Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

A Convenient Prognostic Tool and Staging System for Progressive Supranuclear Palsy

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ABSTRACT: Background: Progressive supranuclear palsy (PSP) causes major disability, shortens life, and as yet has no disease-modifying and little symptomatic treatment. A convenient prognostic tool is needed to assist patients, families, and clinicians in planning care.

Objectives: We calculated times to acquisition of certain disease milestones and death.

Methods: We followed a cohort of 417 patients with PSP–Richardson syndrome from 1995 to 2016, applying the Progressive Supranuclear Palsy Rating Scale (PSPRS) at each visit. We generated median times to acquisition of 13 milestones using the input variables of sex, onset age, rate of disease progression from motor symptom onset to initial visit, and PSPRS score at the baseline. Of the outcome milestones, 5 were stages of a new, provisional PSP staging system. The other 8 milestones comprised death and disabling levels of cognitive loss, gaze palsy, dysarthria, dysphagia, and gait/balance impairment.

Results: We derived median times to milestones, with 25th and 75th percentiles and 95% confidence intervals of the median for baseline PSPRS scores from 25 to 65 (scale range, 0–100). Sex and initial progression velocity significantly influenced the death milestone, but not most of the others. Median time to death ranged from 4.8 years for a man with PSPRS score of 25 and a slow progression velocity from onset to initial visit of 0.51 PSPRS points/month to 1.8 years for a woman with PSPRS 65 and rapid initial velocity of 2.25 points/month.

Conclusions: We have created a convenient, inexpensive, noninvasive reference for counseling patients with PSP–Richardson syndrome on approximate time to encountering 13 life-altering disease milestones.

Median survival in progressive supranuclear palsy (PSP)–Richardson's syndrome is reported by various studies as 6 to 7.4 years from symptom onset.[1–3] Experience suggests that from the time they first understand that PSP is a progressive and poorly treatable condition, patients and families are interested in specific prognostic information. Many patients and families request not only an estimate of survival duration but also of time to disease milestones that may influence decisions to retire from work, hire caregivers, alter the home environment, move to a seniors-oriented or institutional living arrangement, decide on a feeding gastrostomy and not least, prepare psychologically for advanced disability and death. Many also ask if there are simple but formal "stages" for PSP to use as an indicator of their own disease involvement.

Quantification of times to disease milestones may also assist in interventional trial design, where acquisition of one or more important disability milestones may serve as a primary outcome measure. Such data in untreated patients may be useful in calculations of statistical power, as the comparator in futility studies, and perhaps as a primary outcome measure in efficacy studies.

In 2007, we[1] proposed and validated the Progressive Supranuclear Palsy Rating Scale (PSPRS) using serial examinations in patients seen at our center from 1995 to 2005 (Table S1). The analysis included prognostic calculations but its outcome variables comprised only subsequent PSPRS scores, need for gait assistance, and death. The N of 162 produced 95% confidence intervals that in many cases were too wide for patients and families to use for planning purposes. For example, for a patient with a PSPRS score in the 50s, we calculated the likelihood of surviving at least 3 more years as 26%, with a 95% confidence interval of 16.8% to 40.2%. The main purpose of the current study is to generate more precise prognostic information by using the larger

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N now available and to refine the predictions by considering other preexisting variables.

In applying the PSPRS, we have found that patients and families understand a timespan to a disability milestone more easily than a percentage likelihood of an outcome by a specified year. Therefore, the current study uses years to milestones as its outcome measures.

In its prognostic calculations, our 2007 report considered the most recent PSPRS score and its progression over multiple visits, but not the velocity of progression from PSP onset to the time of the visit. To make a single PSPRS examination usable for prognostic purposes, the current analysis stratifies on progression velocity since onset.

Although our 2007 report found no sex difference in rate of disease progression ($P = 0.46$) on univariate comparison, 1 of our 8 multivariate models of disease progression did find a trend of sex on survival, with $\chi^2 = 4.8$, $P = 0.028$. This prompted us to consider sex in our present analysis.

