



Predictive model for falling in Parkinson disease patients



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ABSTRACT

Background/aims: Falls are a common complication of advancing Parkinson's disease (PD). Although numerous risk factors are known, reliable predictors of future falls are still lacking. The aim of this study was to develop a multivariate model to predict falling in PD patients.

Methods: Prospective cohort with forty-nine PD patients. The area under the receiver-operating characteristic curve (AUC) was calculated to evaluate predictive performance of the purposed multivariate model.

Results: The median of PD duration and UPDRS-III score in the cohort was 6 years and 24 points, respectively. Falls occurred in 18 PD patients (30%). Predictive factors for falling identified by univariate analysis were age, PD duration, physical activity, and scores of UPDRS motor, FOG, ACE, IFS, PFAQ and GDS (p -value < 0.001), as well as fear of falling score (p -value = 0.04). The final multivariate model (PD duration, FOG, ACE, and physical activity) showed an AUC = 0.9282 (correctly classified = 89.83%; sensitivity = 92.68%; specificity = 83.33%).

Conclusions: This study showed that our multivariate model have a high performance to predict falling in a sample of PD patients.

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1. Introduction

Parkinson's disease (PD) is a slowly progressive neurodegenerative disorder that eventually lead to gait and balance problems [1]. In PD patients the fall rates doubles the reported rates in community dwelling older people without neurological disease [2,3], ranging from 35% to 90% [4,5], and between 18% and 65% of them are recurrent fallers (≥ 2 falls per year) [6]. Beyond its serious and costly physical consequences [7,8], falls have a negative psychosocial impact creating a spiral of increased fear of falling and reduced physical activity, and increased likelihood of nursing home admission [9].

According to a recent systematic review on recurrent falls in PD [6], between 35% and 90% of participants fell at least once during the reporting periods (range 1–29 months), with an average of 60.5%. Both PD related and comorbid pathologies have been proposed as potential underlying causes of falls, including poor mobility, visual problems, cognitive impairment, environmental obstacles, freezing of gait,

co-morbidities and polypharmacy [5,6,10], making interpreting fall causality challenging [11].

Several retrospective as well as prospective studies have sought to determine risk factors or predictors of falls in PD with inconsistent results. In a recent meta-analysis, the strongest predictor of falling was prior falls in the preceding year [10]. At present, the strongest predictors of future falls in PD patients appear to be the history of previous falls [8, 10,12–15], PD duration [9], increased disease severity [7,8,10,13,16,17], the presence of freezing of gait (FOG) [8,17–19], fear of falling [15,20, 21], impaired balance [8,16,17,18,22,23], impaired mobility [8,17, 24,25]. Other factors are presence of dyskinesia [26,27], more severe motor impairment [15], reduced muscle strength [8,8,17], abnormal posture, poor leaning balance, and leg weakness [8], impaired cognition [7,8,16,18,19,28], impaired executive function [8,28], impaired orientation [18], reduced power of attention and increased reaction time variability [7], levodopa dose [15], comorbidities such as urinary incontinence [9], and, probably, advanced age [29].

However, the current evidence is highly variable. All studies do not confirm the same findings regarding assessed associations and several studies did not show an association between faller status and some factors such as dyskinesia [12,13,15], global cognitive impairment or executive function [12,13,15,30,31]. For example, the disease severity could

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have a low prognostic value possibly due to a U-shaped relation with falls [11]. Thus, despite presenting such a vast clinical problem, verified and consistent falls predictors for falling in PD patients are scarce [11].

In this study, we explore potential risk factors for falling in a sample of ambulatory patients with PD to set up a predictive multivariate model.

2. Materials and methods

2.1. Design of the study

This is a prospective cohort study on diagnostic test for building a predictive multivariate model and for assessing its performance to predict falling in PD patients. For this study the gold standard was the history of falling.

2.2. Population and sample

Participants were consecutively enrolled during the period between April 2012 and April 2015 from the *Instituto Peruano de Neurociencias* and Unit of Cognitive Impairment and Dementia Prevention of the *Clinica Internacional* of Lima, Peru. We included patients with PD diagnosed according to the United Kingdom PD brain bank criteria, older than 60 years old, with Spanish as their native language, with at least 6 years of education, able to ambulate without a walking aids, and with antiparkinsonian treatment taken at stable doses for at least 3 month before recruitment (pramipexole, levodopa/carbidopa, or levodopa/benserazide). During follow-up, the attending physician may change the dose of treatment, but could not include neuroleptics or biperiden.

