Primary Lateral Sclerosis Natural History Study: Primary Lateral Sclerosis Functional Rating Scale and Other Outcomes Assessment

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Objective: The primary lateral sclerosis (PLS) consensus diagnostic criteria and functional rating scale (PLSFRS) were recently established to facilitate and optimize future PLS clinical trials. We examined the trajectory of the PLSFRS and other functional outcome measures and biomarkers in the PLS Natural History Study (PLS NHS) to understand their performance in this prospective cohort.

Methods: The PLS NHS is a prospective, longitudinal, multicenter study of people living with PLS in different diagnostic categories: early (disease duration <2 years); probable (2–4 years); and definite PLS (4–15 years). PLSFRS scores and other functional outcome measures were collected at baseline, 3-, 6-, 9-, and 12-month follow-up visits. Baseline characteristics were compared between the groups. The slopes of the PLSFRS and other functional outcome measures over 12 months were examined in the overall cohort and subgroups using linear mixed-effect models. The associations between baseline characteristics and the rate of PLSFRS decline were analyzed with linear regression models.

Results: A total of 76 participants were included: early (n = 6); probable (n = 26); and definite (n = 44) PLS. Baseline PLSFRS total scores were highest in the early PLS group, followed by the probable and definite PLS groups. In the overall cohort, the PLSFRS total score declined by 0.33 points/month (95% confidence interval [0.27–0.39], adjusted $p < 0.05$). The rate of decline was steepest in the early PLS group, followed by the probable and definite PLS groups. Baseline neurofilament light chain level was associated with the rate of PLSFRS decline over 1 year ($p = 0.001$).

Interpretation: In PLS, the rate of functional decline, as measured by the PLSFRS total score, is faster during the early phase of the disease. Neurofilament light might serve as a prognostic biomarker in PLS.

ANN NEUROL 2025;00:1–11

Primary lateral sclerosis (PLS) is a neurodegenerative disease affecting predominantly the upper motor neurons (UMNs) and their tracts, and is characterized clinically by limb stiffness, spasticity, hyperreflexia, spastic dysarthria, dysphagia, pseudobulbar affect, and in some cases, frontotemporal dementia.[1] PLS progresses at a slower rate compared to other diseases of the motor neurons, such as amyotrophic lateral sclerosis (ALS). However, over time, it causes severe functional loss in multiple areas, such as mobility, hand dexterity, speech, and swallowing.[2–5] PLS is exceedingly rare, although its prevalence is not well established. It has been estimated that ALS clinicians may see 1 to 3 patients with PLS for every 100 patients with ALS, yielding an estimated prevalence in the United States (US) of 300 to 900 persons.[6,7] There is limited knowledge about the pathophysiology of PLS, and clinical research efforts have been hindered by the rarity of the disease. It is still controversial whether PLS is an independent disease entity or an extreme variant of ALS.[8,9] There are no medications approved for PLS, and people living with PLS have never been included in ALS clinical trials. Only 1 clinical trial, a multicenter, 18-week open-label safety and efficacy trial of dalfampridine in PLS, has been designed for PLS without available results at this time (Clinicaltrials.gov ID: NCT02868567).

In recent years, collaborative efforts among international PLS experts have resulted in a few initiatives to improve the clinical trial readiness of this disease. These efforts included studies to improve the understanding of disease progression, validate novel outcome measures, and develop new biomarkers.[10] The PLS Functional Rating Scale (PLSFRS) was developed to more sensitively detect slow functional decline experienced by people living with PLS.[11] Further, new PLS diagnostic criteria were established based on expert consensus reached during the Second International PLS Conference.[12,13] These advances, coupled with recent progress in drug development,[14] provide hope that clinical trials for PLS may be on the horizon. To move a step closer to trials of disease-modifying drugs for PLS, it is essential to further validate outcome measures through a prospective natural history study.[15] Here, we report the primary results of the PLS Natural History Study (PLS NHS), a large and robust multicenter prospective study that includes data on several key outcome measures collected during the first 12 months following enrollment of the cohort.

Patients and Methods

The details of the PLS NHS were previously described.[15] Briefly, the PLS NHS is a multicenter prospective longitudinal cohort study enrolling people with PLS at various stages of the disease. Participants were followed for 2 years. Here we report data collected from baseline to the 1-year follow-up visit.

Study Participants

The study population of the PLS NHS has been previously described.[15] A total of 76 adult participants fulfilling inclusion and exclusion criteria were enrolled from 27 sites

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.78056

Received May 14, 2025, and in revised form Sep 13, 2025. Accepted for publication Sep 16, 2025.