The effect of onset age on progression in our 2007 analysis was complex. Younger onset correlated with longer survival ($P = 0.008$), but the relationship evolved over time. Patients with onset before age 65 years progressed more slowly during the first 2 or 3 years of illness, only to accelerate subsequently, whereas the rate slowed for older-onset subjects. The result was that by 6 or 7 years of illness, the mean scores across all onset-age subject groups converged. We therefore included onset age in our present model.

For these reasons, our analysis calculates times to disease milestones using the following input variables: sex, onset age, PSPRS score at baseline (ie, first or current visit), and velocity of progression (in PSPRS points per month) from onset to baseline, assuming a score of 0 at onset.

The milestones we use as outcomes include specific advanced scores on 8 PSPRS items related to cognition, dysarthria, dysphagia, gaze palsy, gait loss, and postural instability. The gaze palsy milestone combines scores from up-gaze, down-gaze, and right/left-gaze PSPRS items.

As additional outcome measures, we created a series of 5 PSP stages using PSPRS items relating to dysphagia and postural instability, the 2 areas of deficit in PSP that lead most directly to serious morbidity and mortality. Before using the newly devised stages as outcome measures, we attempted to validate them by demonstrating their progression in parallel with the total 28-item PSPRS score.

Methods

Subjects and Data Collection

The National Institute of Neurological Disorders and Stroke–Society for PSP (NINDS-SPSP) criteria were published in 1996,[4] before most of the PSP variants were well described. The Movement Disorder Society PSP Criteria, published in 2017, proposed definitions of most of the variants. Its criteria for the classic "PSP–Richardson's syndrome" are identical to the NINDS-SPSP criteria and are those used in this study.

Author L.I.G. administered the PSPRS to each patient with known or suspected PSP seen in a referral clinic for atypical parkinsonism at the Movement Disorders Center at Rutgers Robert Wood Johnson Medical School in New Brunswick, NJ. All patients met NINDS-SPSP criteria[4] for probable PSP by the time of the most recent visit, although the earlier visits and PSPRS examinations were in many cases conducted before the patient met diagnostic criteria.

The 337 patients included in the data analysis for the provisional staging system development were all of those with PSP examined at least once between January 1, 1995, and June 30, 2013. Only the baseline visits were analyzed for the staging system formulation.

By June 30, 2016, our database included 417 patients, which was the final N used in the prognostic calculations. Of these, 162 (39%) were included in our 2007 analysis reporting and validating the PSPRS.[1] In addition to scores for each of the 28 items on the PSPRS, our database recorded year of birth, sex, and the months and years of PSP motor onset, each visit, and death.

Input Variables

Our prognostic analysis used 4 input variables using data available at baseline: onset age, sex, current PSPRS score, and velocity of PSPRS progression as defined by baseline (ie, first visit) PSPRS score divided by months since PSP onset.

We defined PSP onset as the first occurrence of any motor sign or symptom known to occur in PSP and progressing in concert with other features of PSP appearing subsequently. We considered nonrefractable visual "blurring" to be an expression of gaze fixation difficulty and we considered "dizziness" as an expression of postural instability. Both therefore qualified as the initial motor symptom. When a patient or family could date the gradual onset only to a year, we assigned July as the onset month and if "early" or "late" in a year was reported, we assigned March or October, respectively.

Outcome Variables

To serve as a measure of overall PSP severity in our prognostic calculations, we created a provisional PSP staging system applicable to PSP–Richardson's syndrome. First, we drafted five candidate systems, each conveniently derivable from PSPRS scores and requiring no additional history or examination. Four of the candidates used only PSPRS items relating to swallowing and gait, and 1 used items on swallowing, gait, cognition, and eye movement. For each candidate system, we assessed validity by calculating the R^2 value for the linear correlation between the stage and time (in months) since symptom onset.

