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Predicting early cognitive decline in newly-diagnosed Parkinson's patients: A practical model

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Abstract

Objective: To create a multivariable model to predict early cognitive decline among de novo patients with Parkinson's disease, using brief, inexpensive assessments that are easily incorporated into clinical flow.

Methods: Data for 351 drug-naïve patients diagnosed with idiopathic Parkinson's disease were obtained from the Parkinson's Progression Markers Initiative. Baseline demographic, disease history, motor, and non-motor features were considered as candidate predictors. Best subsets selection was used to determine the multivariable baseline symptom profile that most accurately predicted individual cognitive decline within three years.

Results: Eleven per cent of the sample experienced cognitive decline. The final logistic regression model predicting decline included five baseline variables: verbal memory retention, right-sided bradykinesia, years of education, subjective report of cognitive impairment, and REM behavior disorder. Model discrimination was good (optimism-adjusted concordance index = .749). The associated nomogram provides a tool to determine individual patient risk of meaningful cognitive change in the early stages of the disease.

Conclusions: Through the consideration of easily-implemented or routinely-gathered assessments, we have identified a multidimensional baseline profile and created a convenient, inexpensive tool to predict cognitive decline in the earliest stages of Parkinson's disease. The use of this tool would generate prediction at the individual level, allowing clinicians to tailor medical management for each patient and identify at-risk patients for clinical trials aimed at disease modifying therapies.

Keywords

Parkinson's disease; Cognitive decline; Prognosis; Mild cognitive impairment (MCI)

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1. Introduction

Cognitive impairment is a common feature of idiopathic Parkinson's disease (PD), impacting patients' quality of life and raising costs of care and caregiver burden [1,2]. In an era of increasing focus on patient-centered care and shared medical decision-making, there is a need to develop tools to predict each patient's likelihood of developing cognitive impairment. Moreover, with disease-modifying therapies on the horizon, predicting cognitive decline early in the disease state is crucial to select appropriate patients for clinical trials that may influence the trajectory of cognitive symptoms. The current literature consists largely of bivariate analyses associating cognitive outcomes with individual biomarkers [3,4], motor symptom profiles [5,6], mood variables [7], or individual non-motor symptoms such as sleep disorders [8]. However, clinicians who are treating and providing prognoses to patients must consider multiple patient characteristics simultaneously, and there exists little literature that synthesizes the effect of multiple patient characteristics on cognition.

Prediction models can assist in the prognosis of early cognitive decline (ECD) by combining multiple clinical correlates in a single mathematical equation, thereby allowing clinicians to determine each newly-diagnosed patient's personal risk of ECD, given his or her unique characteristics. The current study aims to create a multivariable model to predict ECD among de novo PD patients. Though a few recent studies have sought to predict cognitive impairment or decline in PD [9,10], ours is unique as it uses higher-resolution metrics for assessment of cognitive function to predict individual cognitive decline compared to each patient's baseline ability in the earliest stages of disease. We propose the exclusive use of baseline assessments that are either already routinely obtained or could be reasonably implemented during a typical neurologist's office visit, such as motor examination, validated self-report questionnaires, and brief cognitive screening measures to allow inexpensive, widespread use of the model.

2. Methods

Study design.

Data were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). PPMI is a large, multicenter, prospective cohort study that follows drug-naïve, de novo PD patients and matched healthy controls, with the primary goal of identifying biomarkers of PD progression. Specific aims and methods have been published [11]; for up-to-date study information, visit www.ppmi-info.org. Each participating PPMI site received approval from an ethical standards committee on human experimentation and obtained written informed consent.

Participants.

Patients were enrolled between June 2010 and April 2013. At baseline, all were required to be over the age of thirty, have been diagnosed within two years but be drug-naïve, and have dopamine transporter deficit evident on 123I-ioflupane dopamine transporter (DATScan®) imaging. Two of resting tremor, rigidity, and bradykinesia were required to have been present, or either asymmetric resting tremor or asymmetric bradykinesia. Global cognitive

functioning must have been intact at screening as indicated by a Montreal Cognitive Assessment (MoCA) score above twenty-six. The current study included all PD patients with cognitive testing scores available at baseline and follow-up year three.

