Development and external validation of a prognostic model in newly diagnosed Parkinson disease

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ABSTRACT

Objective: To develop a prognostic model to predict disease outcomes in individual patients with Parkinson disease (PD) and perform an external validation study in an independent cohort.

Methods: Model development was done in the Comorbidity and Aging in Rehabilitation Patients: The Influence on Activities (CARPA) cohort (Netherlands). External validation was performed using the Cambridgeshire Parkinson's Incidence from GP to Neurologist (CamPaIGN) cohort (UK). Both are longitudinal incident cohort studies that prospectively followed up patients with PD from the time of diagnosis. A composite outcome measure was made in which patients were classified as having an unfavorable prognosis when they had postural instability or dementia at the 5-year assessment (or at the last assessment before loss to follow-up), or had died before this time. The final model was derived with a backward selection strategy from candidate predictor variables that were measured at baseline.

Results: In the resulting model, higher patient age, higher Unified Parkinson's Disease Rating Scale motor examination axial score, and a lower animal fluency score were all associated with a higher probability of an unfavorable outcome. External validation confirmed good discriminative ability between favorable and unfavorable outcomes with an area under the receiver operating characteristic curve of 0.85 (95% confidence interval 0.77–0.93) and a well-calibrated model with a calibration slope of 1.13 and no significant lack of fit (Hosmer-Lemeshow test: $p = 0.39$).

Conclusion: We constructed a model that allows individual patient prognostication at 5 years from diagnosis, using a small set of predictor variables that can easily be obtained by clinicians or research nurses. *Neurology*® 2016;86:986–993

GLOSSARY

CamPaIGN = Cambridgeshire Parkinson's Incidence from GP to Neurologist; **CARPA** = Comorbidity and Aging in Rehabilitation Patients: The Influence on Activities; **CI** = confidence interval; **MMSE** = Mini-Mental State Examination; **PD** = Parkinson disease; **ROC** = receiver operator characteristic; **UPDRS-ME** = Unified Parkinson's Disease Rating Scale motor examination.

Disease progression in Parkinson disease (PD) is highly heterogeneous. Disability is mainly determined by the onset of postural instability and dementia.¹ The time to reach these irreversible milestones varies considerably among patients with PD.² In clinical research, disease heterogeneity generally leads to a higher variance in outcomes, which in turn results in larger sample sizes needed to demonstrate possible treatment effects. This can be a problem especially in trials investigating neuroprotective therapies in PD, as these trials already have high costs due to their need for lengthy follow-up to show effects.³

Through longitudinal follow-up of our incident PD cohorts in the Netherlands and the United Kingdom, we have previously identified a number of baseline clinical characteristics associated with poor outcomes, including older age, non-levodopa-responsive motor symptoms, and deficits on semantic fluency and pentagon copying tests.^{2,4–6} However, these previous analyses have mainly been explorative in nature and while they may allow subgroups of patients

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at higher or lower risk of a poor outcome to be defined, they do not allow prognostication on an individual basis. The latter would be of considerable use in selecting patients for clinical trials. We therefore developed a prognostic model to predict 5-year outcomes for patients with newly diagnosed PD and validated the model in an independent cohort.

METHODS Study populations. Model development was performed using data from the Comorbidity and Aging in Rehabilitation Patients: The Influence on Activities (CARPA) study.^{6–8} The CARPA study is a clinic-based longitudinal prospective cohort study of newly diagnosed patients with PD from outpatient clinics in 6 general hospitals in the Netherlands, recruited between July 2002 and April 2005. Clinical diagnoses of PD were based on the criteria from Gelb et al.,⁹ and were reevaluated at the 5-year assessment by a movement disorder specialist. Patients with a revision of their diagnosis during follow-up were retained in the dataset. Model validation was performed in data from the Cambridgeshire Parkinson's Incidence from GP to Neurologist (CamPaIGN) study.^{2,4,5,10} The CamPaIGN study is a community-based longitudinal prospective study of a population-representative cohort of newly diagnosed patients with PD from the county of Cambridgeshire, United Kingdom, recruited between December 2000 and December 2002. Clinical diagnosis was based on the UK Parkinson's Disease Society Brain Bank criteria.¹¹ Diagnosis was reevaluated by a movement disorder specialist at 3.5 years and 5 years of follow-up. Baseline differences between development and validation datasets were evaluated using independent sample *t* tests and χ^2 tests where appropriate.

