

Assessing fall risk in multiple sclerosis using patient-reported outcomes and wearable gait metrics

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Abstract

Background: Falls in people with multiple sclerosis (pwMS) lead to morbidity and expense.

Objective: Identify clinical metrics associated with falls.

Methods: Eighty-six pwMS completed fall surveys, timed 25-foot walk (T25FW), and motion analysis with Clario Opal devices. Logistic regression models were created.

Results: Median age was 54.5 years (range 21–73), 62% (53) were female. The cohort included 58% with relapsing (50) and 42% with progressive MS (36). Those who reported falling in the last year were older (median age 58 vs 52.5, $p = .03$) and had a higher Patient Determined Disease Step (PDDS) score (median 3 vs 1, $p < .0001$). Falls were associated with worse balance metrics including sway area (median 2.3 degrees² vs 1.2, $p = .01$), jerk (median 3.3 m²/s⁵ vs 1.6, $p = .005$), and slower T25FW (median 11.5 s vs 8; $p < .0001$). A multivariable regression model based on gait aid use and T25FW time >10.8 s ($c = 0.80$) was derived. Having both features portended a probability of falling of 0.97, while having neither, a probability of 0.26.

Conclusions: Falls in pwMS are more frequent in patients who are older, have higher PDDS, slower walking, and worse balance. Gait aid use and T25FW >10.8 s were strongly associated with falls in the past year.

Keywords: Biomarkers, multiple sclerosis, outcome measurement, quality of life, rehabilitation, symptomatic treatment

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Introduction

People with multiple sclerosis (pwMS) are at high risk of falls, with estimates between 50% and 75% of pwMS falling annually.¹ Falls lead to injury, decreased mobility and reduced quality of life.¹ Identifying patients at greatest risk of falls represents an important area for intervention.² Prior studies have shown that frequency of falls in clinical documentation is underestimated by about half,^{3,4} demonstrating the importance of developing predictive clinical tools. Currently, the optimal method for predicting and risk-stratifying patients who may have falls is not yet determined. Fall surveys,⁵ disability scores,⁶ and detailed gait and balance testing⁷ have all shown promise but each has

a differential potential benefit in terms of time, cost, and accuracy. Wearable devices are of interest as they offer objective, quantitative, and replicable data that have extensive potential for the study of MS.^{8–12} Wearable devices may be a useful tool in fall risk stratification and developing specific interventions based on detailed gait metrics.^{3,13} The Clario Opal device, previously called APDM (Clario wearable technologies, Philadelphia, USA), is an inertial measurement unit device that uses a triaxial accelerometer, gyroscope, and magnetometer that can be customized with different setups depending on measurement needs. The Opal device has been demonstrated to reliably measure gait and balance,¹⁴ and has been useful in fall risk

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Predictive Modeling of Fall Risk in pwMS using:

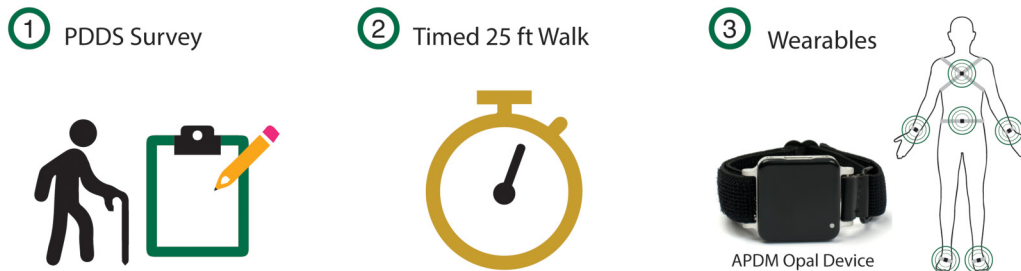


Figure 1. Methodology of survey and gait assessments. At the time of the assessment patients (1) completed surveys of fall history and patient determined disease steps (PDDS), (2) completed two trials of the timed 25 foot walk test, and (3) wearable gait assessment while wearing Opal device over the wrists (2), ankles (2), chest (1), and lumbar back (1).

assessment in Parkinson's disease,¹⁵ and progressive MS gait metrics.¹⁶ A recent study has used this device to evaluate fall risk longitudinally in patients with MS, finding ankle plantar flexion to be an important metric,¹⁷ however this design had limited ability to measure balance using only ankle sensors. Measures of balance, including postural sway and jerk, may be more useful for assessment of fall risk. Jerk, a measurement of postural stability measured as the rate of change in acceleration over time (m^2/s^5), and sway have been shown to account for much of the measurable differences in balance in pwMS,¹⁸ and may be improved with rehabilitation programs.¹⁹ In this study, we used a multimodal approach with surveys, traditional measures of walking speed, and in clinic gait analysis using a six sensor Opal system to characterize a cohort of pwMS and identify clinical metrics associated with falls.

