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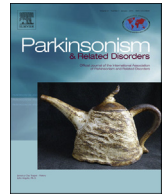
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## Parkinson's disease severity levels and MDS-Unified Parkinson's Disease Rating Scale



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### ABSTRACT

**Background:** Severity of PD is usually assessed by means of the motor and disability-based Hoehn and Yahr staging (HY), or clinician and patient global perceptions. Scores of more detailed assessments, as the MDS-UPDRS, have not been translated to a grading that allows assignment of score sections to severity levels. The objective of the present study is to determine cut-off points for PD severity levels based on the MDS-UPDRS.

**Methods:** International, observational study. Applied assessments were: HY, MDS-UPDRS, Clinical Impression for Severity Index, and Clinical and Patient Global Impression of Severity. The coincidence in severity level (mild, moderate, severe) of at least two clinical classifications plus the patient's gradation was considered "the criterion of severity". Cut-off values for each MDS-UPDRS subscale was determined by triangulation of: 1) percentile 90 of the subscale total score; 2) receiver operating characteristic (ROC) analysis; and 3) ordinal logistic regression (OLR) model.

**Results:** Sample was composed of 452 consecutive PD patients without dementia, 55.3% males, age  $65.1 \pm 10.7$  years and PD duration  $8.7 \pm 6.3$  years. All HY stages were represented. The "criterion", classified 275 patients (60.8% of the sample) as: mild PD, 149 (54.2%); moderate, 82 (29.8%); and severe, 44 (16%). The following MDS-UPDRS cut-off points between mild/moderate and moderate/severe levels were found: Part 1: 10/11 and 21/22; Part 2: 12/13 and 29/30; Part 3: 32/33 and 58/59; and Part 4: 4/5 and 12/13.

**Conclusion:** Cut-off points to classify PD patients as mild, moderate, or severe on the basis of their MDS-UPDRS scores are proposed.

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### 1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that clinically evolves over time from subtle non-specific

non-motor manifestations of the premotor phase to the most advanced stages in which patients are severely disabled. Progressive disability is due to the combination of motor and non-motor problems and related complications that increase in number and severity throughout the course of the disease making the clinical management more complex and affecting patients' quality of life and independence [1–3].

Since the publication of the Hoehn and Yahr staging [4], measures to evaluate PD have evolved to comprehensive evaluations as, for example, the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [5] and the Non-Motor Symptoms Scale [6] or to assessments focused on a specific aspect such as the Parkinson's Fatigue Scale [7] and the Parkinson's Disease Dyskinesia Scale [8], among others. However, with the increasing complexity of the disorder there is an increased difficulty to determine the severity of the disease in a pragmatic and easily understandable manner [9] and a combination of several global self-reported and administered scales may be needed to approach this objective.

Global measures have the advantage of providing concise information on the overall health state and can be useful for patients selection (for example, cases with "mild disease" for a clinical trial) and classification (for example, assignment of a "very dependent" level for receiving social assistance). In short, the distribution of patients in such categories as mild, moderate, and severe, helps to determine in a pragmatic manner their global health status, facilitates the communication, and allows the decision making process.

The most frequently used global assessment for PD is the Hoehn and Yahr staging (HY) [4,10]. It is based on the disability resulting from motor impairment and balance dysfunction, but does not inform about some motor features and non-motor manifestations. It is widely used for description of PD patients groups and case selection for studies.

The generic Clinical Global Impression (CGI) [11] is a global measure mainly applied in psychiatry, but also used in PD as an outcome into clinical trials and other kind of studies. The CGI has two main components, respectively focused on severity (CGIS) and change (CGIC). The CGI has been criticized as inconsistent and too general [12], but is widely used. The CGIS can be adapted for patients self-assessment (PGIS), a strategy allowing comparisons between rater-based and patient-based evaluation [12].

A recent approach to global evaluation of PD is the Clinical Impression of Severity Index for PD (CISI-PD), a specific instrument based on the global clinical impression on four relevant aspects of PD: motor signs, disability, motor complications, and cognitive impairment, a combination that explained 92% of the CGIS variance [13]. The CISI-PD summarizes the evaluation carried out through the interview, examination, and application of other assessments.

The present study was aimed at determining, using agreed levels of severity among these professional- and patient-based generic scales, the cut-off points for the MDS-UPDRS subscales that could determine levels of disease severity of useful clinical application.