Outcome measure. A composite binary outcome measure was made in which patients were classified as having an unfavorable prognosis when they had postural instability or dementia at the 5-year assessment (or at the last assessment before loss to follow-up) or had died before this time. All other patients were classified as having a favorable prognosis. The presence of postural instability was assessed on the basis of a modified Hoehn & Yahr scale score of 3 or higher.¹² Patients were classified as having dementia using level 1 criteria from the Movement Disorder Society Task Force, operationalized using the Mini-Mental State Examination (MMSE) in addition to the clock drawing test in the CARPA study and a phonemic fluency test in the CamPaIGN study.^{13–18} Patients who already met the criteria of an unfavorable outcome at baseline were excluded from further analyses in both datasets.

Candidate predictors. The set of candidate predictors consisted of demographic variables including age, sex, and symptom duration, and clinical characteristics that were assessed at baseline in both cohort studies. Motor impairment was assessed with the Unified Parkinson's Disease Rating Scale motor examination (UPDRS-ME) section and tremor, bradykinesia, rigidity, and axial subscores were calculated using established methods.^{19,20} Equivalent levodopa doses were calculated using our previously published formula.⁴ The Cumulative Illness Rating Scale was used to count the number of organ systems with comorbid disease (range 0–13).²¹ Presence of depressive symptoms was assessed with the Hospital Anxiety and Depression Scale in the

development dataset and by the Beck Depression Inventory in the validation dataset.^{22,23} To overcome differences between development and validation datasets, both scales were dichotomized using recently suggested cutoff values for screening for depression in PD.²⁴ Phonemic fluency was assessed by the Controlled Oral Word Association Test, in which patients are asked to produce as many words as possible starting with the same letter in a 1-minute time frame for a total of 3 individual letters.¹⁷ Semantic fluency was assessed with the animal fluency test, in which patients are asked to name as many animals as possible in a 1-minute time frame.²⁵ Global cognitive function was assessed by the MMSE.¹⁵

Model development. Missing candidate predictors were imputed using multiple imputation, by which 50 different imputed datasets were generated. Regression coefficients and standard errors were averaged using Rubin's²⁶ rules. Missing outcomes were not imputed.²⁷ All candidate predictors were entered into a multivariable logistic regression analysis with stepwise backward selection strategy for each imputed dataset. The Akaike Information Criterion was used as a stopping rule. Candidate predictors that appeared in 50% or more of the multivariable models from the different imputed datasets were retained in the final model.²⁸

Parameters of model performance and model validation. Model performance is divided into 2 main categories: discriminative ability and model calibration. The discriminative ability assesses whether the model is able to differentiate between patients with a favorable and an unfavorable outcome. It is expressed by the Harrel *c* statistic, which is similar to the area under the curve of a receiver operator characteristic (ROC) curve.²⁹ The *c* statistic ranges from 0.50 (indicating a noninformative model) to 1.00 (indicating a model with perfect discrimination between patients with and without an unfavorable outcome). Model calibration assesses to what extent predicted values agree with observed outcomes. It is visualized by the calibration plot in which the calibration curve is estimated by local regression (LOESS).²⁷ The calibration slope has an ideal value of 1. A slope <1 reflects overfitting, meaning that low predictions are too low and high predictions are too high. A slope >1 reflects underfitting, meaning that the predictions are not sufficiently extreme. Overall agreement between predicted and observed outcomes is tested using the Hosmer-Lemeshow goodness-of-fit test, in which a *p* value < 0.05 indicates significant disagreement between predicted and observed outcomes.

Validation of the final model was divided into 3 stages: apparent validation, internal validation, and external validation. For apparent validation, performance parameters were estimated directly in the dataset in which the model was developed. For internal validation, the final model was validated with (*n* = 1,000) bootstrap samples from the development dataset, after which the optimism-corrected *c* statistic and calibration slope were estimated. The use of multiple imputation datasets automatically results in model performance parameters for each individual multiple imputation dataset at apparent and internal validation. Therefore, for each parameter at the apparent and internal validation stage, the median value is shown.³⁰ Missing predictor variables and missing outcomes were not imputed in the external validation dataset. Since patients from the CamPaIGN study whose diagnosis was revised to non-PD were excluded from further follow-up after 3.5 years, only patients meeting diagnostic criteria at the baseline and 3.5-year visits were used for the primary external validation. To investigate whether the missing data

on patients with a revised diagnosis could have had a large influence on the external validity of the model, an additional sensitivity analysis was performed where patients with a revised diagnosis were assigned a favorable or unfavorable outcome based on their final diagnosis on the consensus of 3 authors (D.C.V., R.M.A.D.B., C.H.W.-G.).