Our rationale for considering so few deficit areas in formulation of the provisional stages was based on speed and convenience. As PSP involves so many areas of the central nervous system, attempting to include a majority of them would cause the staging procedure to approach the PSPRS itself in time and

effort required. Instead, we attempted to create a proxy for the full PSPRS by assessing dysphagia and postural instability as these are the 2 most important contributors to PSP morbidity and mortality.

In addition to the stages, we included 7 disability milestones plus death, for a total of 13 outcome variables, all defined in Table 1.

Statistical Analysis

We calculated the mean (with standard deviation) time in months to each of the 13 milestones using every permutation of our 4 input variables.

We used parametric survival regression to assess the contribution of progression, total PSP score, and sex on progression to the outcome variables listed in Table 1. We identified the best-fitting models by comparing multiple parametric survival models, including log-logistic, log-normal, Weibull, and gamma coefficient via Akaike's information criterion. We considered the following covariates for each outcome: onset age, sex, and velocity of progression from onset to the first visit using backward stepwise selection with type 3 Wald chi-square tests to test for significance. Covariates were eliminated using $\alpha = 0.10$. The median gives the time in months to which 50% of the population will survive without experiencing a given outcome. We also calculated 95% confidence intervals for the median as well as the 25th and 75th percentiles. We used the gamma coefficient to model survival times to our outcome variables.

Results

Demographic data, time from onset to first visit, baseline PSPRS score, and number of visits analyzed appear in Table 2. There were no statistically significant sex differences.

Of our 5 candidate staging systems, the 1 providing the best correlation with time since onset ($r = 0.61$; Fig. 1) and with the overall PSPRS ($r = 0.99$; Fig. 2) uses the scores of 4 PSPRS items. These comprise 1 history-based dysphagia item regarding solid foods and 3 exam-based items: dysphagia for liquids as observed by having the patient drink water, gait as evaluated by observation of the patient walking unassisted, and truncal bradykinesia as evaluated by watching the patient arise from a chair without use of the hands. The sum of those 4 scores is

TABLE 1. ***Outcome variables used in the prognostic analysis***

Outcome Variable (Milestone)	PSPRS Items Used to Define Milestone	Definition (Figures Are Item Score Totals)
Stage 0	The stage definitions refer to the total of these scores:	Total = 0
Stage 1		Total = 1–4
Stage 2	#3 (dysphagia for solids by history)	Total = 5–8
Stage 3	#13 (dysphagia for liquid by exam)	Total = 9–12
Stage 4	#26 (gait by exam)	Total = 13–15
Stage 5	#28 (returning to seat by exam)	Total = 16
Severe dysphagia	#3 (dysphagia for solids by history)	>2 (needs purees or tube feeding)
Severe dysphagia	#13 (dysphagia for liquid by exam)	>2 (high aspiration risk or needs tube feeding)
Severe dysarthria	#12 (dysarthria by exam)	>2 (most or all words incomprehensible)
Severe gaze palsy	#14 (upgaze), #15 (downgaze), and #16 (right/left gaze)	Total >8 (moderate to severe overall gaze limitation)
Severe bradykinesia	#25 (arising from a chair)	>3 (unable to arise from chair unassisted, even with use of hands to push from seat)
Severe postural instability	#26 (gait)	>2 (requires assistance or gait aid)
Cognitive impairment	Total of #8 and #9	Total >4 (moderate disorientation and bradyphrenia)
Death	–	Relied on report by family

