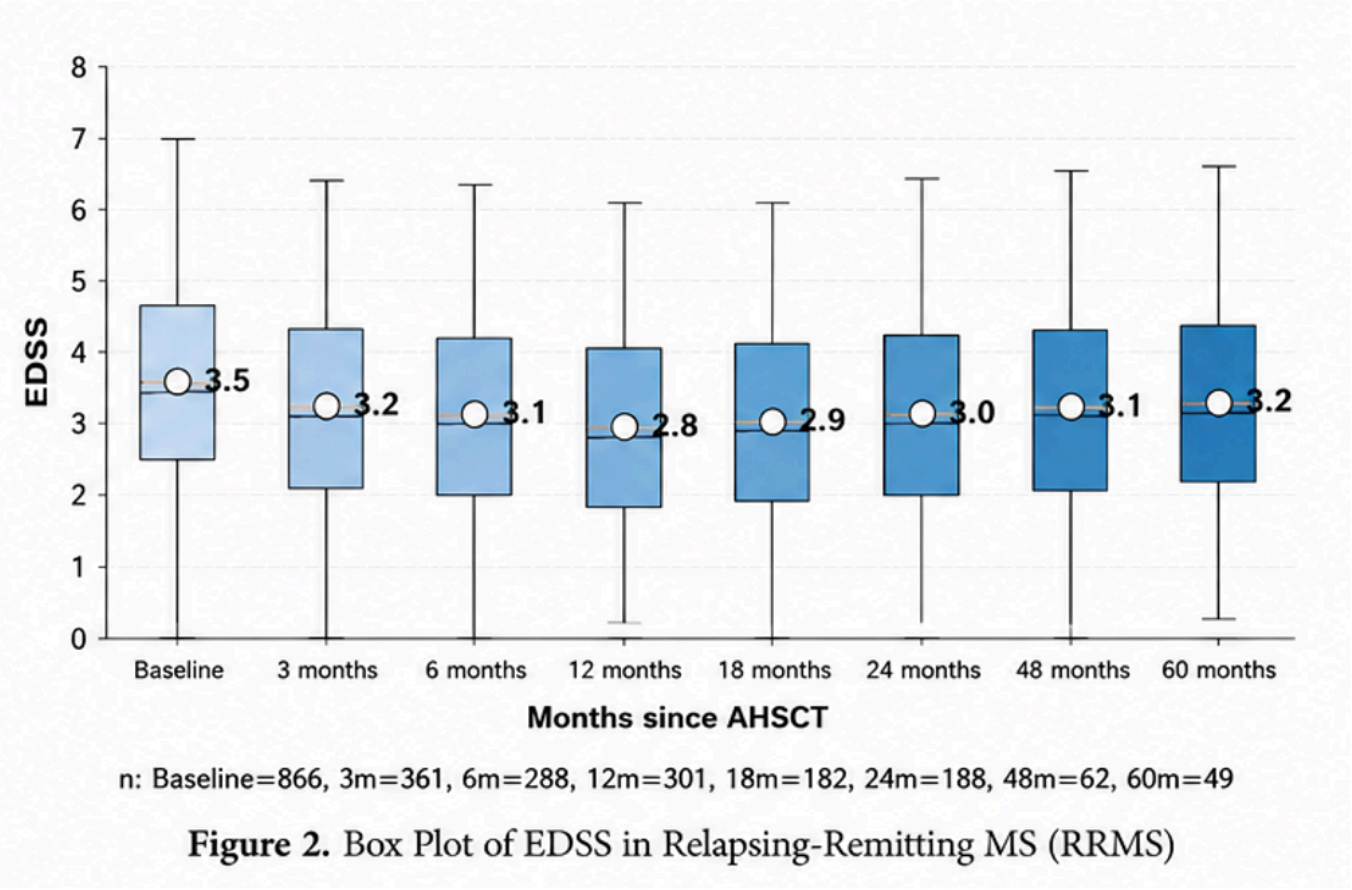


Figure 2. Box Plot of EDSS in Relapsing-Remitting MS (RRMS)

Figure 2

See image above for figure legend.