Methods

Patient identification

This study was approved by the Institutional Review Board of Mayo Clinic, Rochester, Minnesota (Institutional Review Board 08-007846), and all patients gave written consent for the use of their medical records and gait analysis for research purposes. Patients seen in the MS clinic at Mayo Clinic in Rochester, MN with a diagnosis of MS were offered enrollment into the Center for MS and Autoimmune (CMSAN) biorepository with wearable gait assessment (Figure 1). A total of 86 pwMS were enrolled that had survey and gait assessment completed, all patients were included.

Survey evaluation

Patients filled out surveys using tablet devices at the time of gait assessment. Surveys included Patient

Determined Disease Steps (PDDS)^{20–23} (https://www.narcoms.org/_files/ugd/826c66_b39d4958805541efbd f3dd2b81ec80d5.pdf) and quantification of falls in the last year. Patients were asked if they had fallen in the last year, and falls were reported as: none in the last year, less than once per month, 1 per month to 1 per week, or more than 1 per week.

Gait assessment

Participants completed two trials of a timed 25-foot walk (T25FW) assessment with patients instructed to walk at their natural pace in comfortable shoes. The fastest of the two trials was analyzed. Patients then completed one trial of gait and balance tasks on a firm surface while wearing Opal V2R Devices (Clario, Philadelphia, USA), including: (1) standing with feet apart eyes open, (2) standing with feet apart eyes closed, and (3) stand up and walk (SAW). Patients were monitored for 30 s while standing quietly with feet 15 cm apart and their hands on their hips with eyes open and closed on a firm surface. During the SAW trial, the patients started standing, upon hearing a tone they were directed to walk at their natural pace and walked 10 feet until reaching a marker on the floor, turned 180 degrees, returned and walked 10 feet back, and repeated this cycle.

Opal devices were placed over the sternum (one sensor), lumbar back (one sensor), bilateral wrists (two sensors), and feet (two sensors) (Figure 1). The Opal device includes an accelerometer with a dynamic range of ± 200 g, gyroscope with range of $\pm 2000^\circ/\text{s}$, magnetometer with range of ± 8 Gauss, and barometer with range of 300–1100 hPa. Gait metrics were recorded at a sampling rate of 128 Hz in Mobility Lab software version 2 (Clario, Philadelphia, USA) and processed according to

provided program specifications which uses data from all sensors to create a three-dimensional motion matrix to calculate gait parameters. During the quiet standing tasks, sway area (degrees²) and jerk (m²/s⁵) were evaluated. SAW metrics evaluated included lower limb gait speed (m/s), and lower limb double support time (as a percentage of gait cycle time). The faster leg was used for analysis of speed. Gait testing was performed with a gait aid in those who required it to safely complete these tests (unilateral, $n=6$; bilateral, $n=3$; all who had fallen in the last year). Devices are calibrated monthly and additionally as needed if device error occurs according to device specifications.

Statistical analysis

Continuous variables were analyzed with Wilcoxon rank sum and categorical variables with chi square tests. All tests were two-sided and p -values less than .05 were considered statistically significant. We used univariable and multivariable logistic regression analyses with falls in the last year as a binary outcome to assess the associations with predictor variables. The area under the receiver operating characteristic (ROC) curve was estimated as the ability of the model to discriminate between individuals who fell in the last year and those who did not. An area under the ROC estimate of 0.7–0.8 was regarded as acceptable, 0.8–0.9 as excellent, and more than 0.9 as outstanding.²⁴ We used ROC curve analysis to identify the cutoff to dichotomize T25FW time. A PDDS cutoff of 3 or less (no gait aid) and 4 or more (gait aid) was used for binomial review. Analysis was performed with SAS software version 9.4 (SAS Inc., Cary, NC).

Data availability

Anonymized data used for this study are available from the corresponding authors on reasonable request.