Early cognitive decline.

Consistent with the Movement Disorder Society Mild Cognitive Impairment task force Level I guidelines [12], we defined ECD as a baseline to year three reduction of at least 1.5 standard deviations on two or more of the following tests: Hopkins Verbal Learning Test Revised (HVLT), which measures verbal memory; Benton Judgment of Line Orientation (JOLO), which is a measure of visuospatial function; Semantic fluency (animals), which measures speeded lexical search; Wechsler Adult Intelligence Scale–3rd Edition Letter Number Sequencing subtest, which measures verbal working memory; and Symbol Digit Modalities Test (SDMT), a measure of processing speed.

Candidate predictors.

All assessments were conducted yearly, and baseline assessments were considered as potential predictors. Demographic variables were age, sex, and education. Disease history variables included side of symptom onset, years since diagnosis (classified as greater than or less than or equal to one), and Hoehn and Yahr stage. Standardized cognitive scores (described above), depression (Geriatric depression scale score > 5), subjective report of cognitive impairment (MDS-UPDRS-I 1.1 score > 0), anosmia (University of Pennsylvania smell identification test score > 17), REM behavior disorder (RBD) (REM sleep disorder questionnaire score > 4), daytime sleepiness (Epworth sleepiness scale score > 7), and presence of nighttime sleep problems, pain, urinary problems, or constipation (MDS-UPDRS-I 1.7, 1.9, 1.10, 1.11) were also considered. The following lateralized continuous motor symptom variables were created by summing appropriate MDS-UPDRS-III items: appendicular rigidity (leg agility, upper and lower rigidity), appendicular bradykinesia (finger tapping, hand movements, pronation-supination, toe-tapping), and tremor (postural, kinetic, upper and lower rest tremor amplitude). Axial features were summed (facial expression, speech, neck rigidity, arising from chair, posture/stability, global spontaneity of movement) and gait problem was coded as present or absent (gait, freezing of gait).

Statistical analysis.

Descriptive statistics were calculated for the sample. Bivariate associations between each candidate predictor and the outcome were assessed with simple logistic regression models. Best subsets selection was used to determine which candidate predictors would be included in the final binary logistic regression model. This technique uses a branch-and-bound algorithm to identify best models for each possible number of predictor variables using the global chi-square statistic. We elected to relax the ten events per variable convention in order to adequately control for the effect of participant education on the outcome [13]. Multicollinearity of the final model was assessed.

The discriminatory ability of the final model was evaluated using the concordance (c) statistic. The c-statistic ranges from 0.5 to 1.0 and reflects the ability of the model to classify patients into correct outcome groups; a value of 0.5 signifies the model is no better than a

coin toss, and a value of 1.0 signifies perfect prediction. Bootstrap resampling was used for validation: one thousand alternate datasets of the same size as the original were generated by resampling the original sample with replacement. The model was then applied to each alternate dataset to calculate Harrell's optimism and adjust the c-statistic accordingly [14]. Model calibration was examined by plotting observed probabilities against predicted probabilities; a well-calibrated model is likely to display consistent performance in discrimination when applied to novel samples. For clinical utility and to visualize the impact of each predictor on the outcome, a prognostic nomogram was created.

Analyses which aimed to test a hypothesis (bivariate associations, post-hoc analyses) were two-tailed with significance of $p < .05$. Analyses were conducted on complete cases using SAS Studio v. 3.5 and R v. 3.3.0.

Post-hoc analyses.

Because subjective experiences of cognitive impairment can be influenced by depression and poor sleep, the associations between subjective cognitive impairment and depression and poor sleep were assessed using Pearson chi-square tests. Baseline standardized cognitive scores were also compared between those who reported cognitive difficulty at baseline and those who did not, using independent-samples t-tests.