Statistical uncertainties were expressed using 95% confidence intervals (CI). Statistical analyses were performed in R version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org/>).

Model presentation. For future users, the regression formula to calculate the probability of an unfavorable outcome is given. In addition, appendix e-1 on the *Neurology*[®] Web site at Neurology.org contains an electronic calculator in Microsoft Excel in which probabilities are automatically calculated when values of predictor variables are entered. The appendix also contains a table showing model sensitivity and specificity to detect an unfavorable outcome for different cutoff values. The present study is reported in compliance with standard guidelines.³¹

Standard protocol approvals, registrations, and patient consents. All patients gave written informed consent. The study was approved by the medical ethical committees of the participating hospitals (Netherlands) and the local research ethics committee (United Kingdom).

RESULTS Details on patient selection and missing data for both cohorts are shown in figure 1. A total of 111 patients were included in the model development dataset, whereas 108 patients were included in

the model validation dataset. Patient characteristics for both cohorts are shown in table 1. Patients from the CamPaIGN cohort were on average 3.4 years older at baseline than patients from the CARPA cohort. The risk of an unfavorable outcome was also higher in the CamPaIGN cohort (absolute risk difference 11.6%).

Model development. The final model is a 3-predictor variable model with higher patient age, higher UPDRS-ME axial score, and lower animal fluency score all giving a higher probability of an unfavorable outcome. The predictor variables and their corresponding regression coefficients in the final model are shown in table 2. Details on model development from the set of candidate predictors are shown in appendix e-2.

Model validation. Parameters of model performance are shown in table 3. ROC curves and calibration plots are shown in figure 2. During external validation, considerable miscalibration was initially found, with patients in the validation set getting probabilities of an unfavorable outcome that were systematically too high. Since we suspected that this could be caused by the influence of language differences on the results of the animal fluency test, we calculated a correction factor based on normative scores for healthy controls from the same age range.^{7,32} Comparison of model calibration with and without the correction factor is

Figure 1 Patient selection

CamPaIGN = Cambridgeshire Parkinson's Incidence from GP to Neurologist; CARPA = Comorbidity and Aging in Rehabilitation Patients: The Influence on Activities; HY = Hoehn & Yahr.

Table 1 Cohort characteristics

	Development set (CARPA, n = 111)	Validation set (CamPaIGN, n = 108)	Validation set (CamPaIGN, sensitivity analysis, n = 118)	p Value ^a
Mean (SD) age at baseline, y	65.6 (10.1)	69.0 (9.8)	68.7 (9.9)	0.01
Mean (SD) age at diagnosis, y	65.2 (10.1)	68.7 (9.8)	68.4 (9.9)	0.01
Mean (SD) symptom duration at baseline, y	1.6 (0.9)	2.2 (1.8)	2.3 (2.4)	<0.01
Mean (SD) duration from diagnosis to baseline assessment, y	0.3 (0.2)	0.3 (0.4)	0.3 (0.4)	0.43
Mean (SD) duration from baseline assessment to outcome at 5 years assessment, y	5.1 (0.3)	5.0 (0.5)	5.0 (0.5)	0.47
No. (%) male	66 (59.5)	62 (57.4)	65 (55.1)	0.76
UPDRS-ME axial score, mean (SD)	1.3 (1.4)	2.8 (2.3)	2.6 (2.3)	<0.01
Animal fluency score, mean (SD)	19.2 (5.5)	16.6 (5.7)	16.7 (5.7)	<0.01
No. (%) with unfavorable outcome	54 (48.6)	65 (60.2)	66 (55.9)	0.09
No. (%) deceased at year 5	18 (16.2)	23 (21.3)	23 (19.5)	0.34
No. (%) HY ≥3 at year 5 (without dementia)	25 (22.5)	27 (25.0)	—	0.67
No. (%) with dementia at year 5 (with HY <3)	3 (2.7)	2 (1.9)	—	0.67
No. (%) HY ≥3 and with dementia at year 5	8 (7.2)	13 (12.0)	—	0.28

Abbreviations: CamPaIGN = Cambridgeshire Parkinson's Incidence from GP to Neurologist; CARPA = Comorbidity and Aging in Rehabilitation Patients: The Influence on Activities; HY = Hoehn & Yahr; UPDRS-ME = Unified Parkinson's Disease Rating Scale motor examination.