Results

Patient characteristics

The cohort included 86 pwMS, including 42 (49%) who reported falling in the last year (Table 1). The median age at time of assessment was 54.5 years. The cohort mostly included white non-Hispanic patients (95%). Those who had fallen were more likely to be older (58 vs 52.5 years, $p=.03$), have progressive MS (62% vs 23%, $p=.0002$) and have higher PDDS (median 3, (range 0–7) vs 1, (range 0–4), $p<.0001$). Among this cohort of pwMS, 43% of those who had fallen used a gait aid (18/42), compared to only 2% who had not fallen (1/44, $p<.0001$).

Gait metrics

Gait metrics are summarized in Table 2. T25FW was slower in those who had fallen in the last year than those who had not (median 11.5 s, IQR 8.9–19.3 vs median 8, IQR 6.8–9.3, $p<.0001$) (Figure 2). Measures of balance were worse in those who fell including sway area with eyes open (2.6 degrees² vs 1.1, $p=.02$) (Figure 3), sway area with eyes closed (2.3 degrees² vs 1.2, $p=.01$), and jerk (3.3 m²/s⁵ vs 1.6, $p=.005$). Gait speed was slower in patients who fell (0.9 m/s vs 1, $p=.001$), and double support time was greater (27% vs 23%, $p=.0006$).

Clinical and gait factors associated with falls

Regression models were created to assess strength of association with falls (Table 3). A univariable model based on numerical PDDS score was strongly associated with falls ($c=0.86$), and when combined with numerical T25FW time it improved the model ($c=0.90$). When all Opal metrics were combined into the model, the strength of the model only improved slightly ($c=0.92$), but overfit the model for the sample size available. ROC curve was used to determine an optimal binary cutoff of T25FW for association with falls (Figure 4), with a cutoff of 10.8 s chosen which optimized sensitivity and specificity. A final binary model using the presence of gait aid (PDDS ≤ 3 vs ≥ 4), and T25FW time of 10.8 s (≤ 10.8 s vs >10.8 s) was strongly associated with falls ($c=0.8$, Figure 5). Among 15 patients who had both features, 14 (93%) fell in the last year. In contrast, of 55 patients with neither of these features, 14 reported falls in the year prior (25%).

Discussion

This study demonstrates that older age, a progressive disease course, slower walking speed, poor balance, and the use of a gait aid are strongly associated with recent falls in pwMS. Advanced gait analysis demonstrated differences in balance metrics and speed, but did not add to the predictive value of these key clinical features, as the association was so strong. A statistically strong binary model for fall risk was chosen, as it balanced both statistical significance, and simplicity to integrate into a clinical setting (use of gait aid, T25FW time). When more advanced tools with wearable gait metrics were added into the model, this minimally improved the strength of the model but increased the time and cost of the assessment. Further studies are needed to understand the added value of wearable analysis in other important clinical questions, including documenting progression and recovery in MS.

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Table 1. Demographic and clinical features.

	Total (n = 86)	No falls in last year (n = 44)	Fall in last year (n = 42)	p-value (falls vs no falls)
Age at assessment, years, median (range)	54.5 (21–73)	52.5 (21–73)	58 (28–72)	.03
Female sex	53 (62%)	28 (64%)	25 (60%)	.7
Race	Black, 1 (1%) Other, 1 (1%) White, 84 (98%)	Other, 1 (2%) White, 43 (98%)	Black, 1 (2%) White, 41 (98%)	.4
Ethnicity	Cuban, 1 (1%) Hispanic or Latino, 2 (2%) Not Hispanic or Latino, 82 (95%) Unavailable, 1 (1%)	Cuban, 1 (2%) Hispanic or Latino, 2 (5%) Not Hispanic or Latino, 40 (91%) Unavailable, 1 (2%)	Not Hispanic or Latino, 42 (100%)	.3
Relapsing MS	50 (58%)	34 (77%)	16 (38%)	.0002
Progressive MS	36 (42%)	10 (23%)	26 (62%)	.0002
PDDS	Normal, 24 (28%) Mild disability, 19 (22%) Moderate disability, 7 (8%) Gait disability, 17 (20%) Early cane, 8 (9%) Late cane, 8 (9%) Bilateral support, 2 (2%) Wheelchair/scooter, 1 (1%) Bedridden, 0	Normal, 20 (46%) Mild disability, 15 (34%) Moderate disability, 4 (9%) Gait disability, 4 (9%) Early cane, 1 (2%) Late cane, 0 Bilateral support, 0 Wheelchair/scooter, 0 Bedridden, 0	Normal, 4 (10%) Mild disability, 4 (10%) Moderate disability, 3 (7%) Gait disability, 13 (31%) Early cane, 7 (17%) Late cane, 8 (19%) Bilateral support, 2 (5%) Wheelchair/scooter, 1 (2%) Bedridden, 0	<.0001
PDDS score, median (range)	1.5 (0–3)	1 (0–4)	3 (0–7)	<.0001
Use of gait aid	Yes, 19 (22%) No, 67 (78%)	Yes, 1 (2%) No, 43 (98%)	Yes, 18 (43%) No, 24 (57%)	<.0001