3. Results

The sample included 351 patients. The sample was predominantly male (66%), White (95%), and highly-educated (mean = 16.3 years, SD = 2.7) with an average age of 60.9 (SD = 9.9). Thirty eight patients (11%) experienced ECD. Of those who declined, twenty-five declined in two tests, eleven declined in three tests, and two declined in four tests. Of the patients who experienced ECD, the highest proportion declined on the HVLT (86.11%), followed by semantic fluency (31.58%), letter number sequencing (26.32%), symbol digit modalities (20.59%), and JOLO (19.44%). Further sample characteristics stratified by ECD and unadjusted odds ratios for preliminary bivariate analyses are presented in Table 1.

The final model included five baseline variables and is presented in Table 2: HVLT retention t-score (reflecting percentage of learned words that were recalled after a 20 min delay), right-sided bradykinesia score, years of education, subjective report of cognitive impairment, and RBD. Model discrimination was good, with an optimism-adjusted c-statistic of 0.749 (unadjusted c-statistic = 0.776; 95% CI 0.691–0.86); given two future patients, one from each outcome group, there is a 75% chance that the model would classify the patient who experienced ECD as higher risk than the patient who did not experience ECD. Calibration was satisfactory (Fig. 1). The nomogram created from the model is presented in Fig. 2. Alternatively, the logistic regression equation for the model could be programmed in a computer interface for clinical use, using Table 2's full model coefficients.

Though the model's primary purpose lies in its holistic utility for prediction, odds ratios for each variable in the model are also presented in Table 2. All variables except RBD displayed significant associations with the outcome. In detail, when holding other variables constant, those who reported subtle subjective cognitive difficulties at baseline had three times the

odds of ECD (95% CI 1.47–6.69, $p = .003$), an increase of one point in bradykinesia score yielded an 20% increase in odds of ECD (95% CI 1.05–1.37, $p = .008$), and every increase of one point on HVLTL retention returned a 6.8% increase in odds of ECD (95% CI 1.04–1.1, $p < .001$). Education provided a protective effect, such that every additional year of education brought an 18% reduction in odds of ECD (95% CI 0.71–0.96, $p = .02$). No collinearity existed among the predictors.

Post hoc analyses.

There was no significant association between baseline subjective cognitive complaints and poor sleep (Chi square test, $p = .31$) or depression (Chi square test, $p = .13$). Those who reported subjective cognitive difficulties at baseline displayed lower scores on SDMT (mean difference = 2.5 points, two-sided t -test, $p = .02$) and on JOLO (mean difference = 0.87 points, two-sided t -test, $p = .009$) than those reporting no cognitive complaints.

4. Discussion

Our findings indicate that it may be possible to predict early cognitive decline among recently-diagnosed PD patients on the basis of clinically-available baseline characteristics. The result of our work provides a convenient tool that can help clinicians objectively assess each newly-diagnosed PD patient's individual risk of ECD. It must be stressed that prognostic models differ from associative regression analyses with regards to goals and interpretation. Associative regression analyses aim to test a relationship for statistical significance and to quantify the magnitude of an effect if one exists. On the contrary, when building a prognostic model, the primary goal is to achieve the best discriminatory ability and calibration possible. That is, the best model is the model that classifies patients into correct outcome groups with the highest degree of accuracy. Because of this goal, prognostic models may include predictors that themselves are not significantly associated with the outcome, so long as they increase the discriminatory ability of the model. Likewise, predictors that have significant associations with the outcome when considered in bivariate analyses may not provide enough value in discrimination to justify inclusion in the final model. Here, we consider the contributions of individual predictors, with the caveat that the primary importance of our results lies in the usefulness of the model as a whole.

Baseline verbal memory retention was the predictor of ECD with the best discriminative ability. This is understandable, given that we found memory function was the most common area of decline over the 3 year follow-up. Essentially, results indicate that the better one's baseline memory ability, the greater the risk of decline. Though a certain degree of regression to the mean is typical in longitudinal studies, the threshold for considering a year three score as having declined was rather strict at 1.5 standard deviations, and the strength of the observed association suggests that those with better memory ability at baseline may indeed have a higher risk of ECD in excess of what would be expected based on regression to the mean. In addition, the importance of the retention variable rather than initial learning indicates that memory screening with instruments like the MMSE or MOCA are not sufficient for use in predicting ECD.

