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Eyes closed single-leg stance test detects subtle sensorimotor decline in early multiple sclerosis

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Title page

Title: Eyes Closed Single-Leg Stance Test Detects Subtle Sensorimotor Decline in Early Multiple Sclerosis

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Abstract

Background: High-efficacy therapies for multiple sclerosis (MS) have led to an increase in patients presenting with lower Expanded Disability Status Scale (EDSS) scores, necessitating robust, sensitive measures to detect early sensorimotor impairment.

Objectives: To identify and validate a balance-based clinical assessment tool capable of detecting subtle sensorimotor deficits in individuals with early-stage MS.

Methods: This prospective case-control study enrolled 71 patients with MS and 45 matched healthy controls (HCs). Subgroup analysis included patients with early-stage MS (EDSS ≤2.0; n=30) and 28 matched HCs. Participants performed ten postural balance tasks using wearable inertial sensors. We developed a composite score integrating the most sensitive measures, which was subsequently validated in an independent external cohort.

Results: Timed 25-Foot walk (T25FW) failed to distinguish early MS from HCs, whereas eyes-closed single-leg stance (SLS) duration demonstrated superior discriminative ability (AUC=0.75 ± 0.06; validation: AUC=0.85 ± 0.07). Only 19% of people with early MS completed the 30-second SLS test versus 71% of HCs. SLS duration showed moderate correlation with the EDSS (r=-0.63). The composite score combining SLS, 9-Hole Peg Test and T25FW improved overall diagnostic performance (AUC=0.82 ± 0.03, r=0.74).

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Conclusions: The eyes-closed SLS test is a simple, no-cost tool that showed moderate to strong clinical validity for detecting early sensorimotor impairment in pwMS. Its diagnostic utility is further optimized when integrated with standard clinical assessments, supporting its potential as a pragmatic outcome measure in the era of high-efficacy therapies.

Keywords: multiple sclerosis, postural balance, single leg stance, early disability detection, sensorimotor impairment, balance assessment.

INTRODUCTION

Multiple Sclerosis (MS) is a complex neuroinflammatory disorder characterized by heterogeneous clinical manifestations affecting motor, sensory, and cognitive functions. The therapeutic landscape for MS has undergone a remarkable transformation over the past two decades, with the advent of highly effective disease-modifying therapies substantially altering the natural history of the disease, leading to a contemporary patient population with significantly lower disability levels, and slower progression rates [1–3]. This paradigm shift means that traditional outcome measures, developed for more severely affected patients, may now lack the sufficient sensitivity to detect subtle but clinically meaningful changes in early-stage disease [4–7].

The Expanded Disability Status Scale (EDSS) [8], developed more than four decades ago, remains the gold standard for disability assessment despite well-recognized limitations. Its ordinal nature, physician-dependent scoring,

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and emphasis on ambulatory function render it insensitive to early functional changes, particularly in individuals with minimal clinical disability [5]. Similarly, the Timed 25-Foot Walk (T25FW), a standard measure of ambulatory function [9] and lower limb component of Multiple Sclerosis Functional Composite (MSFC) [10], has demonstrated limited discriminative ability in early-stage people with MS (pwMS) who typically maintain preserved walking speed [11–13]. This creates a significant diagnostic gap, where subclinical functional impairments in sensorimotor reserve can accumulate undetected, potentially delaying opportunities for timely interventions.

Balance impairment is a prime candidate to fill this gap. Previous studies have shown that balance impairment is prevalent in MS [13,14]. Importantly, balance deficits can manifest even in the earliest stages of the disease, often preceding clinically apparent gait limitations [6,15–17]. The pathophysiology of balance dysfunction in MS is multifactorial, involving disintegration of proprioceptive control and complex disruptions across the somatosensory, visual, and vestibular systems that are essential for maintaining postural control [18–22]. Postural control impairment can also be detected in patients with a negative Romberg sign when more sensitive measurement methods are used [23]. These findings indicate that postural control systems are among the earliest to be affected by the MS disease process, making balance assessment a potentially valuable tool for early disability detection.

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Recent advances have introduced sensor-based technologies utilizing inertial measurement units (IMUs), which have shown promising sensitivity in capturing subtle balance and gait abnormalities in minimally disabled pwMS [11,13,15,23–27]. However, their widespread adoption in routine clinical practice remains limited due to high costs, technical demands, and complex data interpretation. These limitations underscore the need for simple, cost-effective, and clinically practical performance-based tests that can be readily integrated into routine neurological examinations while maintaining high sensitivity for early disability detection.

Given the requirement for sensitive, pragmatic, and clinically meaningful outcome measures in the era of highly effective disease-modifying therapies for MS, we investigated whether challenged balance tasks could sensitively detect sensorimotor impairment in patients with early-stage MS. This study aimed to identify and validate a robust, balance-based clinical protocol for quantifying sensorimotor deficits in this population.

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METHODS

Study cohorts and ethics

This prospective case-control study follows the STROBE guideline for observational studies. Approval for this study was granted by the Koç University Ethical Committee (2020.418.IRB.157), aligning with the Declaration of Helsinki. Written informed consent was obtained from all participants.

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The study included a discovery cohort and an independent, external validation cohort. The discovery cohort consisted of individuals with MS (All MS group) and age- and sex-matched healthy controls (All HC group). PwMS in the initial discovery cohort were prospectively recruited at the Koç University Hospital Neurology Clinic between September 2021 and August 2022. Inclusion criteria of the MS group were: 1) an EDSS score ≤6, 2) no new relapses in the last six months, and 3) the capability to perform balance tasks without aid. Exclusion criteria included having another condition affecting gait and balance. An age and sex-matched healthy control group (HC) was recruited from patient relatives or hospital staff.