Wearable gait metrics provide insight into the underlying mechanisms of falls in pwMS, particularly deficits in balance and speed. Gait testing was consistent with prior studies which reveal that pwMS who fall typically have a slower walking speed,^{3,25,26} and worse measures of balance with elevated double support time and sway measures.^{26,27} Prior studies have also found association with cognitive impairment, spasticity, urinary incontinence, and fatigue that likely contribute to falls in pwMS.¹

This predictive model of falls supports prior research that demonstrate the utility of gait and balance metrics

and disability status in predicting falls^{17,19,28} and provides novelty in directly comparing these different modalities. A prior study found sway measurements to be associated with fall risk, but did not compare to survey or measurements such as T25FW.²⁸ Our study did not find the wearable measures of balance and gait were more associated with falls than the gross measures of function (presence of gait aid, T25FW time). This is similar to prior meta-analysis that showed fallers have worse measures of balance, but did not reliably predict falls.²⁹ We hypothesize this is because falls occur due to the interaction and dysfunction of multiple factors, that are most accurately assessed in tests of overall motor function. It

Table 2. Gait metrics.

	Total (n = 86)	No falls in last year (n = 44)	Fall in last year (n = 42)	p-value (falls vs. no falls)
Time 25-foot walk time, fastest of two trials, seconds, median (IQR)	9 (7.5, 11.5)	8 (6.8, 9.3)	11.5 (8.9–19.3)	<.0001
Sway area, eyes open, degrees ² , median (IQR)	1.5 (0.8, 3.6)	1.1 (0.7, 2.3)	2.6 (1.1, 6.6)	.02
Sway jerk, eyes open, m ² /s ⁵ , median (IQR)	1.7 (0.8, 5.3)	1.4 (0.8, 2.3)	2.3 (0.8, 7.1)	.2
Sway area, eyes closed, degrees ² , median (IQR)	1.8 (0.8, 3.8)	1.2 (0.7, 2.6)	2.3 (1.4, 9.6)	.01
Sway jerk, eyes closed, m ² /s ⁵ , median (IQR)	2.5 (1.3, 6.5)	1.6 (0.9, 5.0)	3.3 (1.9, 11.1)	.005
Gait speed, m/s, median (IQR)	1 (0.8, 1.1)	1 (0.9, 1.2)	0.9 (0.6, 1.1)	.001
Double support, % of gait cycle time, median (IQR)	25.5 (21.9, 28.9)	23.1 (20.8, 26.8)	26.9 (24.3, 33.1)	.0006