In contrast, years of education was a protective factor in our model. Higher education has repeatedly been shown to reduce risk of cognitive impairment in PD [10,15], as well as in other neurodegenerative disorders [16,17]. Indeed, education level can be considered as a rough proxy of general intellectual abilities. As such, the finding of lower risk with higher educational attainment is consistent with the concept of cognitive reserve, where better general cognitive ability confers some protection from cognitive decline by buffering the functional repercussions of underlying neurodegenerative processes.

Our results demonstrate that early bradykinesia, particularly in the right hemi-body, is a predictor of ECD. This is consistent with well-established knowledge that a non-tremor dominant motor phenotype is associated with cognitive impairment [18]. However, few studies have chosen to distinguish between non-tremor motor symptoms as we have done. Indeed, we found that bradykinesia has greater predictive ability of ECD than does rigidity. This is consistent with prior work examining bivariate relationships between cognitive function and specific cardinal motor features [19]. The additional importance of bradykinesia laterality observed here was unexpected but may shed some light on the mixed findings reported in the literature. Some previous studies investigating lateralization of motor symptoms and cognition have found those with left-side symptom onset perform more poorly on cognitive tests [6], while others have found right-sided symptoms to be associated with cognitive impairment [5]. In addition to small sample sizes, these studies base laterality groupings solely on side of tremor symptoms or on a global rating of overall symptom predominance. Our results suggest that this heterogeneity in the literature may arise from differing categorization strategies and that the most appropriate indicator of laterality in studies of cognitive change should be based on bradykinesia.

Patient complaints of cognitive difficulties were important for the model, such that those who complain were three times more likely to develop ECD. This has been reported before in PD [20]. Often, subjective cognitive complaints are poorly correlated with objective cognitive function but are highly associated with presence of depressive symptoms [21,22]. Here, however, there was no relationship between cognitive complaints and depression, indicating that early PD patients may have reliable insight regarding their own cognitive status. This is consistent with a recent study looking at awareness of deficits in patients with PD-MCI, amnesic MCI and non-amnesic MCI [23]. Indeed, in our sample, those with cognitive complaints had lower baseline JOLO and SDMT, suggesting that patients may be aware of subtle changes in cognitive functioning before multi-domain deficits are detectable via neuropsychological testing.

The presence of RBD served to increase the predictive accuracy of the model, though it was not itself significantly associated with ECD. A few prior studies have demonstrated cognitive differences between patients with and without RBD [24] as well as greater cognitive progression in patients with RBD [25], although the magnitude of these effects has typically been small. Our results are consistent with these studies, suggesting that when considered in conjunction with other clinical characteristics, RBD provides some value in the prediction of ECD.

Concurrently, there were some surprises in the variables that did not contribute to the model. We had anticipated that depression would be relevant based on prior work demonstrating bivariate associations between depression and development of cognitive impairment in PD [26,27]. Of course, multivariable prediction modeling may reveal that bivariate relationships are weakened in the presence of other predictors that better account for the variance in the outcome. Interestingly, a recent study included depression in a multivariable model to predict time to global cognitive impairment [10]. This study used nine global patient cohorts (including some de novo patients) to predict time to global cognitive impairment as assessed by Mini Mental State Examination (MMSE), using both genetic and clinical predictors. They found that depression contributed less than 2% of the variance in presence of cognitive decline over 10 years from disease onset. This suggests that the presence of depression actually has only a small part to play in predicting cognitive decline and its absence in our model may not be very surprising, after all.