^aIndependent sample t test or χ^2 test for comparisons between development set and main analysis validation set (n = 108).

shown in appendix e-2. After correction for language, the resulting formula for the prediction rule is as follows:

$$P_{\text{unfavorable outcome}} = \frac{1}{1 + e^{-(\text{age} \times 0.059 + \text{UPDRS-ME axial score} \times 0.3794 + \text{animal names} \times \text{language correction factor} \times -0.0684 - 3.1246)}}$$

For Dutch, the language correction factor = 1; for English, the correction factor = 1.267. For all other languages, the correction factor can be calculated if a mean score is available for healthy controls aged 60–70 years. The correction factor then is equal to 22.3/(mean score).

Sensitivity analysis including patients with a revised diagnosis. By consensus, the patient in whom the diagnosis was revised to vascular parkinsonism was assigned an unfavorable outcome. The other 9 patients whose diagnosis was revised away from PD in the validation dataset were assigned a favorable outcome. Repeated validation of the model in the dataset that included the patients with a revised diagnosis (n = 118) did not substantially change model performance parameters (table 3). The calibration plot showed slight overestimation of the probability of an unfavorable outcome compared to the main analysis (figure 2).

DISCUSSION The present study shows that a relatively simple equation based on 3 clinical parameters measured at diagnosis can give reliable predictions

concerning the prognosis of PD over the next 5 years. The UPDRS-ME and the animal fluency test can be administered by clinicians and research

nurses in a short time frame without specialist equipment, thus this predictive model is easily translatable to the clinic.

The main purpose of this study was to develop a model that could aid in patient selection and stratification in clinical trials. We specifically chose a composite outcome including the presence of postural instability or dementia because these are important determinants of disability in PD that are both non-levodopa-responsive.^{5,6} In future clinical trials investigating disease-modifying effects of dopaminergic cell-based therapies, patients with PD who are likely to develop one of these non-levodopa-responsive symptoms within 5 years can be selectively excluded. Conversely, this high-risk group can be positively selected for trials of other types of disease-modifying therapies, to enable changes in outcome to be assessed within a shorter time period.

While the primary purpose of developing the prognostic model was for use in patient selection and stratification for clinical research, it may also be

Table 2 Regression coefficients of the final model

	Estimate	Standard error	p Value
Intercept	−3.1246	2.2335	—
Age	0.0590	0.0273	0.033
UPDRS-ME axial score	0.3794	0.1804	0.038
Animal names score	−0.0684	0.0477	0.155

Abbreviation: UPDRS-ME = Unified Parkinson's Disease Rating Scale motor examination. The 3 predictor variables appeared in more than 50% of the multivariable models generated in the different imputed datasets (see appendix e-2 for more details). Regression coefficients and standard errors were averaged using Rubin's²⁶ rules.

useful to counsel individual patients regarding prognosis, and enable the clinician to better plan management. The upper and lower boundaries of the 95% CI of the calibration curve indicate that systematic misclassification of more than 15% is unlikely, making the model acceptable for patient counseling. In addition, the sensitivity analysis showed that the model can robustly cope with patients in whom the diagnosis is eventually revised. This is important as approximately 8% of the patients diagnosed with PD will eventually be given another diagnosis.³³ When using the model for patient counseling, an important caveat is that patients with a high probability of an unfavorable outcome will still not know whether this is because of impending balance disorders, dementia, or death. On the other hand, the model is able to reliably identify patients with a good prognosis.

One of the major strengths of the present study is that the model was developed and validated in 2 completely independent cohorts of newly diagnosed patients with PD. This is important as the majority of clinical trials investigating disease-modifying therapies in PD will include patients shortly after diagnosis. In

addition, the period around the time of diagnosis is typically when patients seek counseling regarding their prognosis. Though the clinical diagnosis of PD was based on different criteria in both cohorts, both criteria are well-established in PD research, and reevaluation of the clinical diagnosis during follow-up has shown that the proportion of revised diagnoses is comparable to earlier studies.^{9,11,33} Furthermore, the model proved to be robust across the 2 cohorts in spite of these differences in diagnostic methods and the differences in age and symptom duration at baseline.