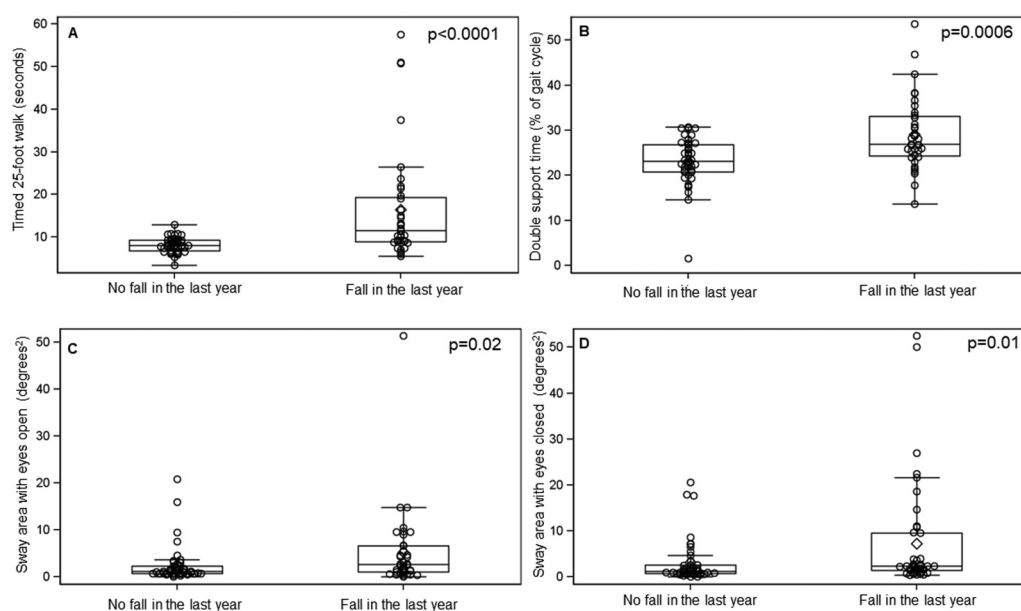


Figure 2. Gait and sway measurements compared in patients who fell in the last year and those who did not. (A). Timed 25-foot walk time (s) of the fastest of two trials compared in those who did not fall in the last year (median 8, IQR 6.8–9.3) was faster compared to those who did (median 11.5 s, IQR 8.9–19.3, $p < .0001$). (B). Double support time was greater in those who had fallen (median 27%, IQR 24–33) compared to those who had not (median 23%, IQR 21–27; $p = .0006$). (C). Sway area with eyes open was greater in those who had fallen (median 2.6 degrees², IQR 1.1–6.6) than those who had not (median 1.1 degrees², IQR 0.7–2.3, $p = .02$). (D). Sway area with eyes closed was greater in those who had fallen (median 2.3 degrees², IQR 1.4–9.6) than those who had not (median 1.2 degrees², IQR 0.7–2.6, $p = .01$).

would be worthwhile to compare the sensitivity of these tasks with wearable monitors to more challenging balance tasks,³⁰ but the more challenging tasks may not be feasible to integrate into clinical practice.

Other methodology of measuring postural sway and gait metrics should be explored in future work.²⁷ Prospective validation of this model is important as patients may under or over recall falls