For the analysis of the early-stage disease, which is the focus of our study, we defined the subgroup of participants with the EDSS scores between 0 and 2 (0≤EDSS≤2) as the Early MS group, and their age and sex-matched controls as the Early HC group.

The external validation cohort was recruited from Kocaeli University Hospital, Kocaeli, Türkiye, to confirm the primary findings independently. Participants underwent the same assessment protocol as the discovery cohort, including the postural balance assessment. To ensure consistency, postural balance analysis was conducted by the same researcher (K.A.) using the same sensor-based system at both study sites.

Clinical measures

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Clinical data and EDSS score were obtained by the MS experts. Additionally, we assessed cerebellar dysfunction using the Scale for Assessment and Rating of Ataxia (SARA) score [28] hand dexterity via the 9-Hole Peg Test (9-HPT; calculated as the mean of two trials per hand, averaged across both hands) [29], and functional mobility using the Timed 25-Foot Walk (T25FW) duration [9]. The 12-item Multiple Sclerosis Walking Scale (MSWS12) was filled out by the participants as a measure of patient-reported outcome for subjective walking performance [30].

Postural balance assessment protocol

Postural balance assessments were conducted using the inertial measurement unit (IMU) based wireless APDM OPAL sensors (MobilityLab, Oregon, USA). Recordings of the discovery cohort were done at the Movement Analysis Laboratory at the Koç University Research Center for Translational Medicine (KUTTAM), and the validation cohort were recorded in a suitable room at Kocaeli University Hospital. Two OPAL sensors were placed on the feet, while one was secured at the L5 lumbar level. Postural sway metrics were automatically computed by MobilityLab software previously validated and explained in detail by Mancini et al [31]. The duration of stance for each task was timed with a chronometer.

To identify the most sensitive postural balance task in early MS, all participants were asked to complete ten balance tests of varying difficulty. Tests were performed barefoot, with arms crossed over the chest and eyes

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focused on a fixed point at eye level on the wall (fixed distance of three meters) for a maximum duration of 30 seconds per test. This duration, derived from the APDM system's default protocol, increases task demand to enhance sensitivity for detecting impairment, consistent with findings in sports-related concussion research [32]. Test termination occurred if the participant stepped off the platform, the non-stance foot touched the ground, the participant opened their eyes during eyes-closed tasks, or the participant requested to stop. Both successful completion status (yes/no) and actual stance duration were recorded as separate outcome measures for all trials. Individual stance duration scores ranged from 0 seconds (for participants unable to maintain the stance) to 30 seconds (for those who completed the full trial). Sensor-based parameters were included in the statistical analysis only for trials successfully completed for the full 30-second duration.

The postural balance tasks included: Standing on a firm surface, feet apart (heels 10 cm apart), eyes open (EO)/eyes closed (EC); standing on a foam pad, feet apart, EO/EC; standing on a firm surface, feet together (toes and heel touching) EO/EC; tandem stance with the right foot forward (Tandem-Right) EO, tandem stance with the left foot forward (Tandem-Left) EO; tandem stance with the dominant foot forward eyes closed (Tandem-EC); and single leg stance on the non-dominant foot eyes closed (SLS). Leg dominance was determined by asking the participants which leg they would use to kick a ball. Participants were permitted breaks between trials as needed. Tasks on the foam were performed on a 48x40x6 cm foam pad (balance-pad, Airex).

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Standing on firm surface (feet apart) and standing on foam pad (feet apart) are components of the modified Clinical Test of Sensory Interaction in Balance (mCTSIB) [33]; standing with feet together-EC, Tandem-EC and SLS are items of the modified Balance Error Scoring system (mBESS) [34].

Statistical Analysis

Normality assessment was performed using the D'Agostino & Pearson and Anderson-Darling tests. Descriptive statistics are presented as mean ± standard deviation (SD) for normally distributed variables and median with interquartile range (IQR) for non-normally distributed variables.

Between-group comparisons were performed using two-sample t-test or Mann-Whitney U tests for continuous variables and Fisher's exact test for categorical variables. Group comparisons included: Early MS vs Early HC, and All MS vs All HC, for demographic characteristics, balance task performance, and sensor-based balance parameters.

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The completion rates of postural balance tests were compared using Fisher's exact test, and task duration comparisons and effect sizes were analyzed using Mann Whitney U-Test and Cliff's delta. For sensor-derived parameters, appropriate parametric or non-parametric tests were selected based on data distribution. Receiver Operating Characteristics (ROC) analysis was used to evaluate the discriminatory ability of balance parameters distinguishing individuals with Early MS from Early HC. The area under the curve (AUC)

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was calculated for significant parameters and AUC between above 0.70 were considered indicative for discriminative ability.

To assess clinical validity, Spearman's rank correlation analysis was performed between key outcomes and clinical measures and MSWS12.

A composite score was developed by calculating z-scores for selected tests (SLS, 9-HPT, T25FW), adapting the structure of the Multiple Sclerosis Functional Composite (MSFC) [10]. To create the composite score, the SLS duration value was multiplied by -1 before integrating. This step aligned its directionality with T25FW and 9-HPT, where higher scores indicate worse performance. The composite score's discriminative ability and correlation with EDSS were assessed using ROC analysis and Spearman correlation.

In the external validation cohort, discriminant ability and clinical utility of SLS duration were assessed using ROC analysis and Spearman correlation, respectively.

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Statistical significance was set at $p < 0.05$. All analyses and visualizations were conducted using GraphPad Prism software (version 8.2, GraphPad Software Inc., La Jolla, CA, USA) and RStudio (version 2025, Posit Software, PBC).

A post-hoc power analysis was conducted using G*power software (version 3.1.9.7, University of Dusseldorf), with SLS duration as the primary outcome, revealed a large effect size (Cohen's d=0.88) between Early MS and Early HC, indicating our sample was adequately powered to detect this difference.