We excluded those subjects with structural and/or functional deficits (visual or auditory deficits) or suffered from any unstable cardiovascular, orthopedic, metabolic, neurological or sensory conditions that would interfere with the balance, gait and performance to realize the tests, the safety of assessment and/or the interpretation of results. Additionally, we excluded to subjects with typical symptoms of Lewy body disease (psychosis, onset of cognitive symptoms before motor symptoms, syncope, and neuroleptic sensitivity), history of diseases (e.g. cerebrovascular illness, hypothyroidism, and central nervous system infections (VIH or syphilis), severe encephalic traumatism, and subdural haematoma) or conditions (e.g. deficit of B12 vitamin, chronic hepatopathy or nephropathy, and addiction or abuse of substances) associated with secondary cognitive impairment, as well as subjects with score >4 for the Hachinski index and >17 for the Beck Depression Inventory-II (which suggests underlying cerebrovascular deficit and depression, respectively) and users of biperiden, neuroleptics, antidepressants and/or anxiolytics. We decided to exclude users of these drugs because their adverse effects have variable effects: 1) increased risk or non-increased risk of falls [32]; 2) deterioration or improvement of parkinsonian symptoms [33]; and 3) decreased performance or normal performance in cognitive tests scores [34–36] (a recognized risk factor for falling). Thus, this is a confounding effect that we try to control it through the restriction method.

2.3. Procedures

All the patients were evaluated using the same questionnaires and tests (clinical or neuropsychological). One questionnaire inquired about time since PD diagnosis, fall history, and physical activity levels. Information about falls sustained by each person was prospectively monitored over 1 year using falls diaries, which was completed by the patients (or their caregivers) and was reviewed by the research team during monthly follow-up at consultancy [37]. Participants were subsequently categorized into fallers (≥ 1 fall during follow-up) and non-fallers according to the following definition of a fall: unintentionally

coming to rest on the ground or other lower surface without overwhelming external force or a major internal event [38].

Fear of falling was determined by the Falls Efficacy Scale-International questionnaire (FESIQ) [39]. We applied the Freezing of Gait Questionnaire for assessing the presence of FOG and its severity was determined by summing questions 3 to 6 of this questionnaire [40].

The clinical tests were the motor section (or part III) of the Unified Parkinson's Disease Rating Scale (UPDRS) [12] and the Pfeffer Functional Activities Questionnaire (PFAQ) [41]. Usually, the motor section of the UPDRS (UPDRS-III) is used as measure of disease severity [42]. Furthermore, the presence of abnormal axial posture was rated as the item 28 of UPDRS-III and dyskinesia subscore was scored as the sum of items 32 and 33 from the UPDRS-III [12].

In addition, neuropsychological testing was performed consisting of the Addenbrooke's Cognitive Examination (ACE) [43], INECO Frontal Screening (IFS) [44], and Global Deterioration Scale (GDS) [45]. These tests were applied at baseline.

The order of testing was standardized for all participants and the assessment was conducted when each person's PD medications were working optimally, usually 1 h after taking the medication. For participants who reported going "off" during the assessment, testing was suspended until they had taken their medication and reported being "on" again. Similarly, for participants who fatigued during the assessment, rest breaks were given and testing recommenced only when the participant reported being able to continue [18].

2.4. Statistical methods

The chi-Square and Mann–Whitney *U* tests were used to compare parameters of fallers and non-fallers. To determine which patient parameters were associated with an increased probability of falling, a logistic regression model was built for each parameter independently and the predictive relevance of each parameter was assessed using the likelihood ratio test. A multiple logistic model was then sought to predict falling. Due to the rather limited number of patients in the present study, a limited number of predictors were included in the model. Therefore, a set of candidate predictors was chosen with consideration to those parameters previously identified to be associated with falling.

Two sets of parameters were considered: clinical (sex, age, PD duration, history and current fear of falling, current physical activity and clinical tests) and neuropsychological (neuropsychological tests). Then, a model was constructed by combining the clinical and the neuropsychological models using Akaike information criterion (AIC) and Bayesian information criterion (BIC). The discriminative performance of the built model to predict the occurrence of falling was assessed using the analysis of receiver operating characteristic (ROC) to calculate the area under

Table 1
Main characteristics of Parkinson's disease (PD) patients.