Our study differs from two other recently published models of cognitive decline in PD [9,10] in several important methodological ways. The first concerns the resolution of cognitive assessment. Liu and colleagues defined cognitive decline based on MMSE scores. The MMSE has the benefit of historically widespread clinical use (which allowed them to amass a large sample of patients from multiple centers). However, this measure also has known shortcomings for measuring cognitive function in PD patients [28,29]. Specifically, the MMSE lacks any measurement for executive dysfunction which is the most common and usually most marked cognitive change in this patient group. Our study, in contrast, identified cognitive decline using formal neuropsychological measures of specific cognitive functions and applied the criteria recommended by the MDS Task Force [12] for qualification of decline. Second, both our study and the Shrag study focused on the earliest years of disease whereas the Liu study included patients with a range of baseline evaluations time and follow-up up to 12.8 years after diagnosis. Most importantly, however, our approach differs from that of previously published studies in that we chose to exclusively consider current standard-of-practice assessment variables that are routinely collected in the course of clinical practice, and are accessible for clinicians without ready access to advanced laboratory and imaging analysis. The goal of the Liu and the Schrag models were to include these more elaborate measurements.

Our model is strengthened by a relatively large sample size; global cohort with entry criteria requiring unequivocally abnormal DAT scan and the absence of other features that suggest alternate diagnoses; prospectively-acquired deep phenotyping of each patient enrolled at baseline and yearly re-evaluation; and our focus on assessment of individual decline, allowing patients to serve as their own baseline, rather than cross-sectional or group-level comparison. Though the model was built using data from an abbreviated neuropsychological battery easily incorporated into clinical flow, more comprehensive neuropsychological testing could allow even greater predictive accuracy. Likewise, it is possible that patients may underreport or lack awareness of symptoms such as RBD that are more accurately detected with objective testing such as polysomnography. Additionally, when clinically implementing the model, it must be noted that it was developed in a sample that was more highly educated than the general population. Results may differ in populations with fewer years of education. Another notable limitation is that 17% of enrolled PD subjects in the

PPMI cohort were lost to follow up by year three, possibly creating selection bias as we do not know the cognitive status over time of these subjects. Finally, the model would benefit from external validation in a separate PD population.

At present our model synthesizes multiple clinical characteristics to provide 75% accuracy in predicting ECD, greatly improving upon current fragmented associations in the literature. Its use would allow clinicians to tailor medical management and counseling about disease progression to each patient's individual risk. This model could also be an important tool in identifying at-risk de novo patients for future clinical trials directed at delaying or preventing cognitive decline associated with PD.

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Fig. 1.

Calibration curve for the model.

Predictions generated from the model are plotted against actual patient outcomes; perfect model calibration creates a 45-degree line. The dotted line (apparent) indicates calibration when the model is applied to the training dataset, and the solid line (bias-corrected) indicates calibration when the model is applied to the bootstrap validation datasets. The bias-corrected calibration curve shows a modest departure when compared to the ideal line. Future predicted probabilities around 0.3 may be very slight overestimates of actual probability, while predictions around .55 could be slight underestimates of actual probability.

Fig. 2.

The prognostic nomogram.

To use the nomogram, locate the patient's position on the scale associated with each predictor. The top axis displays prognostic points. Connect the position on each variable axis with the "Points" [top] axis to determine the number of points corresponding to the appropriate variable position. Total the points for all variables, then find the appropriate position on the "Total points" axis and connect it with the associated position on the "Risk of ECD" [bottom] axis to determine the patient's individual risk of ECD. For example, a patient with REM sleep disorder [10 points], cognitive complaints [30 points], a score of 10 for right-sided bradykinesia [47 points], 16 years of education [-30 points], and a baseline HVLt retention t-score of 70 [84 points] would have a total of 141 points and a corresponding 72% risk of ECD.

Baseline stratified sample characteristics and unadjusted associations between each candidate predictor and early cognitive decline.