TABLE 2. ***Demographic and baseline characteristics***

Characteristic	Total	Women	Men
N (%)	417	209 (50.1)	208 (49.9)
>12 months under observation	223 (53.5)	109 (52.2)	114 (54.8)
≤12 months under observation	194 (46.5)	100 (47.8)	94 (45.2)
Mean (standard deviation)			
Onset age	67.7 (7.7)	68.3 (7.8)	67.1 (7.6)
Months from onset to first visit	45.5 (30.9)	44.0 (32.6)	47.3 (29.1)
Age at first visit	71.5 (7.4)	72.0 (7.5)	71.0 (7.3)
Progressive Supranuclear Palsy Rating Scale at first visit	40.8 (15.1)	41.7 (15.0)	39.9 (15.2)
Number of visits during period of observation	3.7 (3.2)	3.7 (3.4)	3.6 (3.0)

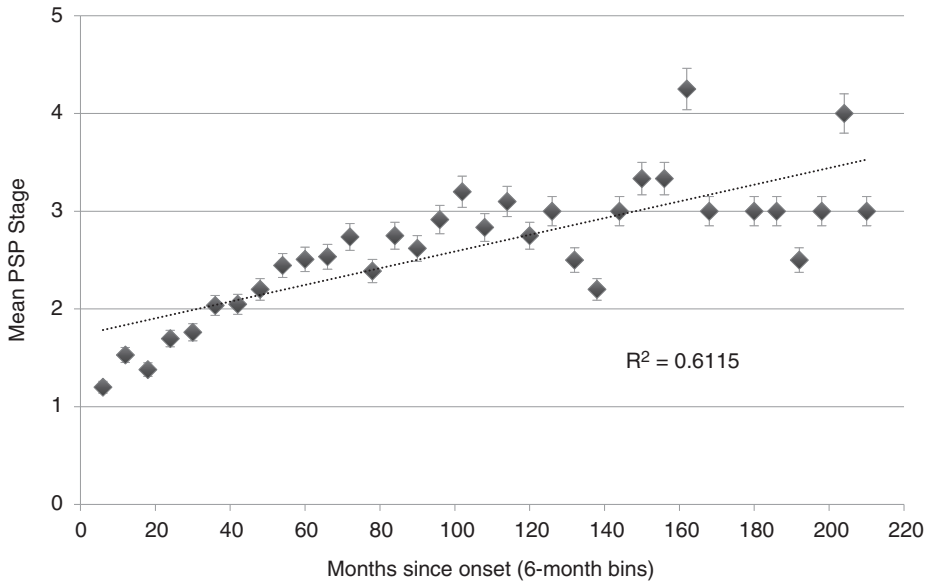

FIG 1. Relationship between months since motor symptom onset (with standard error bars) and PSP stage as defined in Table 1. Our main analysis uses the stages only as disability outcome milestones, not as input variables for the purpose of calculating time to the other outcome milestones. PSP, progressive supranuclear palsy.

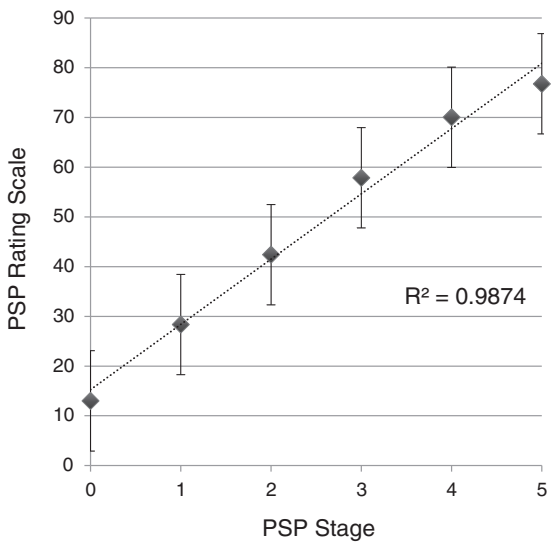

FIG 2. Relationship between total PSP Rating Scale score and PSP stage (with standard error bars) as defined in Table 1. PSP, progressive supranuclear palsy.

distributed into 5 bins (including a bin for a score of 0) as shown in the top 6 rows of Table 1.