## 2. Methods

### 2.1. Design

Multicenter, international, observational, cross-sectional study.

### 2.2. Patients

Consecutive patients with diagnosis of PD by a neurologist with expertise in movement disorders, according to international criteria [14], were recruited. Patients suffering for other chronic disabling conditions impeding or interfering with the evaluation of PD impact were excluded from the study. Patients unable to directly answering written questionnaires were helped by a trained person out of the patient's relationships and of the usual health professionals attending them. Patients with moderate or severe cognitive deterioration, according to MDS-UPDRS

Part I – item 1 equal or greater than 3 and CISI-PD Cognition 4 or higher, were not included in the analysis.

Each participant site obtained approval from the local Ethics Committee or Institutional Review Board and patients had to give their signed consent to participate in the study.

### 2.3. Assessments

In addition to demographic and PD historical information, the following assessments were applied:

*MDS-UPDRS Spanish version* [5,15], a comprehensive scale composed of four parts: Part I – Non-Motor Experiences of Daily Living, which includes thirteen items: six rater-based and seven for patient self-assessment; Part II – Motor experiences of daily living, with 13 patient-based items; Part III – Motor examination, including 18 items (33 scores); and Part IV – Motor complications, formed of six items on dyskinesia and fluctuations. Each item scores from 0 (normal) to 4 (severe) and for each part, total scores are obtained from the sum of the corresponding item scores.

*HY* original version, that classifies the course of PD in five stages [4,10].

*CISI-PD* [13,16], an instrument that provides a clinical estimate of PD severity based on four outstanding PD aspects: motor signs, disability, motor complications, and cognitive status. Each domain scores from 0 (normal) to 6 (very severe) and the total score ranges from 0 to 24 points.

*Global Impression of Severity*. The 7-option clinician-based (CGIS) [11] and a 6-option patient-based global impression of severity (PGIS, with the option "severe" representing the collapse of the "markedly ill" and "severely ill" options that may be difficult to differentiate for patients) were included in the respective case report forms.

### 2.4. Data analysis

Descriptive statistics (central tendency and dispersion measures; proportions) were applied to characterize the variables in the sample. Levodopa-equivalent daily dose was calculated according to Tomlinson et al., 2010 [17].

Concordance among the four global evaluations was estimated by means of the Kendall's coefficient of concordance. Given the different structure of the four scales, a value  $\geq 0.60$  was considered satisfactory. Percentage of agreement between the scales was also determined.

The global evaluations were transformed to three severity categories – mild, moderate, and severe – according to previous studies or response options wording: HY classification (stages 1 and 2, mild; stage 3, moderate; and stages 4 and 5, severe) [10]; CISI-PD (1–7, mild; 8–14, moderate;  $\geq 15$ , severe) [16]; CGIS (2–3, mild; 4, moderate; 5–7, severe); and PGIS (1–2, mild; 3, moderate; 4–5, severe) (Table 1).

The coincidence in degree of severity of at least two of the three clinical classifications plus the patient's gradation was adopted as "the criterion of severity" for this study. Comparison between groups broken down by these severity levels was carried out with the Kruskal–Wallis test. Bonferroni correction for multiple comparisons was applied.

Cut-off values for each MDS-UPDRS subscale by each severity level were determined by means of: 1) percentile 90 of the subscale total score; 2) receiver operating characteristic (ROC) analysis; and 3) ordinal logistic regression (OLR) model, calculating the probability curves for each category of severity and the cut-off points between these curves. The OLR was applied to ascertain the relationship between a continuous variable independent (the MDS-UPDRS subscales) and a dependent variable of ordinal type (the severity levels classification), allowing to obtain the cut-off points of the independent variable model logit associated with the 'k' (three, in the present study) categories of the dependent variable. As foreseeably the three described methods would not coincide in their results, a triangulation by average of the three corresponding values was planned to estimate the value most probably close to the true cut-off point for each situation.

## 3. Results

The sample for the present study, from 9 different centres of seven countries, was composed of 452 patients, 55.3% males, with age (mean  $\pm$  SD) 65.1  $\pm$  10.7 years (range: 22–91) and PD duration 8.7  $\pm$  6.3 years (range: 0–40). HY staging was: 69 (15.3%) were in stage 1; 163 (36.0%) in stage 2; 133 (29.4%) in stage 3; 70 (15.5%) in stage 4; and 17 (3.8%) in stage 5. Additional characteristics of the sample are shown in Table 2.