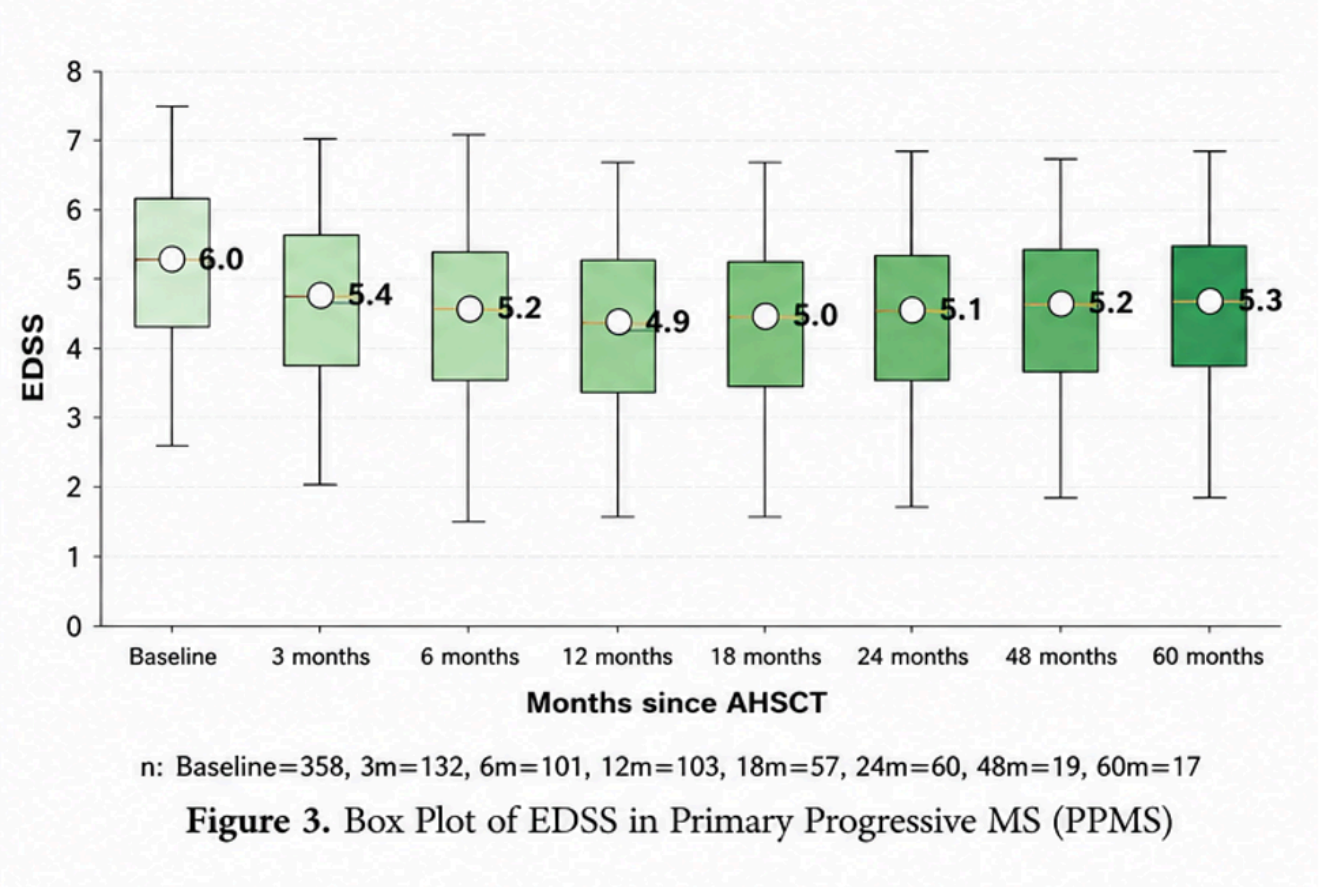


Figure 3. Box Plot of EDSS in Primary Progressive MS (PPMS)

Figure 3

See image above for figure legend.