For all of our outcome milestones other than severe postural instability and death, only the total PSPRS score at baseline was a significant predictor of time to reach that milestone. Total baseline PSPRS was marginally associated with time to reach stage 2 ($P = 0.032$) with stronger evidence for all other outcomes ($P < .001$). For the severe postural instability outcome milestone, we found a significant predictive relationship not only for the total baseline PSPRS, but also for sex ($P < .001$). For death as the outcome milestone, we found a predictive relationship not only for baseline PSPRS but also for both onset-to-baseline progression velocity ($P = 0.013$) and sex ($P = 0.022$), with women progressing to death more quickly than men.

Discussion

To implement our prognostic tool in the clinic, the physician would refer to Table 3 for time to disability milestones and to Table 4 for time to death. For Table 3, only the baseline total PSPRS score and, for 1 of the milestones, sex, are the statistically relevant input variables. For Table 4, the input variables are baseline total PSPRS, progression velocity from symptom onset to baseline (as PSPRS points per month), and sex.

A large literature has delineated prognostic factors in PSP, but there has been little or no attempt to use easily obtained data to calculate specific prognostic expectations of use to patients and families. Unfavorable risk factors cited have included male sex[1,2,4]; older onset[2,4,5]; younger onset[6]; initial progression velocity[4,7]; early appearance of dysarthria,[7] dysphagia,[5,7–10] dementia,[5,11,12] depression,[12] falls,[6,7,10] incontinence,[10] subjective diplopia,[7] or downgaze palsy[6];

TABLE 3. ***Prognostic estimates for disability milestones in PSP***

		Years to Reach Disability Milestone			
PSPRS at Baseline	Disability Milestone	25th %ile	Median	75th %ile	95% CI of Median
25	Stage 2	1.4	0.8	0.5	0.71–0.97
35		1.1	0.6	0.4	0.52–0.81
25	Stage 3	3.2	2.2	1.4	1.91–2.53
35		2.2	1.5	1.0	1.37–1.68
45		1.5	1.1	0.7	0.92–1.19
55		1.0	0.7	0.5	0.59–0.88
45	Stage 4	4.1	2.9	1.9	2.50–3.31
55		3.2	2.1	1.4	1.80–2.56
65		2.3	1.6	1.1	1.25–2.05
45	Stage 5	7.3	4.9	2.4	3.41–6.99
55		5.2	3.4	1.7	2.51–4.68
65		3.6	2.4	1.2	1.78–3.26
35	Moderate dysphagia for solids	7.6	4.6	2.9	3.63–5.86
45		5.2	3.1	2.0	2.55–3.84
55		3.5	2.1	1.3	1.71–2.62
65		2.4	1.4	0.9	1.11–1.86
25	Moderate dysarthria	5.5	3.5	2.1	2.86–4.19
35		3.8	2.4	1.4	2.07–2.71
45		2.6	1.6	1.0	1.41–1.86
55		1.8	1.1	0.67	0.91–1.35
65		1.2	0.8	0.5	0.57–1.00
25	Needs purees	3.9	2.5	1.5	2.14–3.02
35		3.5	2.2	1.3	1.95–2.51
45		3.0	1.9	1.1	1.66–2.22
55		2.6	1.7	1.0	1.35–2.07
65		2.3	1.5	0.8	1.07–1.96
25	Moderate ocular gaze palsy	4.3	2.5	1.4	2.03–2.99
35		3.2	1.8	1.1	1.59–2.14
45		2.4	1.4	0.8	1.15–1.65
55		1.8	1.0	0.6	0.79–1.34
65		1.3	0.8	0.4	0.53–1.11
25	Needs help to arise from chair	3.8	2.4	1.5	2.03–2.86
35		2.7	1.7	1.0	1.52–1.93
45		1.9	1.2	0.7	1.05–1.42
55		1.4	0.9	0.5	0.69–1.09
65		1.0	0.6	0.4	0.44–0.86
Men	Needs help with gait most of the time				
25		1.8	1.2	0.7	0.97–1.39
35		1.3	0.8	0.5	0.69–0.98
45		0.9	0.6	0.4	0.46–0.74
55		0.6	0.4	0.3	0.29–0.58
65		0.4	0.3	0.2	0.19–0.45
Women					
25		2.6	1.7	1.1	1.45–2.08
35		1.9	1.2	0.8	1.04–1.45
45		1.3	0.9	0.5	0.70–1.09
55		0.9	0.6	0.4	0.45–0.84
65		0.7	0.4	0.3	0.29–0.66
25	Moderate cognitive loss	6.1	4.1	2.4	2.92–5.70
35		4.4	3.0	1.7	2.30–3.86
45		3.2	2.2	1.3	1.74–2.71
55		2.4	1.6	0.9	1.24–2.02
65		1.7	1.2	0.7	0.85–1.58