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across the United States and Canada after providing informed consent. Inclusion criteria were age over 25 years, PLS diagnosis, disease duration less than 15 years, ability to walk independently, presence of bulbar symptoms, absence of genetic variants for hereditary spastic paraplegia, absence of unstable medical conditions, absence of significant lower motor neuron degeneration determined by electromyography (EMG). Participants with evident cognitive impairment and those enrolled in clinical trials were excluded. Participants whose disease duration was less than 2 years were included and classified as "early PLS," those whose disease duration was between 2 and 4 years were classified as "probable PLS," and those whose disease duration exceeded 4 years as "definite PLS." Although the probable and definite PLS categories are based on the recently published diagnostic criteria by Turner et al,[12] early PLS was defined for the first time in the PLS NHS to include individuals with exclusive UMN changes who did not yet meet the duration criteria for probable or definite PLS. The Columbia University PLS NHS coordination center received institutional review board (IRB) approval for the entire study, with each participating site receiving local IRB approval individually.

Procedures

Baseline evaluation included eligibility assessment, physical examination, neurological examination, slow vital capacity (SVC), Penn UMN Score (PUMNS), timed up-and-go (TUG) test, cognitive testing, durable medical equipment (DME) review, medication review, PLSFRS, pa-ta-ka test, finger- and toe-tapping, ALS Assessment Questionnaire 5 (ALSAQ-5), Neuro-quality of life (Neuro-QoL), Rasch Overall ALS Disability Scale (ROADS), Blood and Urine Sampling. DME and medication review, PLSFRS, pa-ta-ka test, finger- and toe-tapping, ALSAQ-5, Neuro-QoL, and ROADS were collected at 3-, 6-, 9-, and 12-month follow-ups via virtual visits by a single trained research coordinator (G.J.). SVC, PUMNS, and TUG tests were collected every 6 months at study sites. Blood and urine samples were collected again at 1-year follow-up. EMG studies were completed at 1-year follow-up.

Outcome Measures

PLSFRS. The PLSFRS is a PLS-specific clinimetric scale developed by adding 2 intermediate levels of function to the first 10 questions of the ALSFRS-R, to more sensitively reflect a functional change in people with PLS. Identical to the ALSFRS-R, the PLSFRS includes 12 questions in 4 domains including gross motor tasks, fine motor tasks, bulbar functions, and respiratory functions. PLSFRS total scores range from 0 to 68, with a higher score indicating better function. Its internal consistency, intrarater, interrater, and telephone test–retest reliability and construct validity have been fully established.[11] The PLSFRS total score (sum of all scores from 12 questions), bulbar subscore (sum of questions 1–3), fine motor subscore (sum of questions 4–6), gross motor subscore (sum of questions 7–9), and respiratory subscore (sum of questions 10–12) were used in the analysis.

Roads. ROADS is a patient-reported outcome measure developed for people with ALS to assess overall disability. The scale contains 28 items, each scored at 0, 1, and 2. ROADS total scores range from 0 to 56, with a higher score indicating better function. This recently validated questionnaire is linearly weighted, has high test–retest reliability, and showed improved item targeting compared with the ALSFRS-R. ROADS total score was converted to linearly weighted normed total score and used in the analysis (range 0–146)[16]

PUMNS. The PUMNS is a cumulative score of clinimetric measurements, including right and left muscle stretch reflexes (0–4), the jaw reflex (0–4), and the modified Ashworth scale.[17] The PUMNS demonstrated high intra- and interrater reliability.[17] The PUMNS was administered by approved site physicians. PUMNS total score was used in the analysis.

Pa-ta-ka Test. The oral diadochokinetic rate (pa-ta-ka repetition speed) was used to assess bulbar speech dysfunction. This has been used to evaluate bulbar function in people with ALS as a part of the Tufts Quantitative Neuromuscular Exam (TQNE).[18–21] A member of the study team connected with the participant through virtual visits. Participants were asked to repeat the sequence /pɑ tɑ kɑ/ as quickly as possible for a span of 10 seconds. The number of repeats completed was counted and recorded.

Finger and Foot Tapping. The finger and foot tapping task was used to demonstrate the degree of UMN impairment.[18,19,22] A member of the study team connected with the participant through a secure video conferencing platform. Participants were instructed to tap their thumb and forefingers together as many times as possible within the 10-second duration. Similarly, participants tapped their foot as quickly as possible within 10 seconds, and the numbers were recorded. Finger and foot tapping was performed separately on the right and left. The average of right and left counts was used.

TUG Test. The TUG gait test measured the amount of time it takes for the participant to independently stand up, walk for 3 meters (with or without an assistive device

such as a cane or walker), turn around, walk back to the chair, and sit back down.[23] The time to complete the task was recorded and analyzed.