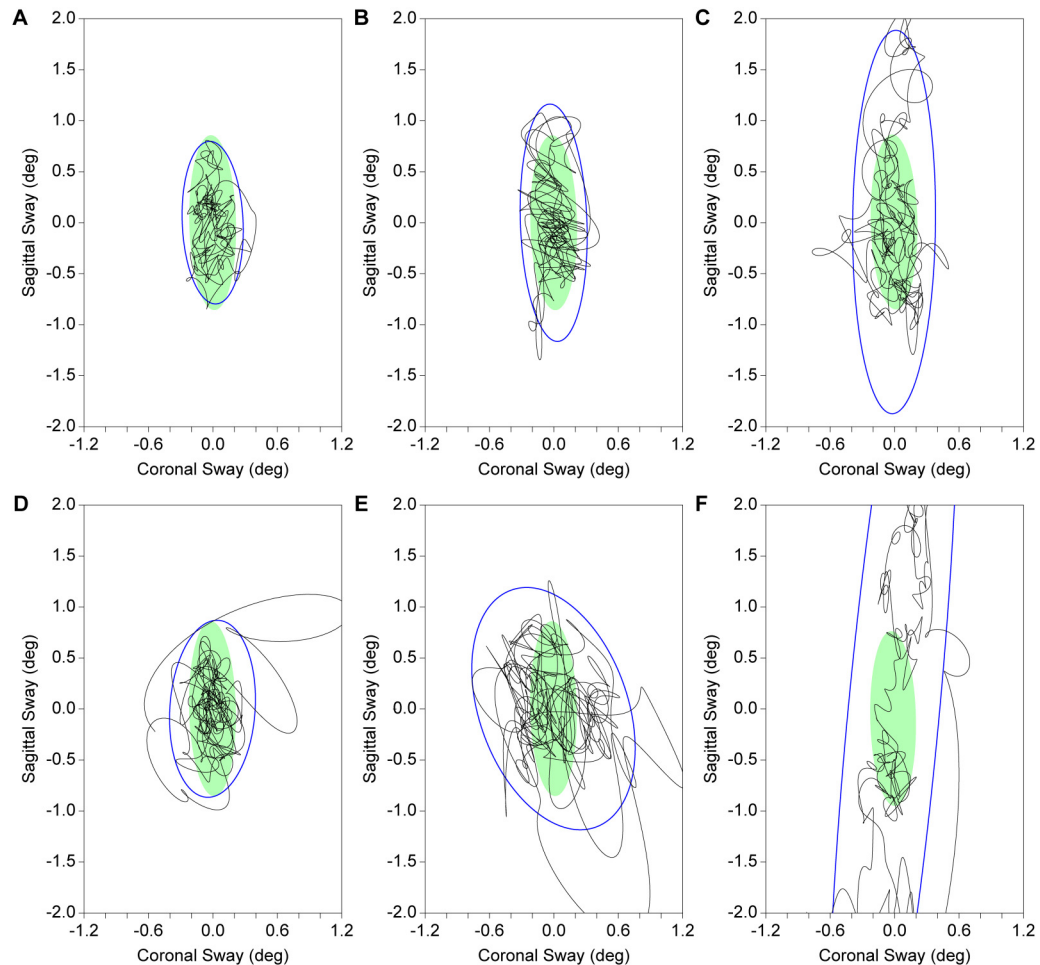


Figure 3. Lumbar sway tracings with feet apart eyes and open. Sway tracings from individuals measured on Opal device placed over lumbar region as measured in the transverse plane in patients standing on a firm surface with feet apart and eyes open shown in black, with the patient's average shown in blue. Green oval shows healthy control average data provided by Clario. Selected patients represent the median and interquartile range of those who did not fall (A–C, median 1.1 degrees², IQR 0.7–2.3) and those who did fall (D–E, median 2.6 degrees², IQR 1.1–6.6, $p = .02$).

retrospectively,³¹ and to evaluate the strength of these factors compared to the history of falling itself.⁵ Further work to understand falls in pwMS who use gait aids, specifically exploring if patients have falls while using the gait aid or under other conditions may help to direct rehabilitation strategies.³²

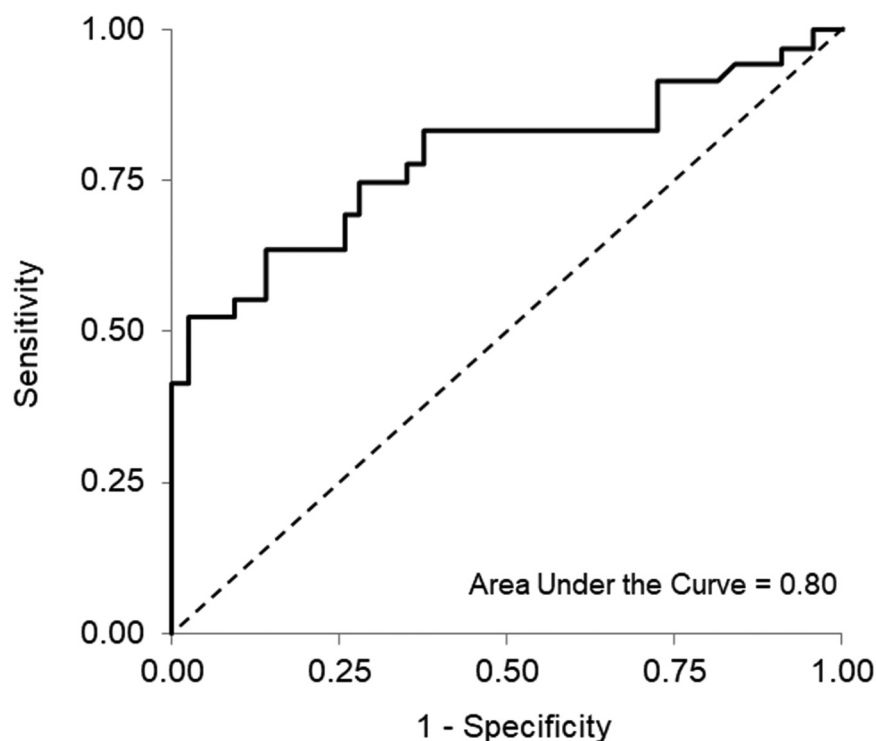
This fall prediction model has the potential to be integrated in clinical practice. The United States Preventative Task Force, a panel of experts that gives recommendations for preventive medicine, recently published updated recommendations for interventions for community dwelling individuals over the age of 65, recommending exercise interventions in those at risk, and to consider multifactorial intervention.³³ However, consensus guidelines for fall prevention in MS do not yet exist as the optimal

interventions for pwMS are yet to be determined.³⁴ Interventional studies for fall prevention in MS to date have had variable results,^{34,35} possibly related to inconsistent outcome measures. In our practice, we favor a multifactorial intervention approach.³² We refer most patients to our rehabilitation team to ensure optimization of gait aids, spasticity management, and create an individualized exercise plan. We work to minimize polypharmacy and educate patients and families on fall prevention. We also recommend working with primary care to ensure other comorbidities such as osteoporosis and need for blood thinners is assessed to reduce associated morbidity. In the future, remote monitoring of falls in pwMS^{3,13} may improve clinical care and serve as a reliable outcome metric in fall-prevention trials in pwMS.