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RESULTS

Characteristics of the discovery cohort

A total of 71 individuals with multiple sclerosis (All MS) and 45 healthy controls (All HC) were recruited as the discovery cohort. Given the study's focus on detecting early disability, we performed a separate analysis on the subgroup of participants with Early MS (0≤EDSS≤2, n=30) and corresponding age- and sex-matched healthy controls (Early HC, n=28). The demographic and clinical characteristics of participants are detailed in Table 1 and Supplementary Tables 3 and 4.

In the All MS group, durations for both T25FW ($p<0.001$) and 9-HPT ($p<0.001$) were significantly longer than in the All HC group, as expected. However, in the Early MS group, T25FW duration did not significantly differ from the Early HC group, indicating limited sensitivity for detecting subtle disability in this population.

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Table 1: Demographic and clinical characteristics of the discovery cohort.

	Early MS (n=30)	**Early HC (n=28)**	**p-value**	**All MS (n=71)**	**All HC (n=45)**	**p-value**
Age, years Mean ± SD	30.6 ± 8.3	31.3 ± 8.4	ns	39.5 ± 12.6	39.7 ± 13.7	ns
Sex F:M (F%)	19:11 (63%)	19:9 (68%)	ns	52:19 (73%)	27:18 (60%)	ns

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Height, cm Mean ± SD	169.2 ± 11.3	167.7 ± 9.6	ns	166.3 ± 10	167.2 ± 9.3	ns
BMI, kg/m² Median (IQR)	24 (21.7-27.5)	25.2 (20.7-27.5)	ns	24.6 (21.9-27.7)	25.2 (21.1-28.1)	ns
Duration since diagnosis, years Median (IQR)	4.5 (2.8-11.2)	-	-	8 (3-13)	-	-
Duration since the last relapse, months Median (IQR)	36 (24-60)	-	-	48 (24-96)	-	-
EDSS, score Median (IQR)	1.3 (1-2)	-	**-**	2.5 (1.5-4)	-	**-**
FS scores- Cerebellum, (n%) 0 1 2 3 4	(97%) - (3%) - -	-	-	(72%) (3%) (18%) (6%) (1%)	-	**-**
SARA, score Median (IQR)	0 (0-0.1)	-	**-**	1 (0-3)	-	**-**

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9-HPT, seconds Median (IQR)	20.9 (19.8-22.1)	19.3 (17.8-21)	**0.008**	22.3 (20.6-27.1)	19.9 (18.1-22.1)	**<0.001**
T25FW, seconds Median (IQR)	4.6 (4.2-4.8)	4.4 (4.1-4.9)	ns	4.9 (4.5-6.7)	4.4 (4.1-5)	**<0.001**
MSW-12, score Median (IQR)	13 (12-18.5)	-	-	21.5 (13.3-37)	-	-

Abbreviations: BMI, Body Mass Index; EDSS, Expanded Disability Status Scale; FS, Functional Systems, SARA, Scale of Assessment and Rating of Ataxia; 9-HPT, Nine hole peg test; T25FW, Timed 25-Foot Walk; MSW-12, 12-Items MS Walking Scale.

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The eyes closed single-leg stance test is the only postural balance task that can discriminate individuals with early MS from healthy controls

Among the 10 balance tasks, only the Single Leg Stance (SLS) test distinguished the Early MS group from the Early HC group. A higher percentage of participants in the Early HC group successfully completed the 30-second SLS test (71%) compared to the Early MS group (19%, $p < 0.001$; see Figure 1). Additionally, the median stance duration was significantly shorter in the Early MS group compared to the Early HC group ($p < 0.001$; see Table 2). Cliff's delta values indicated moderate to large effect sizes for Early MS (-0.46) and All MS (-0.62), suggesting robust performance in detecting disability in both MS groups.

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For the All MS group, completion rates were significantly lower than in the All HC group for the feet apart-eyes open (FA-EO), feet together-eyes closed (FT-EC), Tandem-Right, Tandem-Left, Tandem-EC and the SLS tests (see Figure 1 and Table 2 for details).