ALSAQ-5. To measure quality of life, participants completed the self-administered shortened ALSAQ-5.[24] ALSAQ-5 is a patient-reported health status outcome. Higher scores indicate a higher quality of life. ALSAQ-5 includes 5 items to briefly assess the impacts of motor neuron disease on participants, minimizing the burden of completing the questionnaire. The ALSAQ-5 total score was used in the analysis.

Neuro-QoL. To measure functional ability and quality of life, we administered the patient-reported upper and lower extremity portions of the Neuro-QoL measurement system.[25] Neuro-QoL upper extremity (UE) and lower extremity (LE) total scores were used in the analysis.

SVC. Vital capacity was measured by SVC at each site with spirometry. SVC (%) with an upright sitting position was used for analysis.

Neurofilament Light. Plasma samples collected at baseline visits were used for neurofilament light (NfL) measurement. Samples were collected in the morning after overnight fasting. When overnight fasting was not possible, the samples were collected after at least 3 hours of fasting. Plasma NfL levels were measured using a harmonized enzyme-linked-lectin-assay (ELLA) assay developed by Protein Simple following the manufacturer's guidelines. This assay used the antibodies developed by Uman, which are also used by the assays developed by Quanterix and Siemens. The assay has an analytical range of 5.4–20,-580pg/ml. Levels lower than 5.4pg/ml (level below detection) was considered 0. All samples were measured in technical triplicate, yielding a mean concentration that was used in the study. This assay has been used previously in the ALS population and is comparable to the Simoa assay.[26,27]

Statistical Analysis

Demographics, disease history, baseline functions, baseline NfL, ALS diagnosis, and death at 1 year were compared between PLS groups with analysis of variance (ANOVA) for continuous and Chi-square for categorical variables. Longitudinal changes in outcome measures, including PLSFRS, ROADS normed sum-scores, and PUMNS total scores, and counts for pa-ta-ka, finger- and toe-tapping, PUMNS, SVC, and TUG were analyzed with linear mixed-effect models to assess average slopes among the overall cohort and each group. The correlations between functional outcomes were examined using Pearson correlation analysis with baseline measurements. Associations between baseline NfL level with baseline PLSFRS total score and PLSFRS slope of decline were examined with a linear regression model, adjusted for age, sex, disease duration, and baseline PLSFRS score among the overall cohort and definite PLS group. Frequencies of DME use at baseline and at 1-year follow-up were compared with Chi-square tests. Baseline NfL levels were compared between those with and without ALS diagnosis at 1-year follow-up with the Mann–Whitney test. Bonferroni's adjustments were used for mixed-effect models (36 comparisons) and correlation analysis (105 comparisons) to control for the overall familywise error rate at 5% because of multiple comparisons. R version 4.4.1 was used for all analyses.

Results

Participant Demographics and Disease Characteristics

A total of 76 participants were included: 6 early PLS, 26 probable PLS, and 44 definite PLS. Age, sex, race, and ethnicity were similar between groups. The average disease duration was 18 months in the early PLS group, 41 months in the probable PLS group, and 102 months in the definite PLS group. Baseline PLSFRS and ROADS total scores were highest in the early PLS group, followed by the probable PLS group, and lowest in the definite PLS group. Plasma NfL level was highest in the early PLS group, followed by the probable and definite PLS groups. Percentages of those who converted to ALS by 1-year follow-up were 0% (0/6) in the early PLS, 12% (3/26) in the probable PLS, and 5% (2/44) in the definite PLS groups. One participant from the definite PLS group died of traumatic brain injury (Table 1).

Change in Functional Scores over Time

PLSFRS total scores declined by an average of 0.33 points/month, 95% confidence interval [CI]: (0.27–0.39), during 1-year follow-up, most rapidly in the early PLS group (1.3 points/month, 95% CI: [1.1–1.5]), followed by the probable PLS (0.37 points/month, 95% CI: [0.29–0.45]) and definite PLS (0.2 points/month, 95% CI: [0.12–0.28]) groups. Similarly, the ROADS normed score declined by an average of 0.5 points/month (95% CI: [0.4–0.6]), most quickly in the early PLS group (1.8 points/month, 95% CI: [1.4–2.2]), followed by probable (0.55 points/month, 95% CI: [0.39–0.71]) and definite PLS (0.32 points/month, 95% CI: [0.22–0.42]) groups. All adjusted p-values are less than 0.05 (Fig 1).