	Median	Interquartile range
Sex: female ^a	24	40.68
Age (yrs)	67	11
PD duration (yrs)	6	3
UPDRS-III (score)	24	8
Dyskinesia scale (score)	1	1
Abnormal axial posture ^a	33	55.93
Freezing ^a	32	54.24
FOG (score)	4	3
ACE (score)	73	10
IFS (score)	20	7
PFAQ (score)	9	7
GDS (score)	1	1
Falls (number of events)	6	12
Fear of falling (score)	26	4
Physical activity (hours per week)	24	6

Abbreviations: UPDRS-III: unified Parkinson's disease rating scale, motor score; FOG: freezing of gait.

^a Variables showed as count and percentage.

Table 2
Clinical, neuropsychological and functional characteristics of patients by history of falling.

	Non-fallers		Fallers		p-Value
	Median	Interquartile range	Median	Interquartile range	
Sex: female ^a	8	44.44	16	39.02	0.70
Age (yrs)	61	7	69	7	<0.001
PD duration (yrs)	4	1	7	3	<0.001
UPDRS motor (score)	20	6	26	6	<0.001
Dyskinesia scale (score)	1	1	2	1	0.24
Abnormal axial posture ^a	8	44.44	25	60.98	0.24
Freezing ^a	5	27.78	27	65.85	<0.01
FOG (score)	2	2	5	2	<0.001
ACE (score)	89	16	71	6	<0.001
IFS (score)	24	6	18	6	<0.001
PFAQ (score)	4	1	10	6	<0.001
GDS (score)	1	1	2	1	<0.001
Fear of falling (score)	25	7	27	5	0.04
Physical activity (hours per week)	28	6	23	4	<0.001

^a Variables showed as count and percentage.

curve (AUC). We used the Hosmer-Lemeshow goodness-of-fit test to assess the calibration model. The interrelation of the regression variables and collinearity was studied. Data analyses were carried out in STATA version 12.0 (*Stata Corporation, College Station, Texas*) at a 95% confidence level ($\alpha = 0.05$).

2.5. Ethical aspects

This study was authorized by The Research and Teaching Unit of the *Clinica Internacional* and was approved by The Ethics Committee of the *Universidad de San Martin de Porres*. Written informed consent was obtained from all participants before the first assessment.

3. Results

Fifty nine patients were recruited from the *Instituto Peruano de Neurociencias* and the *Clinica Internacional*. In this group of patients, 40.7% were female and the median of age and PD duration were 67 years and 6 years, respectively. The proportion of falling was 30.5% and at least half of patients had history of 6 or more falls or had current fear of falling. The median of the value of PFAQ was 9. At least half of patients do not achieve >24 h of physical activity per week. The median of the values of UPDRS-III, dyskinesia scale and FOG were 24, 1, and 4 respectively. At least 54% of patients had abnormal axial posture or freezing. Regarding the neuropsychological tests, the median of the values of ACE, IFS and GDS were 73, 20 and 1, respectively [Table 1].

In the univariate analysis, our data did not show significant differences by sex, dyskinesia scale and presence of abnormal axial posture between patients who have a history of falls of those who had no history

of falls. The rest of analyzed variables were significantly different between the two comparison groups [Table 2].

3.1. Predictive model

The set of candidate clinical predictors for the multiple logistic regression model of prospective falling included the variables identified in the model constructed based on AIC and BIC criteria (PD duration, FOG, ACE, physical activity, and number of falls). This model showed an adjusted R-squared of 0.6335 and values of AIC and BIC of 325.20 and 335.58, respectively [Table 3].

The predictive performance of the constructed model was very good (AUC = 0.9282) [Fig. 1] and the accuracy was good (correctly classified = 89.83%). This model predicted falling with a sensitivity of 92.68%, specificity of 83.33%, positive and negative predictive values of 92.68% and 83.33%, respectively. The p-value for Hosmer-Lemeshow goodness-of-fit test was 0.87.

4. Discussion

This study showed a high performance (high discrimination and good fit) of the purposed multivariate model (PD duration, FOG, ACE, and physical activity) to predict falling in our sample of PD patients. These finds are consistent with previously reported by other studies [8,10,12–14,17]. Moreover, our multivariate model is plausible since its components directly measures the disease progression [46].