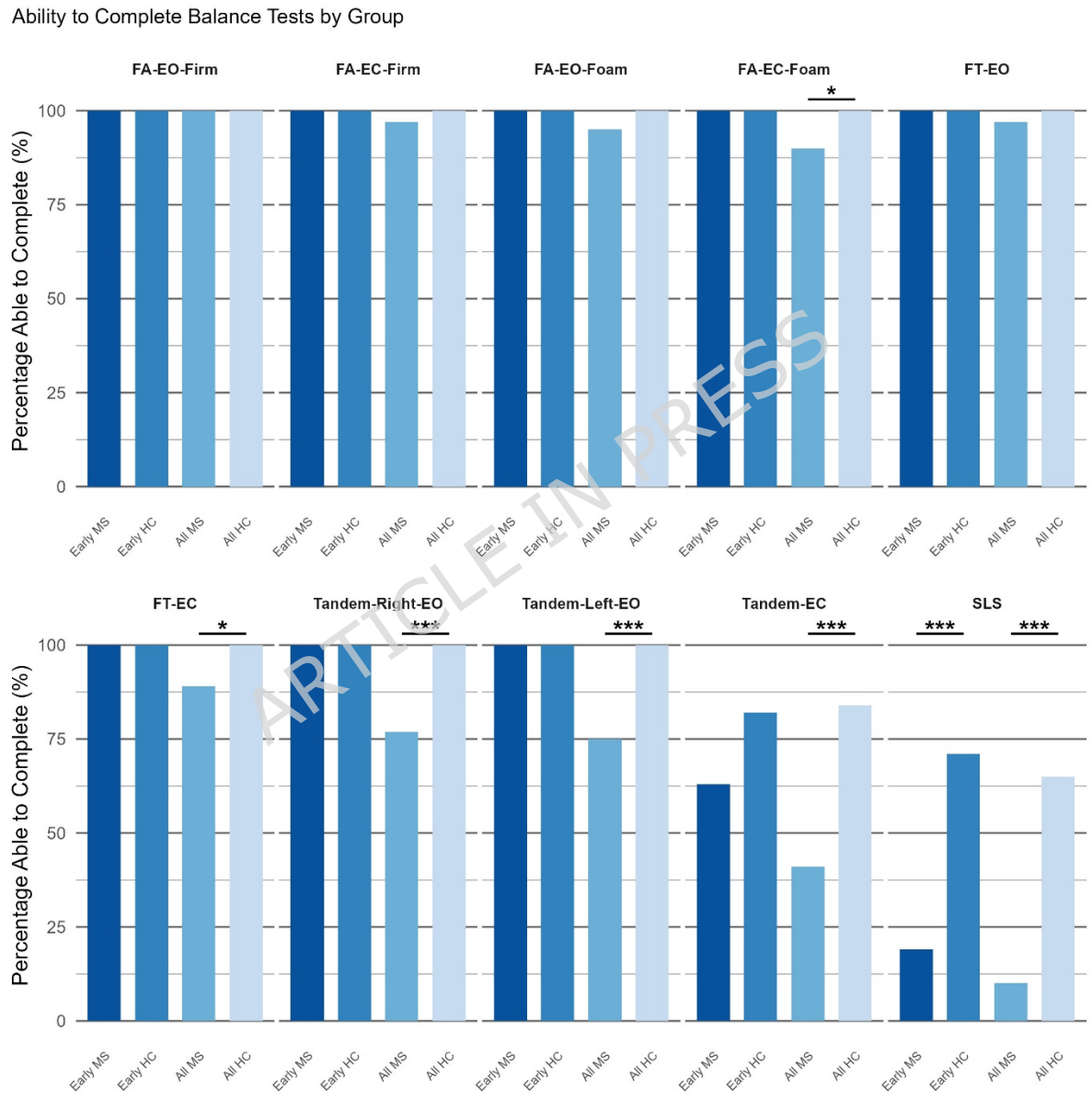


Figure 1: Completion rates for balance tests in the discovery cohort. Bars represent the percentage of participants in each group who successfully

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completed the full 30-second duration for each balance tests. Asterisks represent the significance level with p-value of *, $p<0.05$; ***, $p<0.001$. Abbreviations: FA-EO, feet apart eyes open; FA-EC, feet apart eyes closed; FT-EO, feet together eyes open; FT-EC, feet together eyes closed; SLS, single leg stance.

Table 2. Statistical comparison of the median durations of the postural balance tests.

Balance tests	**Early MS (n=30)**	**Early HC (n=28)**	**Cliff's delta**	**p-value**	**All MS (n=71)**	**All HC (n=45)**	**Cliff's delta**	**p-value**
FA-EO-Firm, seconds Mean	30	30	0	na	30	30	0	na
FA-EC-Firm, seconds Median (IQR)	30 (30-30)	30 (30-30)	0	na	30 (30-30)	30 (30-30)	-0.03	ns
FA-EO-Foam, seconds Median (IQR)	30 (30-30)	30 (30-30)	0	na	30 (30-30)	30 (30-30)	-0.05	ns

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FA-EC-Foam, seconds Median (IQR)	30 (30-30)	30 (30-30)	0	na	30 (30-30)	30 (30-30)	-0.10	**0.02**
FT-EO, seconds Median (IQR)	30 (30-30)	30 (30-30)	0	na	30 (30-30)	30 (30-30)	-0.03	ns
FT-EC, seconds Median (IQR)	30 (30-30)	30 (30-30)	0	na	30 (30-30)	30 (30-30)	-0.11	**0.01**
Tandem-Right, seconds Median (IQR)	30 (30-30)	30 (30-30)	0	na	30 (30-30)	30 (30 – 30)	-0.23	**<0.001**
Tandem-Left, seconds Median (IQR)	30 (30-30)	30 (30-30)	0	na	30 (25-30)	30 (30-30)	-0.25	**<0.001**

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Tandem-EC, seconds Median (IQR)	30 (22.3-30)	30 (30-30)	-0.17	ns	16 (6-30)	30 (30-30)	-0.50	**<0.001**
SLS, seconds Median (IQR)	15 (8.4-28)	30 (20-30)	-0.46	**<0.001**	8.4 (2.9-17)	30 (14-30)	-0.62	**<0.001**

Abbreviations: FA-EO, Feet Apart-Eyes Open; FA-EC, Feet Apart-Eyes Closed; FT-EO, Feet Together-Eyes Open; FT-EC, Feet Together-Eyes Closed; SLS, Single Leg Stance. na, not applicable; ns, not significant

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Analysis of effect sizes across SLS, 9-HPT, and T25FW durations in early MS

The scatterplots depicting the durations of SLS, 9-HPT, and T25FW are presented in Figure 2. The durations of 9-HPT (mean difference: -1.65; 95% CI: -2.86, -0.42, p=0.008) and SLS (mean difference: 10; 95% of CI: 1.2, 15; p<0.001) were significantly longer in the Early MS group compared to the Early HC group, whereas no significant difference was observed for T25FW duration (mean difference: 0.005; 95% of CI: -0.27, 0.28; p=0.97). The effect size for SLS duration was larger than that for 9-HPT duration (Cliff's delta: -0.46 vs. 0.42).