Concerning treatment for PD, 86.5% of patients received levodopa, 57.5% dopamine agonists, 49% a combination of both; and 36.6% other anti-PD drugs such as MAOB inhibitors or amantadine. Thirty-eight patients (8.4%) underwent functional surgery for PD.

Table 3 shows the distribution of the sample broken down by the PD severity levels (mild, moderate, severe) derived from the HY, CISI-PD, CGIS, and PGIS as described in the Data analysis section.

**Table 1**  
Parkinson's disease severity classification based on global evaluations.

	Normal	Mild	Moderate	Severe
<i>Clinical assessments</i>				
Hoehn and Yahr staging	0	1–2	3	4–5
Clinical Impression of Severity Index for Parkinson's disease	0	1–7	8–14	15–24
Clinical Global Impression of Severity	1	2–3	4	5–7
<i>Patient self-assessment</i>				
Patient Global Impression of Severity	0	1–2	3	4–5

The correlation between these scales ranged from 0.84 (CGIS with CISI-PD levels) to 0.56 (HY with PGIS levels) and the Kendall's coefficient of concordance among the four classifications was 0.65 ( $p < 0.0001$ ). The percentage of agreement between their respective severity levels classifications ranged from 87% (HY with PGIS) to 95% (CISI-PD with CGIS).

For a definitive classification of patients, the “criterion of severity”, consisting in the agreement between at least two grading systems out of the three clinician-based (HY, CISI-PD, and CGIS) plus the PGIS was used. The “criterion”, classified 275 patients out of 452 (60.8% of the sample) as: mild PD, 149 (54.2%); moderate, 82 (29.8%); and severe, 44 (16%). Values of the variables in the study, broken down according to these severity levels, are shown in [Table A \(Supplementary material\)](#). All historic and evaluative values were significantly different between the established severity categories.

Cut-off points for the four MDS-UPDRS sections were determined by percentile 90, ROC analysis, and OLR ([Table 4](#)). As foreseen, the obtained cut-off values were not coincident, although differences between methods were only around 2–3 points. The mean values among the three methods (triangulation) offer a theoretical approach to the true cut-off point values ([Table 4; Supplementary material, Figs. 1 and 2](#)).

#### 4. Discussion

Estimations about the severity of a chronic disease are necessary, but also may be elusive when a recognized objective marker of severity does not exist. In this situation, the estimates are based on subjective appraisal and clinical experience.

For neurodegenerative diseases and specifically for PD, the continuum between onset and advanced phases is very variable in the expression and rate of progression. Presence and severity of symptoms throughout time is heterogeneous, with a wide

**Table 2**  
Characteristics of the sample.

	Mean	SD	Median	CI95%	Range
Age at PD onset	56.5	11.2	57	55.50–57.58	17–80
Years since diagnosis	7.8	6.0	7	8.09–9.26	0–37
Duration of treatment	7.6	6.0	6	7.23–8.35	0–37
Education (years)	11.7	5.4	12	11.17–12.17	0–36
MDS-UPDRS 1	11.1	7.0	10	10.45–11.76	0–34
MDS-UPDRS 2	15.3	11.4	13	14.29–16.40	0–49
MDS-UPDRS 3	35.2	21.2	31	33.29–37.21	0–97
MDS-UPDRS 4	4.6	5.0	3	4.19–5.11	0–18
CISI-PD	8.4	5.1	8	7.92–8.87	0–21
Levodopa daily dose	626.0	467.8	600	582.79–669.27	0–4000
DA-LEDD	133.2	158.3	80	118.56–147.83	0–1380
Total LEDD	759.2	490.9	750	713.85–804.61	0–4000

SD: standard deviation. CI95%: confidence interval 95%. PD: Parkinson's disease. MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale. CISI-PD: Clinical Impression of Severity Index for Parkinson's disease. DA-LEDD: dopamine-agonist levodopa-equivalent daily dose. Total LEDD: levodopa daily dose + Dopamine-agonist levodopa-equivalent daily dose.