Pa-ta-ka counts (0.5 count/month, 95% CI: [0.32, 0.68], adjusted $p < 0.05$) and finger tapping (0.53 counts/month, 95% CI: [0.25–0.81], adjusted $p < 0.05$) declined

TABLE 1. Demographics, Disease History, and 1-Year Outcome of the Participants

	Early PLS (n = 6)	Probable PLS (n = 26)	Definite PLS (n = 44)	*p*
Age (SD)	61.2 (10.5)	59.1 (11.5)	63.4 (9.9)	0.3
Sex, M (%)	3 (50)	13 (50)	26 (59)	0.7
Race	White 6 (100)	White 25 (96), Asian 1 (3.8)	White 42 (96), Black 1 (2), Asian 1 (2)	0.9
Ethnicity (%)	Non-Hispanic 6 (100)	Non-Hispanic 24 (92)	Non-Hispanic 42 (95)	0.7
Disease duration, months (SD)	18.2 (5.7)	40.7 (8.3)	101.7 (36.2)	<0.001
Baseline PLSFRS total score	54.5 (8.4)	44.8 (8.3)	39.3 (8.7)	<0.001
Baseline ROADS normed total score	94.8 (11.8)	85.6 (10.6)	79.3 (8.8)	<0.001
Neurofilament light, pg/ml (SD)	100.5 (70.0)	51.3 (34.6)	32.2 (29.3)	<0.001
ALS diagnosis by 1 yr (%)	0 (0)	3 (12)	2 (5)	0.4
Death (%)	0 (0)	0 (0)	1 (2)	0.7

ALS = amyotrophic lateral sclerosis; M = male; ml = milliliter; pg = picogram; PLS = primary lateral sclerosis; PLSFRS = primary lateral sclerosis functional rating scale; ROADS = Rasch Overall ALS Disability Scale; SD = standard deviation; yr = year.

over time in the early PLS, while no significant change was noted in the probable and definite groups. Foot tapping, TUG time, PUMNS score, and SVC (%) did not significantly change over 1 year in any of the groups (Fig 2).

Estimates of the mean and standard deviation of the rate of decline in the total score of the PLSFRS and ROADS over 12 months were calculated using linear mixed effects models and used to perform power calculations for a hypothetical PLS clinical trial. Table 2 provides the corresponding sample size required in a 1:1 randomized controlled trial to achieve 80% power at 5% significance (2-sided). In the overall cohort, estimated sample sizes were very similar between PLSFRS and ROADS as the outcome. When the sample size was estimated in the definite PLS group only, estimated sample sizes were much larger compared to those of the overall cohorts, slightly lower with ROADS as the outcome.

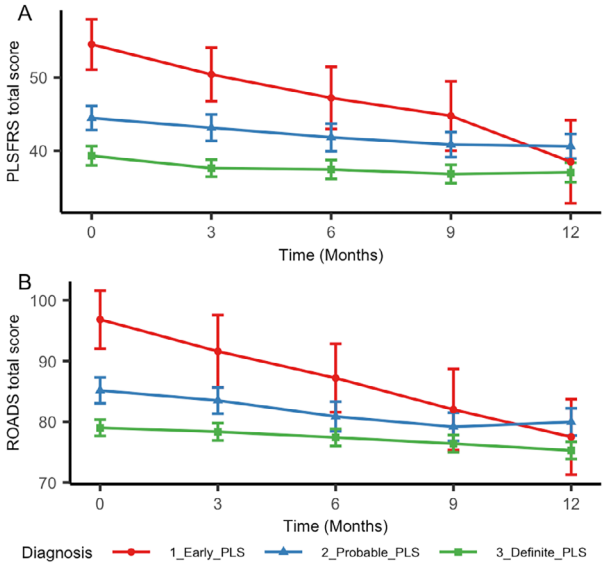

FIGURE 1: Longitudinal change of (A) primary lateral sclerosis functional rating scale (PLSFRS) and (B) Rasch Overall Amyotrophic Lateral Sclerosis Disability Scale (ROADS) among early, probable, and definite primary lateral sclerosis (PLS) groups.

Associations between Outcomes

The baseline PLSFRS total score correlated strongly with the ROADS total score ($r = 0.85$), and moderately with finger tapping ($r = 0.58$) and foot tapping ($r = 0.56$). It correlated negatively with PUMNS ($r = -0.46$) and ALSAQ-5 ($r = -0.40$), as higher scores indicate worse outcomes for these scales as opposed to PLSFRS. Significant correlations were found between the PLSFRS gross motor subscore and foot tapping ($r = 0.72$) and Neuro-QoL LE ($r = 0.85$), between the PLSFRS fine motor subscore and finger tapping ($r = 0.62$) and Neuro-QoL UE ($r = 0.73$), and between the PLSFRS bulbar subscore and pa-ta-ka ($r = 0.51$). TUG time correlated with PLSFRS fine motor subscore ($r = -0.42$) and Neuro QoL UE ($r = -0.38$). SVC did not correlate significantly with any other outcome measures. All adjusted *p*-values <0.05 (Fig S1).