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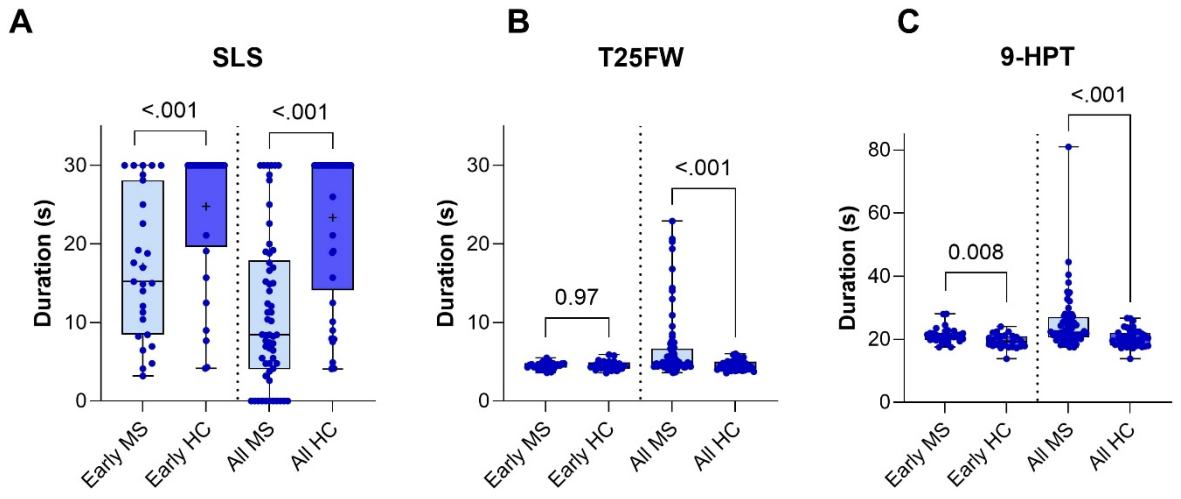


Figure 2: Performance on core functional tests in early and all MS cohorts. Scatter plots show individual data points for (A) Single-Leg Stance (SLS), (B) Timed 25-Foot Walk (T25FW), and (C) 9-Hole Peg Test (9-HPT). Horizontal lines indicate the median and interquartile range. P-values were derived from Mann-Whitney U-test comparing MS and HC groups.

Discriminative value of sensor-based sway metrics in early MS.

We next evaluated whether sensor-based sway metrics could effectively detect early disability in MS. To mitigate potential selection bias, tasks that were not completed by a substantial proportion of patients with MS, specifically the tandem stance and SLS, were excluded from the selection process for sensor-based parameters (Figure 1, Supplementary Table 1). Among the remaining assessments, sensor-based metrics derived from three balance tasks (standing on a foam pad with feet apart, eyes open/closed; and standing on a firm surface with feet together, eyes closed) consistently revealed statistically significant differences between the Early MS and Early

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HC groups (Supplementary Table 1). Parameters yielding the highest discriminative value included sway area, RMS sway (total, coronal and sagittal), and range (total, coronal and and), and path length (sagittal) with AUC values ranging from 0.66 to 0.73 ($p < 0.05$; Supplementary Table 2).

SLS duration shows the highest discriminatory ability in early MS

After identifying the most disability-sensitive balance tasks and sway metrics for early-stage MS, we evaluated their discriminative performance against the T25FW and 9-HPT using ROC curve analysis. While the T25FW failed to distinguish patients with early-stage MS from HCs, the 9-HPT showed acceptable discriminative ability (AUC=0.71 ± 0.07, p=0.008). Among all parameters, SLS duration yielded the highest AUC (AUC=0.75 ± 0.06, p=0.002) (Figure 3).

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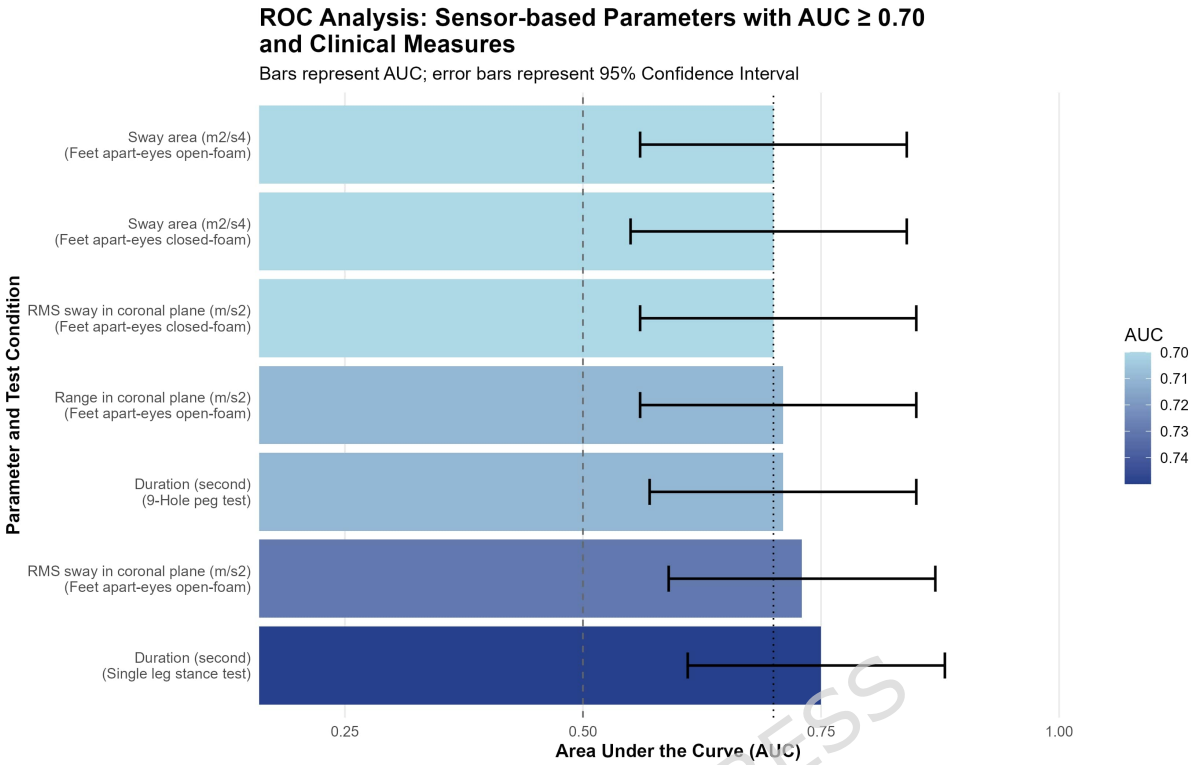