**Table 3**  
Distribution of the sample broken down by severity levels based on the applied global evaluations.

	HY	CISI-PD	CGIS	PGIS
Mild	232 (51.3%)	222 (49.1%)	205 (45.3%)	189 (41.8%)
Moderate	133 (29.4%)	162 (35.8%)	154 (34.1%)	170 (37.6%)
Severe	87 (19.3%)	68 (15.1%)	93 (20.6%)	93 (20.6%)

HY: Hoehn and Yahr staging. CISI-PD: Clinical Impression of Severity Index for Parkinson's disease. CGIS: Clinical Global Impression of Severity. PGIS: Patient Global Impression of Severity.

variability among patients, making difficult to define limits for disease severity gradation. As recently shown, a discrepancy between the gradation of motor and non-motor disorders is commonly observed [9,18].

However, having available a consistent method for classifying PD patients as mild, moderate, or severe would entail advantages for a diversity of settings from daily practice to social-health policy. Such method could be implemented on the appearance of specific symptoms, the number of symptoms, or thresholds reached in measures of severity or disability. Nonetheless, in the absence of a defined and appropriate anchor, the determination of cut-off values for these measures would be arbitrary.

Using global measures has the disadvantages of subjectivity and scant precision, but conceptually is more close to the intended classification. In the present study, we used a combination of this kind of measures resulting from the patient evaluation and clinical impression (HY, CISI-PD, CGIS) and patient self-assessment (PGIS). The coincidence in the gradation derived from estimations coming from both sources was considered “the criterion” to definitively setting a case as mild, moderate, and severe, as doctors and patients – simultaneously and independently – consider this is the severity level to which the patient can be assigned. This coincidence was possible in only 61% of the cases, due to the conditions imposed for the elaboration of the criterion, but is consistent and allows the extrapolation of the outcomes for the complete sample. It is worthy of note that neither neurologists nor patients knew about the intention of this study, which was conceived to this purpose but embedded in other explicitly aimed at evaluation of disability in PD.

The Unified Parkinson's Disease Rating Scale has been the most widely used scale to measurement impairment and disability in PD [19]. After a careful revision of this scale, the Movement Disorders Society sponsored its revision and the development of the MDS-UPDRS which retains the strength of the UPDRS, adds some elements not covered by this scale, resolves ambiguities, and provides

**Table 4**  
Cut-off points of the MDS-UPDRS.

MDS-UPDRS	Method			Triangulation cut-off values
	Centile 90	ROC	OLR	
<i>Part 1</i>				
Mild/moderate	11/12	8/9	11.4/11.5	10/11
Moderate/severe	20/21	23/24	20.5/20.6	21/22
<i>Part 2</i>				
Mild/moderate	12/13	12/13	13.5/13.6	12/13
Moderate/severe	28/29	30/31	29.2/29.3	29/30
<i>Part 3</i>				
Mild/moderate	35/36	27/28	33.4/33.5	32/33
Moderate/severe	57/58	57/58	60.5/60.6	58/59
<i>Part 4</i>				
Mild/moderate	3/4	4/5	4.5/4.6	4/5
Moderate/severe	11/12	13/14	11.4/11.5	12/13

ROC: receiver operating characteristic analysis.

OLR: ordinal logistic regression.

MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale.

detailed instructions. It includes 50 items divided in 4 non-summative sections. Although a conceptual framework of slight/mild/moderate/severe is offering for each individual question, such frame of level of affectation is not offered for the numerical result of each section. Here it is needed to be said again that neither the UPDRS nor the MDS-UPDRS have been designed for such conceptual framework classification on levels of severity.

However, in the MDS-Task Force publication on the UPDRS authors stated that future goals should include the definition of scores that correlate with clinically pertinent designations, such as “minimal,” “mild,” “moderate,” and “severe” PD [19]. According to this statement, the objective of the present study was to explore whether different scores of the individual sections of the UPDRS may suggest categorical levels of disease severity which may be of utility at bedside use. To our knowledge, a similar gradation is not available for the MDS-UPDRS and the present study would be, therefore, the first attempt for furnishing such a clinically relevant classification.

To have available a consistent method for classifying PD patients as mild, moderate, or severe would entail advantages for a diversity of settings from daily practice to social-health policy. Such method could be implemented on the appearance of specific symptoms or complications, number of symptoms, or threshold reached in measures of severity or disability, but that task immediately seems to be complex. We think that the concordance of global scores from three clinical validated scales together with one scale of patient self-evaluation could provide a reliable method for definition of severity levels.