These estimates to milestone acquisition are applicable only to patients who have not yet acquired that milestone. The lone statistically significant input variable for most of the milestones is total PSPRS at the baseline visit (ie, the visit at which the estimate is made). The "Needs help with gait most of the time" milestone is the only one for which sex is also a statistically significant contributor. Definitions of the stages and other disability milestones appear in Table 2. Results for clinically implausible combinations of input variables are not shown. For PSPRS item descriptions and scoring rubrics, see Table S1 or reference 1. PSP, progressive supranuclear palsy; PSPRS, Progressive Supranuclear Palsy Rating Scale; CI, confidence interval.

TABLE 4. ***Prognostic estimates for time to death in PSP***

		Women Years to Death				Men Years to Death			
PSPRS at the Current Visit	Velocity (PSPRS Points Per Month from Onset to Initial Visit)	25th %ile	Median	75th %ile	95% CI of Median	25th %ile	Median	75th %ile	95% CI of Median
25	0.51	5.7	4.2	2.9	3.46–4.98	6.6	4.8	3.3	4.02–5.72
	0.62	5.7	4.1	2.9	3.43–4.91	6.6	4.7	3.3	3.99–5.64
	0.73	5.6	4.1	2.8	3.40–4.85	6.5	4.7	3.3	3.95–5.57
	0.87	5.5	4.0	2.8	3.36–4.77	6.4	4.6	3.2	3.91–5.47
	1.01	5.5	4.0	2.7	3.32–4.69	6.3	4.6	3.2	3.86–5.38
	1.16	5.4	3.9	2.7	3.27–4.62	6.2	4.5	3.1	3.81–5.29
	1.37	5.3	3.8	2.6	3.20–4.52	6.1	4.4	3.0	3.73–5.17
	1.78	5.0	3.7	2.5	3.06–4.35	5.8	4.2	2.9	3.57–4.96
	2.25	4.8	3.5	2.4	2.89–4.18	5.5	4.0	2.8	3.38–4.76
35	0.51	4.9	3.5	2.4	3.01–4.10	5.6	4.1	2.8	3.51–4.71
	0.62	4.8	3.5	2.4	2.99–4.05	5.6	4.0	2.8	3.48–4.64
	0.73	4.8	3.4	2.4	2.96–3.99	5.5	4.0	2.8	3.45–4.57
	0.87	4.7	3.4	2.4	2.92–3.93	5.4	3.9	2.7	3.41–4.49
	1.01	4.6	3.3	2.3	2.89–3.87	5.3	3.9	2.7	3.37–4.42
	1.16	4.6	3.3	2.3	2.85–3.80	5.3	3.8	2.6	3.32–4.34
	1.37	4.5	3.2	2.2	2.78–3.72	5.1	3.7	2.6	3.26–4.25
	1.78	4.3	3.1	2.1	2.66–3.59	4.9	3.6	2.5	3.12–4.08
	2.25	4.1	2.9	2.0	2.50–3.46	4.7	3.4	2.4	2.94–3.93
45	0.51	4.1	3.0	2.1	2.57–3.46	4.8	3.4	2.4	2.99–3.96
	0.62	4.1	2.9	2.0	2.54–3.41	4.7	3.4	2.4	2.96–3.90
	0.73	4.0	2.9	2.0	2.52–3.36	4.7	3.4	2.3	2.94–3.85
	0.87	4.0	2.9	2.0	2.49–3.31	4.6	3.3	2.3	2.91–3.78