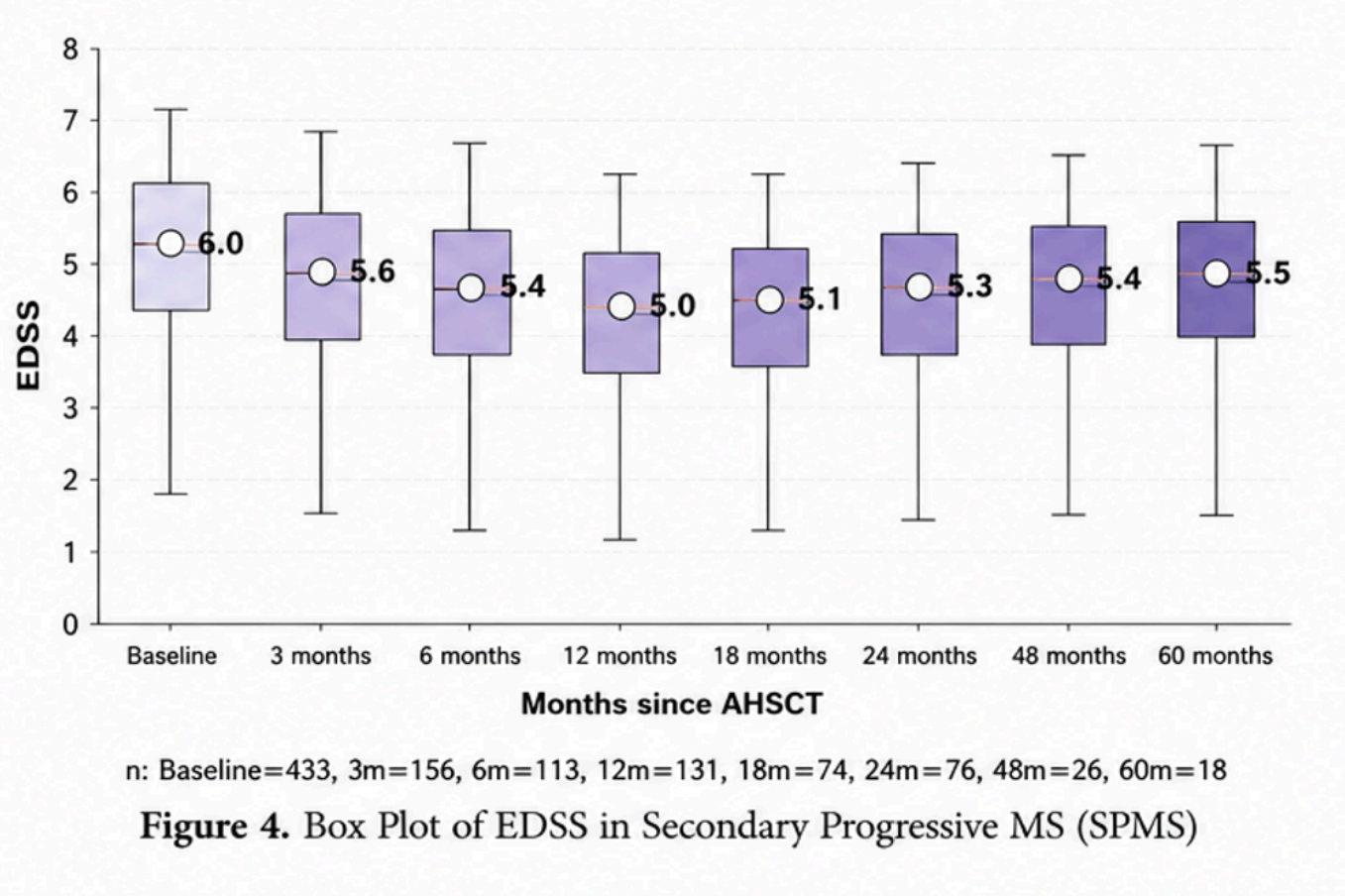


Figure 4. Box Plot of EDSS in Secondary Progressive MS (SPMS)

Figure 4

See image above for figure legend.