Another major strength is that both cohorts consist of unselected patients with PD who did not participate in clinical trials and are representative of the general PD population. Though the CARPA study is a clinic-based cohort study rather than a strictly population-based one, selection bias is likely to be negligible as general practitioners in the Netherlands nearly always refer patients with a clinical suspicion of PD to a neurologist. Furthermore, the model has been shown to be valid in the CamPaIGN cohort, which is a community-based population-representative cohort.¹⁰ The use of unselected cohorts has the drawback that the total number of included patients is relatively low, causing some imprecision in estimating model performance parameters. In addition, during a backward selection, the first model is fit with a relatively large number of potential predictors considering the number of participants. In theory, this could have led to model instability. However, the selected predictor variables are largely in line with those found in our earlier reports.^{2,4–6} Future validation in a third independent cohort might still increase the robustness of the present study. Since the present model is only validated for newly diagnosed patients with PD, additional independent validation in a cohort with prevalent patients with PD is also needed to investigate whether predictions also hold

Table 3 Model performance parameters

Validation stage	Performance parameter	Estimate
Apparent validation	c Statistic (95% CI) ^a	0.765 (0.677–0.854)
	Hosmer-Lemeshow test ^a	p = 0.339
Internal validation	Bootstrap-corrected c statistic ^a	0.748
	Calibration slope ^a	0.914
External validation (main analysis)	c Statistic (95% CI)	0.848 (0.770–0.926)
	Calibration slope	1.134
	Hosmer-Lemeshow test	p = 0.389
External validation (sensitivity analysis)	c Statistic (95% CI)	0.842 (0.769–0.916)
	Calibration slope	1.130
	Hosmer-Lemeshow test	p = 0.523

Abbreviation: CI = confidence interval.

^aDuring apparent and internal validation, these parameters are generated in 50 imputed datasets. Therefore, for each parameter the median is shown.

Figure 2 Receiver operator characteristic (ROC) curves and calibration plots at external validation

Upper panels: ROC curve main analysis (A) and sensitivity analysis (B). The dotted red reference line corresponds to a *c* statistic of 0.50, indicating a noninformative model. Tabulated sensitivity and specificity values for different cutoff values of predicted probabilities can be found in appendix e-1. Lower panels: calibration plot main analysis (C) and sensitivity analysis (D). The calibration curve is estimated by local regression (LOESS).²⁷ The 95% confidence interval of the curve is represented by the shaded area. The dotted red reference line corresponds to perfect calibration with a calibration slope of 1. When the calibration curve is above the reference line, the probabilities of an unfavorable outcome are underestimated; when it is beneath the reference line, the probabilities are overestimated. The black dots represent the individual patients in the external validation dataset.

true for patients who already have a PD diagnosis for a longer time.

Another important issue with the current model is that for future use in non-Dutch-speaking or non-English-speaking countries, normative values for the animal fluency test are needed. Use of the model in another language without correcting for language differences might lead to miscalibration. We were not able to correct for the influence of educational level and potential cultural differences, although available evidence suggests that the latter do not have a relevant effect on fluency scores.³⁴ If normative animal fluency

values are unavailable, we would recommend administration of the animal fluency test in an age-matched control group of approximately 70 healthy controls (comparable to the number of controls we used) to allow the appropriate correction factor to be calculated.

We have developed a predictive model allowing prognostication of outcome in individuals with newly diagnosed PD and demonstrated that this model is valid in 2 independent PD populations. This model is easily translatable to the clinic, requiring only basic clinical information, and has potential value in aiding the selection of patients for clinical trials.

AUTHOR CONTRIBUTIONS

Daan C. Velseboer: study design, acquisition of data, analysis and interpretation of data, drafting of the manuscript. Rob M.A. de Bie: study design and supervision, analysis and interpretation of data, critical revision of the manuscript. Luuk Wiekse: analysis and interpretation of data, critical revision of the manuscript. Jonathan R. Evans: acquisition of data, critical revision of the manuscript. Sarah L. Mason: acquisition of data, critical revision of the manuscript. Thomas Foltynie: acquisition of data, critical revision of the manuscript. Ben Schmand: acquisition of data, critical revision of the manuscript. Rob J. de Haan: analysis and interpretation of data, critical revision of the manuscript. Bart Post: acquisition of data, critical revision of the manuscript. Roger A. Barker: study design, critical revision of the manuscript. Caroline H. Williams-Gray: study design and supervision, acquisition of data, analysis and interpretation of data, critical revision of the manuscript.

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Submissions must be 1,250 words or less with five or less references. A maximum of two figures or two tables (or combination) can be incorporated if necessary. For complete submission requirements, please go to *Neurology.org* and click on “Information for Authors.” The submissions will be reviewed by the editors and may be edited for clarity.

Interested submitters can register and upload manuscripts under the section “Global Perspectives” at <http://submit.neurology.org>. Please send inquiries to Kathy Pieper, Managing Editor, *Neurology*; kpieper@neurology.org.