	1.01	3.9	2.8	2.0	2.46–3.26	4.5	3.3	2.3	2.87–3.72
	1.16	3.9	2.8	1.9	2.42–3.21	4.5	3.2	2.2	2.83–3.66
	1.37	3.8	2.7	1.9	2.37–3.14	4.4	3.2	2.2	2.77–3.58
	1.78	3.6	2.6	1.8	2.25–3.03	4.2	3.0	2.1	2.65–3.44
	2.25	3.4	2.5	1.7	2.12–2.92	4.0	2.9	2.0	2.49–3.32
55	0.51	3.5	2.5	1.8	2.13–2.98	4.0	2.9	2.0	2.48–3.42
	0.62	3.5	2.5	1.7	2.11–2.94	4.0	2.9	2.0	2.46–3.37
	0.73	3.4	2.5	1.7	2.09–2.91	3.9	2.9	2.0	2.44–3.32
	0.87	3.4	2.4	1.7	2.06–2.86	3.9	2.8	2.0	2.41–3.27
	1.01	3.3	2.4	1.7	2.04–2.82	3.8	2.8	1.9	2.38–3.22
	1.16	3.3	2.4	1.6	2.01–2.77	3.8	2.7	1.9	2.34–3.17
	1.37	3.2	2.3	1.6	1.96–2.72	3.7	2.7	1.9	2.29–3.1
	1.78	3.1	2.2	1.5	1.87–2.62	3.5	2.6	1.8	2.19–2.98
	2.25	2.9	2.1	1.5	1.76–2.53	3.4	2.4	1.7	2.07–2.87
65	0.51	3.0	2.1	1.5	1.74–2.62	3.4	2.5	1.7	2.03–3.00
	0.62	2.9	2.1	1.5	1.72–2.59	3.4	2.4	1.7	2.01–2.96
	0.73	2.9	2.1	1.5	1.71–2.55	3.3	2.4	1.7	1.99–2.93
	0.87	2.8	2.1	1.4	1.68–2.52	3.3	2.4	1.7	1.96–2.88
	1.01	2.8	2.0	1.4	1.66–2.48	3.2	2.3	1.6	1.94–2.84
	1.16	2.8	2.0	1.4	1.63–2.44	3.2	2.3	1.6	1.91–2.79
	1.37	2.7	2.0	1.4	1.60–2.39	3.1	2.3	1.6	1.87–2.73
	1.78	2.6	1.9	1.3	1.52–2.31	3.0	2.2	1.5	1.78–2.63
	2.25	2.5	1.8	1.2	1.43–2.22	2.9	2.1	1.4	1.68–2.53

The left-most column refers to the PSPRS at the "current visit," when the estimate is being made. The second column refers to the progression velocity in PSPRS points per month from the initial symptom to the first visit, even if that is not the current visit.
PSP, progressive supranuclear palsy; PSPRS, Progressive Supranuclear Palsy Rating Scale; CI, confidence interval.

Richardson's disease phenotype[13,14]; sleep disturbances[15]; higher cerebrospinal fluid neurofilament light chain[16–19] or total tau[16]; and lower cerebrospinal fluid phospho-tau/total tau ratio.[19] An excellent literature review[20] analyzing a total of 1911 previously reported patients with PSP concluded that shorter overall survival was associated with early appearance of dementia, falls, or dysphagia and with greater scores on the Neuroprotection and Natural History in Parkinson-Plus Syndromes Parkinson-Plus Score or Clinical Global Impression of Disease Severity Scale.