The performance of our purposed multivariate model is higher than showed for Paul et al. (AUC = 0.87) [47], but lesser than showed in the study of Hoskovcová et al. (AUC = 0.995) [15]. However, the study of Hoskovcová et al. had other aim, included other variables, and compared PD patients with healthy control subjects, which tends to increase the value of AUC.

Several notable differences were found between PD fallers and non-fallers in univariate analysis. Similarly to previous studies [7,8,10,12,13,16,17,17,18–21,47], PD fallers had a significantly greater disease severity, FOG, and higher scores in questionnaires of fear of falling and lesser physical activity, compared to PD non-fallers. However, variables such as age, PD duration and GDS were previously evaluated but it did not show to be statistically significant [11,15,48,49]. We thought that these differences are plausible because a higher age, PD duration and GDS implies a higher individual vulnerability or fragility. In fact, has been suggested that age causes the progress of the disease [29].

The published background studies have not evaluated other statistically significant variables (ACE, IFS, and PFAQ). These variables are important due measures the cognitive (ACE) and executive functions (IFS), as well as the instrumental activities of daily living (PFAQ). There are several studies using MMSE [11,18,47,49] and Frontal Assessment Battery [15,18,47] for these purposes, and lesser value of MMSE significantly contributes to fall risk in people with PD [18,49]. We suggest that these variables are adjustment variables that always should be considered.

Conversely, we could not confirm the predictive value of several factors identified previously, namely increased disease severity [7,10,13,16,17], fear of falling [20,21], and abnormal axial posture [8]. However,

Table 3
Statistical criterion used for model selection.

	Akaike information criterion					Bayesian information criterion				
	m0	m1	m2	m3	m4	m0	m1	m2	m3	m4
Falls (count)	380.63					382.71				
ACE (score)		344.78					348.93			
PD duration (yrs)			330.91					337.15		
Physical activity (hours per week)				327.43					335.74	
FOG (score)					325.20					335.58

m0: null model (only outcome); m1 to m4: model with 1 to 4 independent variables.

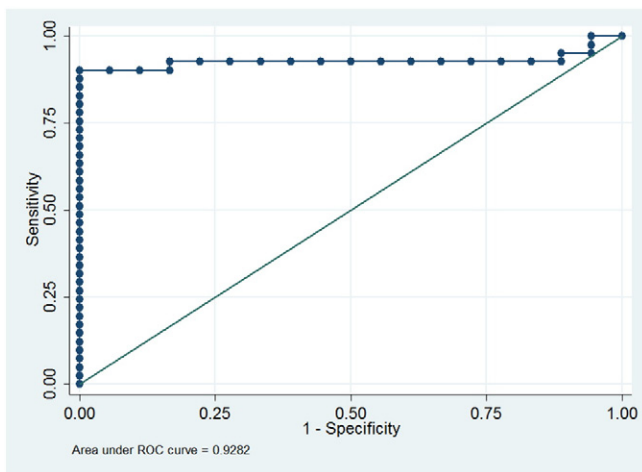


Fig. 1. ROC curve for the discrimination between faller and non-faller by means of the application of purposed predictive multivariate model in 59 PD patients.

these variables may have a value as risk factor but not as predictors and, thus, such marker variables only can to provide an insight into why occur the future falls.

4.1. Limitations

There are some limitations to the present study. Because the use of history of falls as grouping variable, we could not assess its predictive value for occurrence of falling. Additionally, there were insufficient numbers of fallers in this study to subdivide them according to fall frequency. Further research is required to assess the predictive performance for history of high frequency of falls or recurrence of falling.

In our study we did not consider other variables such as impaired balance [8,17,22,23,47], reduced mobility [17,24,25], gait velocity [11, 12], stride time variability [15], cadence [15], daily dose of dopaminergic medication, and depressive symptoms [15,50], etc. Future studies should consider this and other relevant variables.

5. Conclusion

In summary, a multivariate model including PD duration, FOG, ACE, and physical activity constitutes a reliable, brief, and simple predictive model with high precision and calibration for assessing the probability of future falling in PD patients. Thus, it is a valuable tool for easy and early predictive assess at the care centers of PD patients.

Conflict of interest statement

We declare that we have no conflict of interest.

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