Figure 3: Discriminative ability of the top-performing sensor-based and timed balance and clinical measures. The bar plot displays the Area Under Curve (AUC) from ROC analyses discriminating between Early MS and Early HC participants. Only parameters with an AUC> 0.70 are shown. Error bars represent the 95% Confidence Interval.

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SLS shows clinical validity as a measure of disability in MS

Next, we conducted correlation analysis between the clinical and digital disability measures in the All MS cohort (Figure 4). The SLS duration demonstrated moderate-to-strong correlations with the EDSS (r=-0.63, p<0.001), SARA scores (r=-0.73, p<0.001), 9-HPT (r=-0.64, p<0.001) and T25FW durations (r=-0.64, p=0.004), indicating good concurrent validity

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comparable to established clinical measures. Sensor-based parameters recorded on foam also exhibited moderate to high positive correlations with EDSS and SARA scores, T25FW and 9-HPT durations, and MSW12 scores.

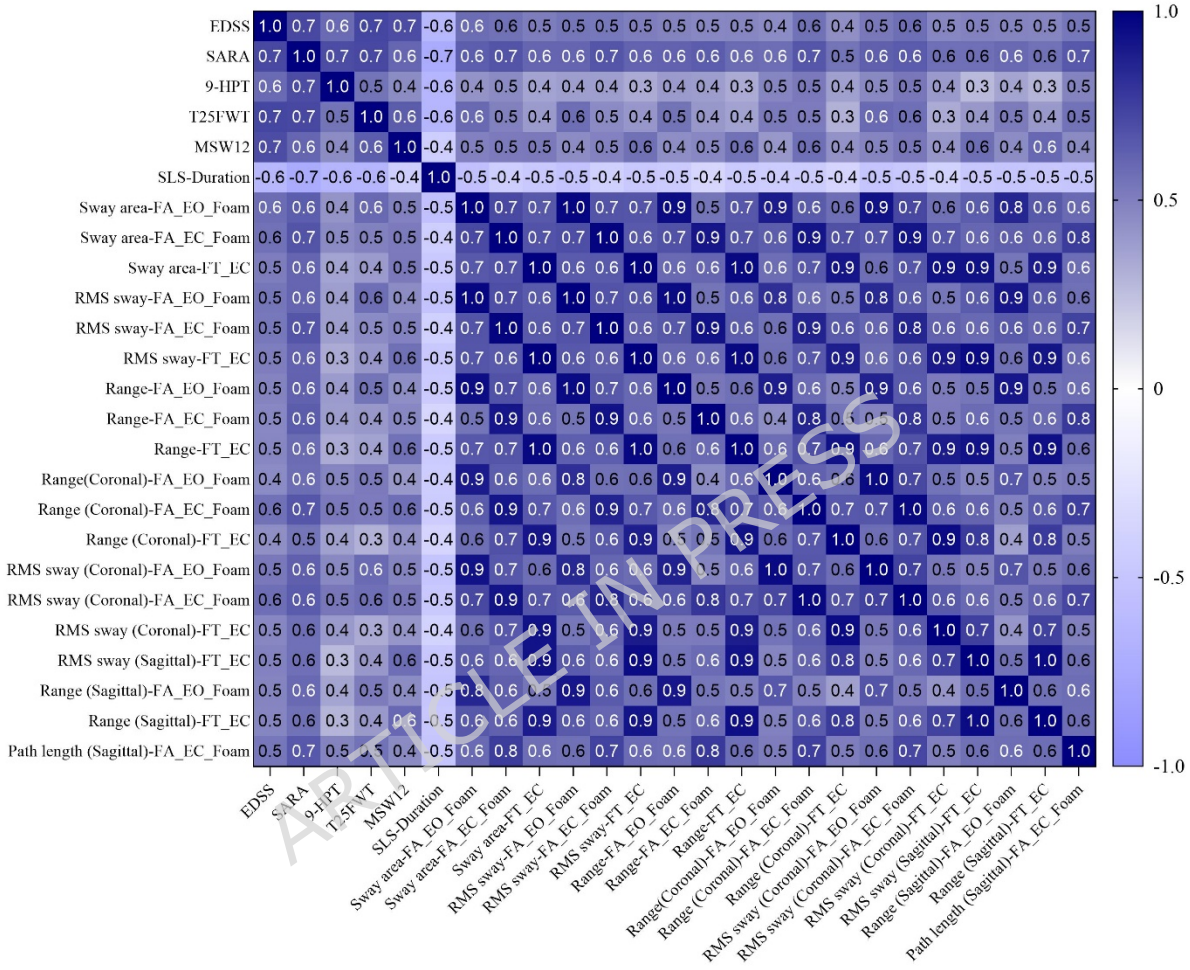


Figure 4: Heatmap of correlations between balance measures and clinical outcomes in the All MS cohort. The matrix displays Spearman's rank correlation coefficient (r) between the most discriminative balance parameters and established clinical measures. Darker colors indicate stronger correlations. Abbreviations: EDSS, Expanded Disability Status Scale; SARA, Scale of Assessment and Rating of Ataxia; 9-HPT, Nine hole peg

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test; T25FW, Timed 25-Foot Walk; MSW12, 12-Items MS Walking Scale; FA_EO_Foam, feet apart eyes open on foam; FA_EC_Foam, feet apart eyes closed on foam; FT_EC, feet together eyes closed.