In the overall cohort, higher baseline NfL levels were associated with a faster decline in the PLSFRS total score

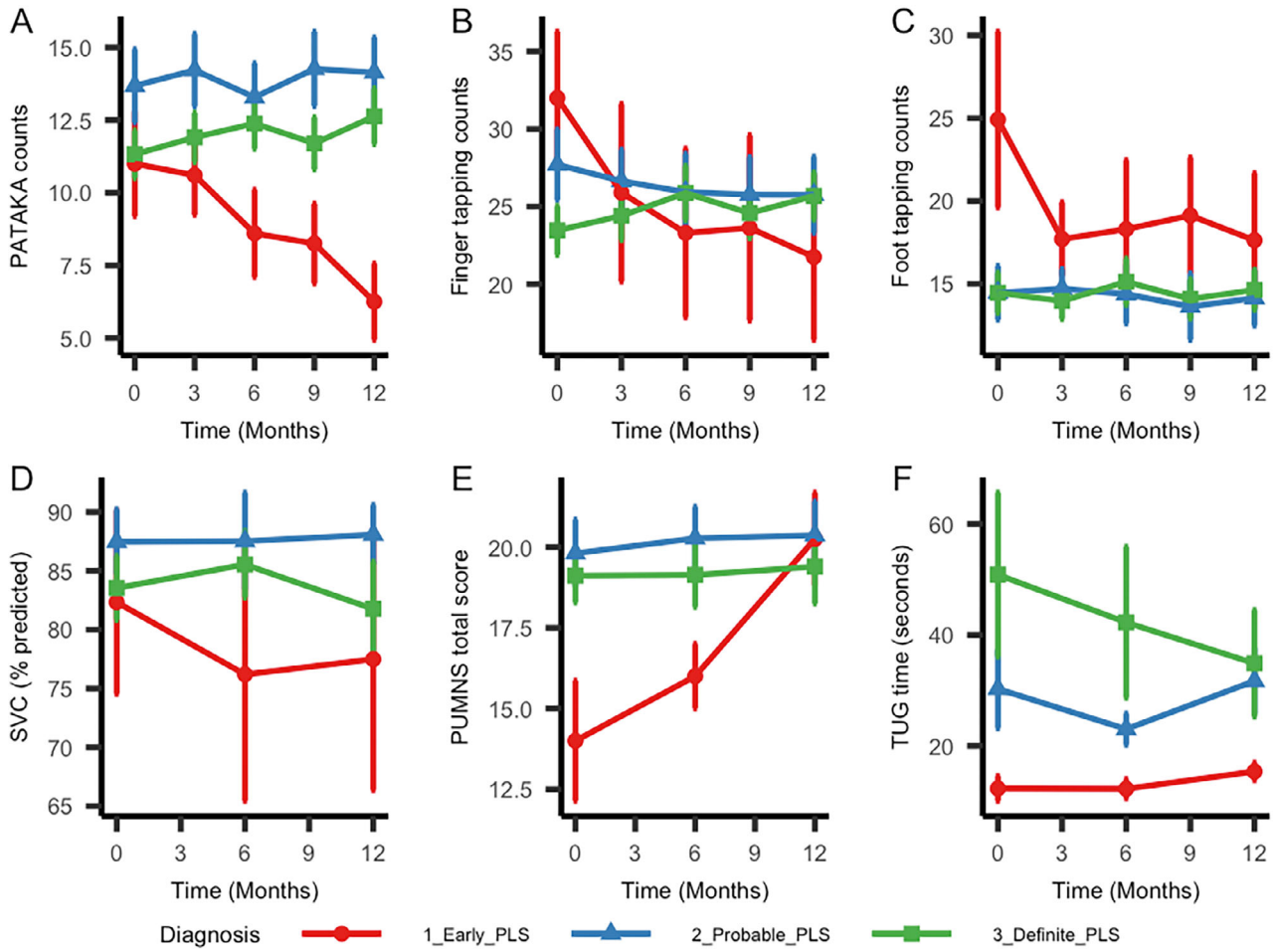

FIGURE 2: Longitudinal change of (A) pa-ta-ka, (B) finger and (C) foot tapping counts, (D) slow vital capacity (SVC) percentage predicted with higher values indicating better outcomes; longitudinal change of (E) Penn upper motor neuron (PUMNS) score and (F) timed up and go (TUG) time with lower values indicating better outcomes.