Table 3. Univariable and multivariable regression models.

Independent variables	Area under curve (c)	OR estimate	OR [95% CI]	Chi-square <i>p</i> -value
Model 1	0.86			
a. PDDS score		2.8	[1.9, 4.2]	<.0001
Model 2	0.78			
a. T25FW time		1.5	[1.2, 1.9]	.001
Model 3	0.90			
a. PDDS score		2.7	[1.6, 4.4]	.0001
b. T25FW time		1.2	[0.9, 1.5]	.2
Model 4	0.92			
a. PDDS score		3.1	[1.7, 5.5]	.0001
b. T25FW time		1.5	[0.85, 2.7]	.2
c. Sway area, open		1.1	[0.81, 1.4]	.6
d. Sway jerk, open		1.0	[0.89, 1.2]	.8
e. Sway area, closed		0.8	[0.6, 1.2]	.3
f. Sway jerk, closed		1.1	[0.91, 1.2]	.5
g. Speed		129	[0.3, 999]	.1
h. Double support		1.1	[0.9, 1.2]	.4
Model 5	0.80			
a. Gait aid yes versus no		11.9	[1.2, 114.5]	.03
b. T25FW time >10.8 s yes versus no		7.9	[1.4, 44.9]	.02

PDDS: Patient Determined Disease Step.

**Figure 4.** Timed 25-foot walk receiver operating characteristic curve. A time of 10.8 s was optimal cutoff for optimizing both sensitivity (52.8) and specificity (97.7).