For trained clinicians is not difficult to link UPDRS motor scores to a severity stage. As an example, Lang and co-workers stated that patients with a Part III UPDRS score of 30 or below in off stage were not enough disabled to undergo DBS whereas scores of 30 or above in on stage reflect too much affectation to be considered a candidate for surgery [20]. However such precision cannot be achieved by other than experts in movement disorders and an objective limit statistically determined would be welcome for clinical practice daily use.

Concerning limitations of the study, future studies with other samples and using a different approach can find other results, but the sample size in our study, the strength of the statistical methods applied, and the proximity of their results are promising. Triangulation, offering a balanced value among those coming from different approaches, has a strong logical basis and has been proposed in other settings sharing a similar context of uncertainty on the authentic value among several available [21,22]. Depression is a common and core non motor symptom in PD impacting on patients' disability and quality of life. It may be argued that depression may affect self-assessments. However, this symptom must be considered into the gamut of non motor manifestations contributing to the severity of the disease and cannot be excluded. To diminish the impact of any circumstance influencing self-evaluation the cut-off scores were obtained only on data from coincident gradation by patient and doctor. This way, potential bias of patient self-evaluation was discarded or attenuated.

Forty per cent of patients did not meet “the criterion of severity” established for this study. To determine the MDS-UPDRS cut-offs these patients could not be considered. However, once the cut-off points are settled they can be applied to any patient assessed by means of the MDS-UPDRS.

In conclusion, we found through the agreement between clinician-based evaluations and patient self-assessment, a reliable categorical classification of PD severity (mild, moderate, severe) to which cut-offs for MDS-UPDRS scores could be assigned by consistent statistical methods. This way, the severity level can be directly determined from the scores of the MDS-UPDRS subscales

and this gradation may be of clinical utility. We propose the values shown in the column “Triangulation cut-off values” in Table 4 to classify PD patients' condition as mild, moderate, or severe on the basis of their MDS-UPDRS scores.

### Authors' roles

1 – Conception and Design – Pablo Martínez-Martín, Marcelo Merello

Acquisition of data – Mario Alvarez; Tomoko Arakaki; Víctor Campos Arillo; Pedro Chaná; William Fernández; Nélida Garretto; Juan Carlos Martínez-Castrillo; Mayela Rodríguez-Violante; Marcos Serrano-Dueñas; Diego Ballesteros

Analysis of data – Pablo Martínez-Martín, Carmen Rodríguez-Blázquez, Jose Manuel Rojo-Abuin

Interpretation of data – Pablo Martínez-Martín, Carmen Rodríguez-Blázquez, Jose Manuel Rojo-Abuin, Marcelo Merello

2 – Drafting of the manuscript – Pablo Martínez-Martín and Marcelo Merello Critical review of the draft – All the coauthors.

3 – Final approval of the submitted manuscript – All the coauthors.

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Pablo Martínez-Martín received honoraria from speaking engagements at scientific meetings of Abbvie and Teva, and from serving in a scientific advisory board of Abbvie; grants from Carlos III Institute of Health [FIS], IMSERSO, Reina Sofia Foundation, and Michael J. Fox Foundation. He is Chair of the IPMDS Committee for Development of Rating Scales. His employment is at Carlos III Institute of Health.

Carmen Rodríguez-Blázquez has nothing to declare. Her employment is at Carlos III Institute of Health.

Mario Alvarez has not disclosures to declare. His employment is at International Centre of Neurological Restoration (CIREN).

Tomoko Arakaki has not disclosures to declare. Her employment is at Hospital Ramos Mejía.

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Kallol Ray Chaudhuri has received funding from Parkinson's UK, NIHR, UCB, European Union and has received honorarium from UCB, Abbott, Britannia, US Worldmeds, Otsuka pharmaceuticals in the last 3 years and acted as a consultant for Abbvie, UCB, Britannia. His employment is at King's College Hospital.

Marcelo Merello received honoraria from speaking engagements at scientific meetings of Lundbeck and GSK. Received grant support from Allergan and Pfizer and received honoraria as consultant for Medtronic. His employment is at Raul Carrea Institute for Neurological Research (FLENI).

### Conflict of interest

The authors declare no conflict of interests for this study.

### Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.parkreldis.2014.10.026>.

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