Table 1

	Without ECD n = 313	With ECD n = 38	Unadjusted odds ratio (95% CI)	P
Demographics				
Age ^a	60.62 (9.88)	63.58 (9.69)	1.033 (.996–1.071)	.08
Male ^b	205 (65.5)	27 (71.05)	1.293 (.618–2.707)	.5
Education (years) ^a	16.43 (2.72)	15.29 (2.3)	.843 (.736–.966)	.01
Disease history				
Symptom onset side ^b				
Right	174 (55.59)	22 (57.89)	ref	
Left	131 (41.85)	15 (39.47)	.906 (.452–1.813)	.88
Bilateral	8 (2.56)	1 (2.63)	.989 (.118–8.283)	.97
Hoehn & Yahr stage 2 + ^b	164 (52.4)	27 (71.05)	2.23 (1.069–4.652)	.03
1 + year since diagnosis ^b	137 (43.77)	24 (63.16)	2.202 (1.098–4.417)	.03
Motor symptoms				
Rigidity (appendicular, L) ^c	1 (3)	1 (3)	.957 (.797–1.15)	.64
Rigidity (appendicular, R) ^a	2.14 (1.79)	2.66 (1.85)	1.167 (.974–1.398)	.09
Bradykinesia (appendicular, L) ^a	3.42 (3.16)	3.87 (2.65)	1.046 (.941–1.163)	.4
Bradykinesia (appendicular, R) ^a	3.38 (2.78)	4.48 (3.12)	1.139 (1.016–1.277)	.03
Tremor (L) ^c	1 (2)	0 (2)	.973 (.787–1.202)	.8
Tremor (R) ^c	1 (3)	1 (2)	.918 (.74–1.139)	.44
Any gait problem ^b	171 (54.63)	22 (57.89)	1.142 (.578–2.257)	.7
Axial features ^a	4.46 (2.47)	5.18 (2.61)	1.119 (.982–1.275)	.09
Cognitive				
Subjective cognitive impairment ^b	70 (22.36)	17 (44.74)	2.81 (1.406–5.617)	.004
Symbol digit modalities, T score ^{a,d}	45.49 (8.62)	42.43 (8.04)	.96 (.923–.998)	.04

	Without ECD n = 313	With ECD n = 38	Unadjusted odds ratio (95% CI)	P
Semantic fluency, T score ^a	50.75 (9.7)	51.42 (11.53)	1.007 (.973–1.042)	.69
Letter number sequencing, Scaled score ^a	11.48 (2.62)	11.76 (2.73)	1.042 (.916–1.186)	.53
Judgment of line orientation, Scaled score ^a	13.04 (2.66)	12.42 (2.75)	.922 (.818–1.039)	.18
HVLT delayed recall, T score ^a	46.85 (10.34)	52.32 (18.43)	1.04 (1.011–1.07)	.007
HVLT recognition discrimination index, T score ^a	48.32 (10.86)	54.97 (17.73)	1.043 (1.016–1.07)	.002
HVLT retention, T score ^a	49.08 (10.11)	58.18 (17.46)	1.07 (1.038–1.102)	< .001
HVLT total recall, T score ^a	46.97 (10.49)	46.37 (13.78)	.995 (.964–1.026)	.75
Other				
Geriatric depression scale > 5 ^b	101 (32.27)	10 (26.32)	.75 (.351–1.603)	.46
REM sleep disorder questionnaire > 4 ^b	100 (31.95)	17 (44.74)	1.724 (.872–3.411)	.12
Epworth sleepiness scale > 7 ^b	100 (31.95)	8 (21.05)	.568 (.251–1.284)	.17
Urinary problems ^b	152 (48.56)	18 (47.37)	.953 (.486–1.871)	.89
Constipation ^b	97 (30.99)	12 (31.58)	1.028 (.498–2.122)	.94
UPSIT > 17 ^{b,d}	239 (77.1)	31 (81.58)	1.315 (.556–3.114)	.53
Pain ^b	162 (51.76)	15 (39.47)	.608 (.306–1.209)	.16

^aMean (SD).^bn (%).^cMedian (IQR).^d<1% of data missing.

Table 2

Model coefficients and adjusted odds ratios.

	Coefficient	OR (95% Confidence Interval)	P
Intercept	-3.7804		
HVLT: retention	.0656	1.068 (1.036–1.101)	< .001
Right-sided bradykinesia	.1797	1.197 (1.048–1.366)	.008
Years of education	-0.1931	0.824 (0.706–0.963)	.02
Subjective cognitive complaints	1.1418	3.132 (1.466–6.692)	.003
REM sleep disorder	.3725	1.451 (.687–3.065)	.33