Our original goal in devising the PSPRS[1] was to provide clinicians with a tool for serial assessment of patients receiving routine care for PSP. Since its 2007 publication, the PSPRS has become a popular outcome measure for PSP in formal

interventional and observational research. The total PSPRS score has been demonstrated to progress in a linear fashion over most of the course of the illness in patients with PSP–Richardson's syndrome, with an average worsening of approximately 11 points per year.[21] Such linearity suggests that the current PSPRS score may provide a convenient and inexpensive basis for prognostic estimates, especially if corrected for known covariates. We presented a rudimentary version of such a prognostic model in our 2007 description of the PSPRS using data from 162 patients.[1] The current analysis increases the N to 417, allowing us to analyze multiple variables with greater statistical power and to reduce our 95% confidence intervals usefully.

We created and validated a provisional, convenient staging system for PSP as a source of additional outcome milestones. The staging system relies only on dysphagia and gait/balance data from the PSPRS, chosen because of their central role in morbidity and mortality in PSP. Validation of the staging system so far relies on its correlations with time since symptom onset (Fig. 1) and with the full PSPRS (Fig. 2). A recent analysis supports our choice to use only dysphagia and gait/balance in formulating the staging system.[22] It calculated the relative normalized contributions of the 6 PSPRS components to the total PSPRS as the total worsened over time. It found that the "gait" component progressed the fastest relative to the other 5, with 90% of patients reaching the "severe" state in the gait-related items (ie, the worst of the 3 states available in that model) by the time the total PSPRS score reached 40 (of 100). On the other hand, the "bulbar" component was the slowest to progress relative to the others. For those PSPRS items, in patients with a PSPRS score of 40, no patients were "severe" and 35% were "moderate." Even when the total PSPRS reached the very severe score of 90, the fraction with "severe" bulbar score reached only 20%. We therefore conclude that a staging system combining these gait and bulbar components could allow sensitive discrimination in both the earlier and later phases of the disease course.

Our study's weaknesses are that only 1 examiner was involved, most cases were not autopsy confirmed, we relied on medical records and anamnestic reports of patients and families to determine symptom onset dates, and we excluded patients with PSP phenotypes who never reached the point of satisfying the NINDS-SPSP criteria, which describe what was subsequently called PSP–Richardson syndrome. The staging system that we devised as a source of additional output variables must remain provisional until further validated.

Our study's strengths are an N large enough to provide narrow 95% confidence intervals for our prognostic estimates; a duration of observation far exceeding 12 months in a majority of subjects; use of the PSPRS, which has been validated in multiple ways as a PSP outcome measure and for which ample formal trial experience exists; ready availability and convenience of the input variables from bedside history and neurological examination; and perhaps most important, the ability to provide patients and families with a specific time estimate to the appearance of disease milestones important to daily functioning. It would now be useful to assess the validity of our prognostic data in prospective fashion and using multiple examiners. The multiple PSP phenotypes formally defined in 2017[23] should become input variables for a future prognostic study.■

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

L.I.G.: 1A, 1B, 1C, 2C, 3A
P.O.-S.: 1B, 2A, 2B
E.B.B.: 1C, 2B, 2C
F.T.E.: 1C, 2C, 3B

Disclosures

Ethical Compliance Statement: This study was approved by the Institutional Review Board of Rutgers Robert Wood Johnson Medical School. Informed consent was not necessary for this work. All authors confirm that they have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Appendix S1. Rationale for choice of statistical tests.

Table S1. The PSP Rating Scale.[1] This scale is designed to be applied by persons with neurological training. It requires about 10 minutes to administer to a mildly affected patient. Responses to the historical items (1–7) should be decided by the examiner after considering both the patient's and the caregiver's responses. It is important to note that this is not a diagnostic scale, but a measure of neurological damage.