($p = 0.001$). Those with a diagnosis change to ALS had a trend of higher baseline NfL compared to those without diagnostic change (median: 91.4, interquartile range: [36–130] vs 34.0, interquartile range: [18.8–59.8]pg/ml, $p = 0.1$) (Fig 3). In a multivariable analysis, a higher baseline NfL level was independently associated with faster PLSFRS decline after adjusting for age, disease duration, and baseline PLSFRS score ($P = 0.002$). Among the definite PLS group, the baseline NfL level was not significantly associated with PLSFRS decline in either univariable or multivariable analyses ($p > 0.05$). The NfL intra-assay coefficient of variation as a quality control measure was 3%, 95% CI: [0%–7%].

DME Utilization Change over Time

The frequencies of DME use increased notably over time, with a significantly higher proportion of participants reporting the use of walkers at the 1-year follow-up visit compared to baseline. (72% vs 51%, $p = 0.01$). Numerically, the use of manual wheelchairs, power wheelchairs, alternative and augmentative communication devices, and non-invasive ventilators increased at the 1-year follow-up visit, although it did not reach statistical significance (Table 3).

Discussion

PLS is an exceedingly rare disease that has been understudied to date. There are no disease-modifying treatments for this chronic and debilitating disease, and clinical trials are urgently needed. We conducted a multicenter prospective natural history study to better characterize the course of PLS disease progression and lay the groundwork for future clinical trials.

Through this well-defined natural history study of people living with PLS, we evaluated the rate of disease progression in the overall cohort and the subgroups of early, probable, and definite PLS for up to 1 year. The study results demonstrate that the progression of functional loss, as measured by global functional scales

TABLE 2. Sample Size When Using PLSFRS and ROADS in a 1:1 RCT under Different Assumptions on the Treatment Effects

Endpoint	Effect size (% improvement)	Effect size[b]	N per arm[a]
Overall cohort			
PLSFRS 12-month change	20	4.06 vs 3.25	315
	30	4.06 vs 2.84	140
	50	4.06 vs 2.03	50
ROADS 12-month change	20	5.96 vs 4.76	315
	30	5.96 vs 4.17	138
	50	5.96 vs 2.98	50
Definite PLS only			
PLSFRS 12-month change	20	2.5 vs 2.0	740
	30	2.5 vs 1.75	320
	50	2.5 vs 1.25	118
ROADS 12-month change	20	3.86 vs 3.09	580
	30	3.86 vs 2.7	250
	50	3.86 vs 1.93	92

[a]Assume 1:1 RCT, 80% power, 5% type I error, 2-sided.
[b]Mean decline over 12 months (placebo vs treatment).
ALS = amyotrophic lateral sclerosis; N = number; PLS = primary lateral sclerosis; RCT = randomized controlled trial; ROADS = Rasch Overall ALS Disability Scale.

(PLSFRS and ROADS), is faster among those closer to symptom onset and with higher baseline function, whereas a slower decline is seen at later stages. Our observations suggest that PLS disease progression is most prominent in the early phases of the disease. Such a faster decline close to symptom onset has also been reported in previous ALS and PLS studies.[28–30] The progression rate of the early PLS group measured by ROADS was only slightly slower than that reported in a previous study in ALS (1.8 points decline/month in early PLS vs 2.0 points decline/month in ALS).[31] The average rate of PLSFRS decline in the overall cohort was faster than the rate reported in a previous PLS study by Mitsumoto et al[11] (0.3 vs 0.12 points decline/month). This is likely because of a higher proportion of early PLS participants in the current study compared to the previous study, which mostly included definite PLS participants.[11]

Knowledge about the natural history of disease progression is important for clinical trial design. If a future 2-arm placebo-controlled trial were to enroll participants with early, probable, and definite PLS, the sample size required to have an 80% power to demonstrate 30% slowing of PLSFRS decline over 1 year was estimated to be 280 (140 in each arm). Given the rarity of the disease, this would still be difficult, but potentially feasible with international collaboration. If only definite PLS group should be included in the trial, approximately 600 PLS participants would be required, and this number rises above 1,000 if the effect size goes down to 20%. Although these sample sizes are smaller than previous estimates,[32] recruiting over 1,000 definite PLS patients is likely impossible.

Additionally, it would be ideal to initiate treatment as early as possible to prevent neuronal degeneration that might be irreversible.[33] From this perspective, better knowledge of disease progression during the early phases of PLS (<2 years from onset) is needed. Therefore, we advocate for including these early groups in future PLS studies and trials and using stratification to ensure balanced recruitment in each arm. Diagnostic change to ALS, which might occur in a small portion of participants, might be considered as one of the outcomes of the trial.