A Multidimensional Composite Score for Enhanced Clinical Correlation and Diagnostic Sensitivity Across the MS Spectrum

To assess whether incorporating SLS duration adds value to the T25FW and 9-HPT in the All MS cohort, we calculated a composite score by computing and averaging z-scores for all three tests. To ensure that higher scores consistently indicate greater impairment, the z-score for SLS duration was multiplied by –1 before integration.

While the discriminative ability (AUC = 0.82 ± 0.03) of the composite score is comparable to the most sensitive single measures, it provides a superior balance of diagnostic performance and clinical validity across the entire disability spectrum. Specifically, the composite score achieved the highest correlation with the EDSS (r = 0.74) and a highly stable AUC, suggesting that integrating these distinct sensorimotor domains (balance, upper limb function and lower limb mobility) yields a more comprehensive and clinically representative marker of disability than any single measure alone (Table 3).

Table 3. Discriminatory ability and clinical validity of the novel functional composite score in discovery cohort.

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	AUC ± SD	95% CI	Correlation with EDSS (r)	p-value
$T25FW_z$	0.72 ± 0.04	0.63 – 0.82	0.71	**<0.001**
$9\text{-}HPT_z$	0.75 ± 0.04	0.65 – 0.84	0.58	**<0.001**
SLS_z	0.83 ± 0.04	0.75 – 0.91	-0.63	**<0.001**
$Composite_z$ (T25FW + 9 HPT - SLS)	0.82 ±0.03	0.74 – 0.90	0.74	**<0.001**

Abbreviations: AUC, Area Under Curve; SD, Standard Deviation; CI, Confidence Interval; T25FW, Timed 25-Foot Walk; 9-HPT, 9-Hole Peg Test; SLS, Single Leg Stance

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External validation confirms SLS test performance

To confirm generalizability of our findings, we analyzed the data from an external validation cohort including age and sex matched individuals with MS (n=20) and HC (n=19) from Kocaeli University Hospital, Türkiye. The mean (±SD) age of the MS group was 41 (±12), and 39 (±11) for the HC group (p=0.57). EDSS range was 0 to 2 (median, IQR=1.5, 1-1.5). The SLS duration remained significantly reduced in this validation cohort (mean ± SD = 9 ± 7.1), compared HCs (mean ± SD = 20 ± 8.9, p<0.001). The ROC analysis revealed an AUC of 0.85 (SD = 0.07, 95% of CI: 0.72-0.98, p<0.001),

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confirming the excellent discriminative performance of SLS for disability in early MS. SLS duration correlated moderately with EDSS (r=-0.53, p=0.01), supporting its robustness as a surrogate of early disability in MS. The demographical and test results are presented in Supplementary Table 5 and 6, and Supplementary Figure 1.

DISCUSSION

This study demonstrates that the eyes-closed SLS test is a highly sensitive and clinically valid tool for detecting sensorimotor disability in MS. The test shows superior discriminative performance compared to traditional clinical measures and sophisticated sensor-based assessments. Our findings reveal an important disconnect between conventional clinical evaluations and underlying neurological function: while the T25FW failed to differentiate early-stage pwMS from healthy controls, the SLS test demonstrated that 81% of individuals with early MS (0≤EDSS≤2) were unable to stand for the whole test period of 30 seconds, compared to approximately 30% of healthy controls, with significantly reduced stance duration between the groups. The moderate-to-large effect size observed (Cliff's delta -0.46 for Early MS, -0.62 for All MS) and the significant, moderate discriminative ability (AUC=0.75) of the SLS duration underscore its potential as a clinically useful tool for detecting subtle sensorimotor impairment. The robustness of these findings was confirmed in an external validation cohort, where the SLS duration achieved even higher discriminatory ability (AUC=0.85), demonstrating its generalizability across different clinical settings. Moreover, integrating the

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SLS test into a composite score with T25FW and 9-HPT achieved both superior discriminative performance (AUC=0.82) and a moderate correlation with EDSS (r=0.74) compared to the individual measures, reinforcing its potential as a clinical tool.

Our results align with and extend previous research demonstrating that balance is impaired from the earliest stage of MS, including pwMS with minimal or no clinical disability. Martin et al. were among the first to report that balance impairment is detectable in recently diagnosed pwMS with EDSS scores 0-2.5 without pyramidal dysfunction [6] . Later, Spain et al. used IMU sensors to reveal impaired balance under eyes-closed condition on a firm surface, despite no difference in T25FW duration between pwMS (median EDSS score=3) and HC groups [11]. Our study builds upon this foundation by identifying a specific, standardized test that can reliably capture these early balance deficits in routine clinical practice.

The high discriminative performance of the SLS test in our study is consistent with recent literature emphasizing the need for more challenging balance tasks to reveal subtle impairments in early MS [7,26,35]. Such as, Carpinella et al. demonstrated that the modified Romberg test on foam with IMU sensors reveals balance impairments in pwMS with a median EDSS score of 1.5 [15]. Brandstadter et al. reported that both standing and dynamic balance were found to be impaired in pwMS without any objective or subjective gait dysfunction (median EDSS=1) [13]. Moreover, balance metrics had a stronger correlation with MRI volumetric measures compared to EDSS and

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T25FW. Finally, Krieger et al. reported that in pwMS with an EDSS score of zero, subclinical sensorimotor impairment can be detected by high-challenge measures of balance, but not by T25FW and 9-HPT, and a composite balance score was correlated both with MRI T2 lesion volume and thalamic volume [16]. Collectively, these studies and our results demonstrate that subclinical balance impairment is a frequent sign of sensorimotor disability in early MS, and widely used clinical tools such as the EDSS and T25FW may not be sufficiently sensitive to detect such impairments in this stage of MS. Our study advances this concept by showing that a simple, challenging postural balance test, the eyes-closed SLS, can achieve a high discriminative ability without requiring sophisticated instrumentation.