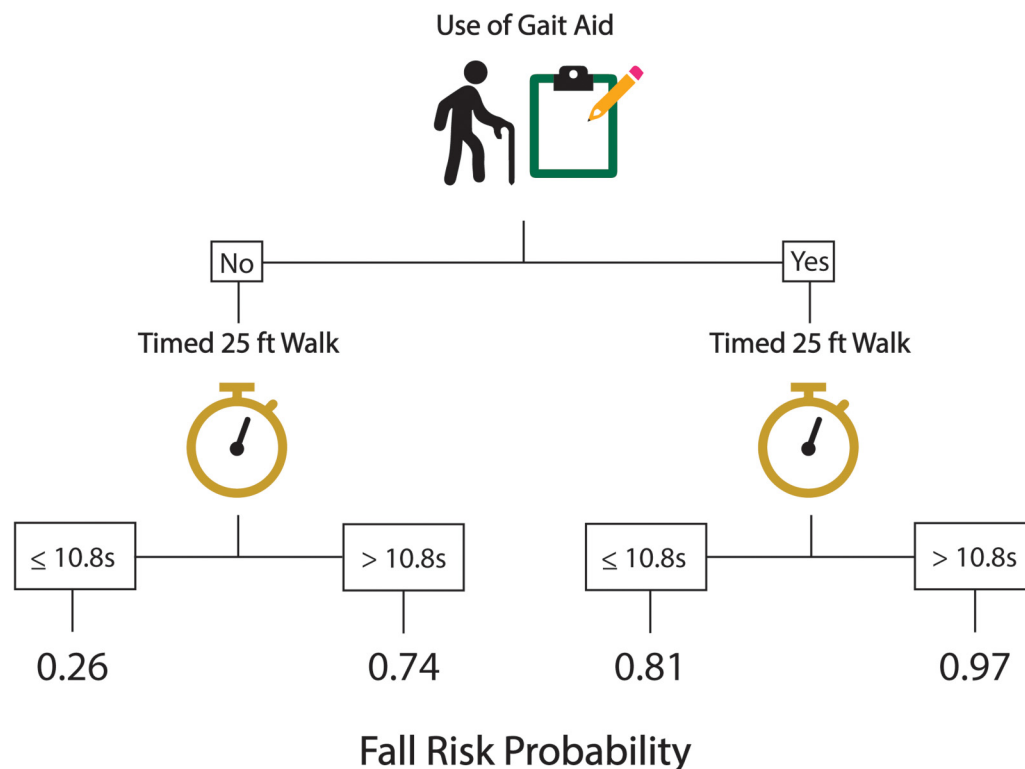


Figure 5. Fall risk decision tree. Clinical tool for assessment of probability of fall based on binary use of gait aid (yes, no) and timed 25-foot walk test (≤ 10.8 s, > 10.8 s). Clinicians may interpret that patients with both characteristics had 97% probability of falls in the last year, while those with neither had a 26% probability. Area under curve of the model was 0.8, considered an excellent model. Clinicians may integrate this model into clinical practice to identify patients who should receive fall-prevention strategies.

This study is limited as all patients were evaluated at one site, but this allowed for consistency of gait methodology between examiners. The cohort included mostly white non-Hispanic patients, validation to a cohort with other ethnicities will be important. Some patients required a gait aid to complete the testing safely, this allowed for measurement of the patient's optimal gait performance. This may have caused underestimation of the differences in balance and speed and contributed to the decreased predictive value of the wearable assessment for falls. The sway area with eyes open was greater than with eyes closed in those who had fallen, we suspect this may have been impacted by the order of the testing that patients performed or the need for a gait aid.

This study showed that older age, progressive disease, greater disability, slower walking speed, and worse balance metrics are all associated with falls in pwMS. A clinically applicable model using binary presence of gait aid and T25FW time > 10.8 s was strongly associated with falls. Validating this model with prospective fall monitoring and quantification, obtaining

information regarding conditions around falls, and including diverse populations, will improve the clinical utility. Further studies are warranted to determine the optimal interventions in patients at risk.

Data availability

Anonymized data used for this study are available from the corresponding authors on reasonable request.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Samantha Banks was supported by the National Center for Advancing Translational Sciences (NCATS), its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health. Charles Howe and Jay Mandrekar report no disclosures. Farwa Ali is supported by the NIH. Sean Pittock receives grants from Alexion Pharmaceuticals, Viela Bio/Horizon, Adimune, Genentech, Roche; he received personal

fees for consulting for UCB, Astellas, and Arianys, he has two patents issued (8889102; application 12-678350; Neuromyelitis Optica Autoantibodies as a Marker for Neoplasia; and 9891219B2; application 12-573942; Methods for Treating Neuromyelitis Optica (NMO) by Administration of Eculizumab to an individual that is Aquaporin-4 [AQP4]-IgG Autoantibody positive) for which he has received royalties, SJP also has patents pending for IgGs to the following proteins as biomarkers of autoimmune neurological disorders: septin-5, kelch-like protein 11, GFAP, PDE10A, and MAP1B. Jessica Sagen reports no disclosures. Robert Spence reports no disclosures. Kellie Gossman reports no disclosures. Dr Eoin Flanagan has served on advisory boards for Alexion, Genentech, Horizon Therapeutics and UCB; he received research support from UCB; he has received speaker honoraria from Pharmacy Times and royalties from UpToDate; he is a site principal investigator in a randomized clinical trial of Rozanolixizumab for relapsing myelin oligodendrocyte glycoprotein antibody-associated disease run by UCB; he is a site principal investigator and a member of the steering committee for a clinical trial of satralizumab for relapsing myelin oligodendrocyte glycoprotein antibody-associated disease run by Roche/Genentech; he has received funding from the NIH (R01NS113828); he is a member of the medical advisory board of the MOG project; he is an editorial board member of *Neurology*, *Neuroimmunology and Neuroinflammation*, the journal of the neurological sciences and neuroimmunology reports; he has a patent submitted on DACH1-IgG as a biomarker of paraneoplastic autoimmunity. Orhun Kantarci reports no disclosures. Mark Keegan receives royalties from the publication of “Mayo Clinic Cases in Neuroimmunology” (OUP). Oliver Tobin receives research funding from the NIH, Mayo Clinic Center for Multiple Sclerosis and Autoimmune Neurology and Mallinckrodt Inc; he receives royalties from the publication of “Mayo Clinic Cases in Neuroimmunology” (OUP).

Ethical statement

This study was approved by the Institutional Review Board of Mayo Clinic, Rochester, Minnesota (Institutional Review Board 08-007846).

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Patient consent

All patients gave written informed consent for the use of their medical records and gait analysis for research purposes.

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