The higher rate of progression among the early PLS group may raise concerns for a potential higher diagnostic change to ALS in this subgroup. Notably, none of the 6 participants classified as early PLS were diagnosed with ALS during their first year of follow-up since enrollment. Of the 5 participants who were diagnosed with ALS during this period, 3 were from the probable group and 2 from the definite group, suggesting heterogeneity in the timing of diagnostic change. These findings suggest that neither disease duration nor rate of functional decline may serve as reliable indicators of impending lower motor neuron involvement.

Previous retrospective chart review studies have shown that progression to ALS is less frequent after 4 years of symptom onset, but it can occur even several years after initial onset.[8,34] In a recent PLS NHS in the Netherlands, 8 patients with a suspected diagnosis of PLS and a disease duration less than 2 years at baseline were included as the "undetermined" group, along with 6 probable and 37 definite PLS patients.[30] At the 3-year follow-up, 3 of 37 (8%) patients in the definite group, and 2 of 6 (33%) in the probable group received the diagnosis of ALS based on El Escorial criteria.[35] Among 8 patients in the undetermined group, 2 progressed to ALS, 4 were diagnosed with PLS, and 2 remained undetermined, with only 1 region of UMN involvement. In our study, we too observed that this diagnostic change can occur after 4 years, with 2 participants (5%) converting at 5 and 7 years after symptom onset. However, conversion frequency was much lower in the probable PLS group (12%)

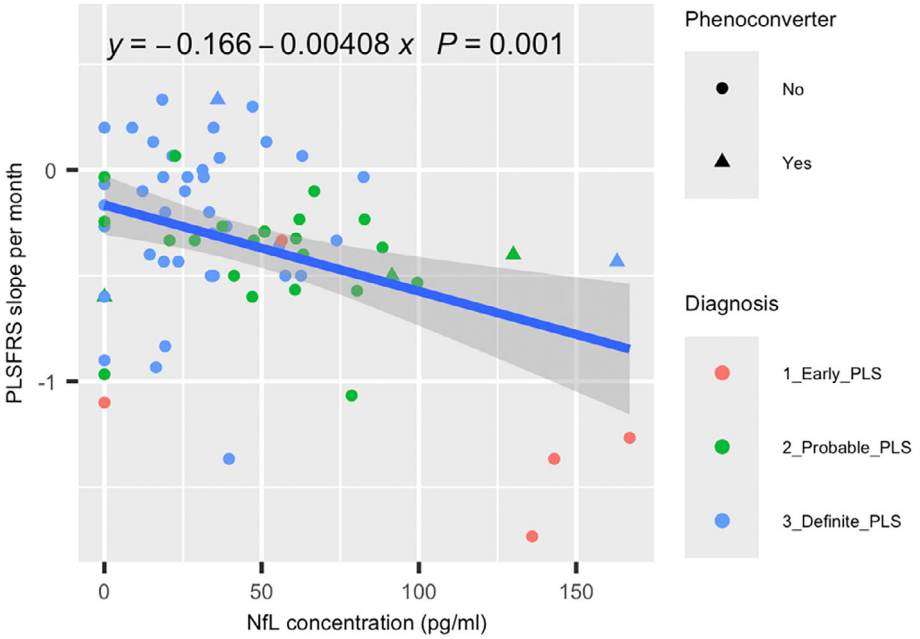

FIGURE 3: Primary lateral sclerosis functional rating scale (PLSFRS) slope (change of total score per month) over 1 year and baseline neurofilament light plasma levels. Different color codes were used to indicate primary lateral sclerosis (PLS) groups (diagnosis) and different shapes were used to indicate those with or without later diagnosis of amyotrophic lateral sclerosis (ALS) (phenoconverter).

in our study compared to the report from the Netherlands, and none of the early PLS groups in our study converted to ALS. The discrepancies in the results might be because of different durations of follow-up and small sample sizes in both studies, especially in the early groups. Ongoing long-term follow-up for up to 7 years of our cohort participants is in progress and will provide further insights.

TABLE 3. Frequencies of Durable Medical Equipment Use

	Baseline (n = 76)	1-yr follow up (n = 70)	*p*
Orthosis (leg, neck, finger, etc.)	15 (19.7%)	15 (21.4%)	0.9
Cane	25 (32.9%)	24 (34.3%)	0.9
Walker	39 (51.3%)	51 (72.9%)	0.01
Manual wheelchair	15 (19.7%)	18 (25.7%)	0.5
Power wheelchair	10 (13.2%)	14 (20%)	0.3
Alternative and augmentative communication device	8 (10.5%)	12 (17.1%)	0.3
Noninvasive ventilator	18 (23.7%), 10 BIPAP, 8 CPAP	22 (31.4%), 12 BIPAP, 10 CPAP	0.2
In/exsufflator	5 (6.6%)	5 (7.1%)	0.9
Gastrostomy	2 (2.6%)	2 (2.9%)	0.9

BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; yr = year.