While we found that sensor-based sway metrics demonstrate statistically significant differences between early MS and healthy controls, particularly during challenging conditions such as standing on foam surfaces, their discriminative performance (AUC 0.66-0.73) was slightly lower than the SLS duration (AUC 0.75). To our knowledge, this is the first study that has investigated the discriminative performance and clinical validity of SLS duration in comparison to sensor-based sway metrics. Measuring SLS duration has distinct advantages compared to sensor-derived parameters. SLS duration can be interpreted easily by clinicians, requires minimal equipment for measuring and can be administered rapidly. Conversely, sensor-based assessments provide detailed biomechanical insights that may be valuable for research applications and a mechanistic understanding of

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balance dysfunction. The moderate to strong correlations observed between foam-based sensor parameters and clinical outcome measures (EDSS, SARA, T25FW, 9-HPT, MSWS-12) suggest that these measurements also capture clinically relevant aspects of postural control.

The eyes-closed SLS is a critical component of the mBESS, which has an established clinical utility in detecting mild traumatic brain injury, particularly in sports concussion [34]. Despite, the eyes-open SLS test was more widely used in neurology, the eyes-closed SLS test has only rarely been tested in neurological disorders. The eyes-open SLS test has been used to measure fall risk and postural instability in the elderly population with or without Parkinson's disease [36,37]. Chomiak et al. found that low a SLS duration is a strong predictor of lower UPDRS-III motor performance [36]. Oliveira et al. used a force platform to measure center of pressure area and sway velocity during the SLS test and reported that these parameters can differentiate fallers and non-fallers [37]. In the MS field, the SLS has previously been employed as a component of broader postural assessment batteries, comparing different disability levels, with or without IMU-sensors [7,38–41]. Berg-Hansen et al. demonstrated significant differences in 60-second eyes-open SLS performance between healthy controls and MS groups with lower (EDSS<4) and higher (EDSS≥4) disability, with sensor-derived parameters showing increased sensitivity in the higher disability cohort [40]. Our findings corroborate previous research by Fry et al. [42], who reported a significant correlation between SLS duration and EDSS (r=-0.645,

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p<0.001) in a heterogenous MS cohort (mean EDSS= 3.8 ± 1.72). In our study, we use the eyes-closed version of SLS to achieve an increased sensitivity for detection of sensorimotor disability, as in the mBESS test, and our results demonstrate that eyes closed SLS duration has a high discriminatory ability in MS, including the early-stage. We also showed the good clinical validity of the eyes-closed SLS duration, evidenced by moderate correlations with established outcome measures (EDSS: r=-0.63; SARA: r=-0.73; T25FW: r=-0.64; 9-HPT: r=-0.64), demonstrating that this simple assessment captures clinically meaningful aspects of MS-related disability.

These findings are not surprising when one considers the number of neurological systems that need to be intact to stand still on one foot with eyes closed. We propose that the eyes-closed SLS test functions as a neurological stress test that simultaneously challenges the integrity of multiple neural networks, including somatosensory pathways, vestibular processing, cerebellar coordination and corticospinal control [18,43,44]. The high failure rate (81%) in patients with otherwise normal cerebellar functional scores and Romberg tests suggests that subtle lesions across these interconnected pathways may act additively during this demanding postural task [45]. While individual functional testing may appear normal due to compensatory mechanisms and neural reserve, the SLS test's requirement for near-simultaneous optimal function across multiple systems and anatomical segments, such as trunk and lower extremities, reveals the cumulative impact of distributed MS-related dysfunction [43,44]. Therefore, eyes-closed SLS

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test can detect loss of sensorimotor reserve before it becomes clinically apparent through traditional neurological examination.

By incorporating SLS performance with established MSFC components (T25FW and 9-HPT) in a composite score, we showed that SLS test improves the discriminant and clinical validity of the individual components that measure sensorimotor function. This preliminary evidence suggests potential value for clinical trials and research applications, though longitudinal validation is required to establish clinical utility and predictive value for disease progression.

Limitations

The major limitation of this study is the cross-sectional design, which prevents the assessment of predictive value for disability progression. Also, unmeasured confounding factors such as fatigue may have influenced balance performance and introduced a bias that was not controlled for in our analysis. The proposed composite score does not incorporate measures of cognitive dysfunction, which is highly prevalent in MS and warrants inclusion in future digital phenotyping frameworks. Finally, although we validated our findings in an external cohort, large multi-center studies are needed to establish cut-off values and assess performance across diverse populations.

Conclusion

The eyes-closed SLS test offers superior discriminative ability for detecting sensorimotor disability in individuals with early-stage MS, outperforming

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both traditional clinical measures and sensor-based parameters. Its good discriminatory ability and clinical utility extend across the broader MS population. As a simple, objective and cost-effective measure requiring minimal equipment, the SLS test is well-suited for integration into routine neurological examination and clinical scales of sensorimotor disability. Future longitudinal studies are warranted to assess its predictive value and potential role in guiding therapeutic decisions.

Statements and Declarations:

Data availability statement: Data supporting the conclusions are available upon reasonable request to the corresponding author.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Ethical considerations: This study was approved by the Koç University Ethics Committee (2020.418.IRB.157), aligning with the Declaration of Helsinki.

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resources, writing-review and editing. **AV:** Conceptualization, supervision, writing- original draft preparation, writing-review and editing.

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