In this study, we found that baseline NfL levels are associated with the rate of functional decline as measured by the PLSFRS. This finding is consistent with observations in other neurological disorders, such as ALS, where NfL is an established prognostic biomarker for the rate of progression.[36,37] Notably, NfL was not significantly associated with functional decline in the definite PLS group. This might be because of the smaller sample size and homogeneous slow progression in this subgroup. Baseline NfL levels might also inform the development of diffuse LMN degeneration, because they tended to be higher among those who later had diagnostic conversion to ALS. Our finding is in line with previous studies that have shown higher blood NfL levels among ALS patients compared to PLS patients.[37,38] The utility of NfL as a biomarker in PLS clinical trials should be further explored and validated.

PLSFRS declined linearly and was strongly correlated with ROADS, which is a patient-reported global disability scale that was originally developed for ALS. It also correlated with UMN dysfunction and quality of life measures. Subscores from each domain of the PLSFRS correlated moderately to strongly with direct performance-based measurements of function such as finger tapping, foot tapping, and pa-ta-ka repetition. These findings

support the suitability of the PLSFRS as a primary outcome measure in future PLS Trials. ROADS has not been used specifically in a PLS cohort before this study. We demonstrated that ROADS correlate strongly with PLSFRS and might serve as an alternative or adjunct patient-reported outcome measure with the potential added benefits of linear weight, unidimensional character, and ease of administration that does not require rater training.[16]

Performance-based measurements of function, such as TUG, pa-ta-ka, and finger- and foot-tapping, were feasible, however, they did not reflect the progression as sensitively compared to PLSFRS or ROADS. TUG performance was more strongly correlated with arm function than leg function, suggesting that results may have been influenced by other factors, such as the use of assistive devices or the ability to use their arms to assist with the sit-to-stand portion of the task. These findings suggest proceeding with caution when considering these assessments as outcomes for clinical trials. SVC did not decline significantly over time. Notably, among participants who were using noninvasive ventilators, approximately half were using continuous positive airway pressure (CPAP) rather than bilevel positive airway pressure (BiPAP). Respiratory impairments in PLS may be driven by bulbar dysfunction, airway obstruction, and spasticity rather than weakness of the respiratory muscles. This needs to be further studied.

Our study has limitations. Despite considerable effort, the number of participants enrolled in the study was smaller than originally planned, especially in the early group. This was due in part to the rarity of the disease, recruitment challenges during the coronavirus-19 pandemic, and limitations in our recruitment strategy, which may not have reached people with PLS followed in clinics not associated with this study. Increased detection of people with PLS through registries and multinational collaborations may enhance recruitment efforts in future studies. This study included only ambulatory PLS participants within 15 years of disease duration who would have more measurable outcome changes, potentially excluding those with longer disease duration or more rapid progression. We used EMG at baseline and follow-up to detect LMN degeneration sensitively. Still, we cannot completely exclude the possibility that our cohort may include patients whose diagnosis may be changed to UMN-dominant ALS with longer follow-up. A 1-year follow-up duration was not adequate to fully define the natural course of the disease. Further longitudinal follow-up of this cohort is ongoing and will provide information about the rate of disease progression and diagnostic stability beyond the initial year.

In summary, our findings suggest that the rate of progression in PLS is most rapid during the early stages of the disease. Targeting participants with early PLS may help reduce the required sample sizes for future clinical trials. Additionally, blood NfL may serve as a valuable biomarker for predicting disease trajectory and diagnosis change to ALS. The PLSFRS shows promise as a primary clinical outcome measure and may be effectively supplemented with patient-reported tools such as the ROADS. This information needs to be considered in future trial design.

Acknowledgments

The study received grants from the National Institute of Health, Spastic Paraplegia Foundation, ALS Association, Mitsubishi-Tanabe Pharma of America, and MDA Wings Over Wall Street. We appreciate the continuous and generous support from D. Marren and his family for the study. NeuroBank, Department of Neurology, Massachusetts General Hospital, generously offered and conducted data management for this PLS Natural History Study. We are deeply grateful to all the participants and their families for participating in this PLS natural history study, which required extensive phone calls and in-person visits to their study sites. Without their support and continued commitment, we would not have been able to complete the study.

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Potential Conflicts of Interest

Nothing to report.

Data Availability

The data that support the findings of this study are available from the corresponding author, I.L., on reasonable request.

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