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# Rankin scale as a potential measure of global disability in early Parkinson's disease

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## Abstract

We conducted an exploratory analysis of the utility of the modified Rankin Scale (mRS) as a global measure of disability in early Parkinson's diesase (PD) using the baseline data from a large cohort of PD patients enrolled in a longitudinal study of creatine. The mRS is scored 0–6 with lower scores reflecting less disability. For the analysis the mRS score was dichotomized at <2 *versus* ≥2. We explored the association of the mRS with multiple measures of PD-related impairments, including the Unified Parkinson Disease Rating Scale (UPDRS); cognitive function characterized by the Symbol Digit Modalities – verbal, and Scales for Outcomes in Parkinson's disease – cognition (SCOPA-COG); quality of life (Parkinson's disease questionnaire [PDQ-39]) and EuroQOL; Beck Depression Inventory II (BDI); and Total Functional Capacity (TFC). We also investigated the interaction between variables. One thousand seven hundred forty-one patients were included in the analysis of which 374 had a mRS score of 2 or above. In the univariate model, all interested measures except SCOPA-COG ($p = 0.23$) had significant association with mRS ($p < 0.001$) after controlling for confounders. In the multivariate model, UPDRS Part II and III (activities of daily living and motor), BDI, TFC and PDQ-39 were significant ($p < 0.05$). The mRS has a significant association with the wide spectrum of measures of impairment and quality



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of life in early PD and shows good potential to be a global measure of disability in early PD. The sensitivity of the mRS to change and performance of the scale in more advanced PD will have to be established longitudinally.

**Keywords**

Clinical trials; Clinical trials methodology; Parkinson's disease; Rankin scale

## 1. Introduction

Parkinson's disease (PD) is associated with a broad spectrum of motor (rigidity, bradykinesia, tremor, gait and postural instability) and non-motor features (mood, cognition, and autonomic dysfunction) that may contribute to overall disability. While there are multiple validated tools to measure the impact of interventions on specific domains of impairment, there are no well-accepted measures that assess the impact of treatment on overall disability in PD. Regulatory agencies are increasingly required to include disability measures as outcomes of intervention in PD. The modified Rankin Scale (mRS) is a validated global disability measure that has long been widely used as one of the primary outcome measures in stroke clinical trials.[1–3] There is limited experience with the use of mRS as a global disability outcome measure in PD. Two recently completed pilot studies of potential disease modifying agents in early PD demonstrated that mRS was one of the independent predictors of time to initiation of symptomatic treatment.[4] We used the baseline data from a large cohort of PD patients enrolled in a longitudinal study of creatine (Long-term Study-1; LS-1) to conduct an exploratory analysis of the utility of mRS as a global measure of disability in early PD. The objective of this analysis was to explore the association of mRS with other measures of impairment, disability, and quality of life based on the baseline characteristics of the LS-1 cohort.

## 2. Methods

### 2.1. Study design

LS-1 is a multicenter, double-blind, parallel group, placebo-controlled Phase 3 study of creatine in participants with treated PD conducted by the National Institute of Neurological Disorders and Stroke Exploratory Trials in Parkinson's Disease (NET–PD) network. The detailed study design and baseline characteristics of participants enrolled in this trial will be presented elsewhere, but are summarized briefly below. The Institutional Review Board approved this study.

### 2.2. Participants

The target population for this study is patients with early-stage PD (within 5 years from diagnosis) who are receiving stable dopaminergic therapy for symptomatic control of their disease. To be eligible, participants must have taken dopaminergic therapy (levodopa or a dopamine agonist) for at least 90 days and no longer than 2 years. Following baseline evaluation, the patients are randomized to receive either creatine packets 5 gm twice daily or a matching placebo. Throughout the trial, participants can receive any available therapies used to treat PD, with changes permitted over time to allow individual optimization of therapy. In-person evaluations are conducted at baseline and at regular pre-specified time points through the course of the study until the last participant completes 5 years of follow-up. Only data from the baseline visits were utilized in the present analysis. We received written informed patient consent to perform this study.

### 2.3. Outcome measures

The primary outcome measure in our analysis is the mRS score.[3] The mRS is a concise index of global disability which is scored as follows: 0 = no symptoms; 1 = no significant disability despite the symptoms; 2 = slight disability, unable to carry out all previous activities, but able to look after one's own affairs without assistance; 3 = moderate disability, requiring some help, but able to walk without assistance; 4 = moderately severe disability, unable to walk without assistance and unable to attend to one's bodily needs without assistance; 5 = severe disability, bedridden, requiring nursing care and attention; 6 = dead.[3] The scale is usually dichotomized to reflect good *versus* poor outcome. Based on the stroke literature, mRS scores from 0-2 are considered a "favorable outcome."[5] If a good outcome is defined as the ability to perform outdoor activities, mRS score less than or equal to 1 should be used, but if a good outcome is defined by ability to perform complex activities of daily living, mRS score 0-2 is considered to be an appropriate outcome measure.[5]

The study is collecting assessments of multiple dimensions of PD-related impairment. The domains being assessed include motor disability characterized by the Unified Parkinson Disease Rating Scale (UPDRS) Parts I-IV;[6] ambulatory capacity (sum of 5 UPDRS questions: falling, freezing, walking, gait, postural stability)[6] and activities of daily living scale;[7] cognitive function characterized by the Symbol Digit Modalities – verbal[8] and Scales for Outcomes in Parkinson's disease – cognition (SCOPA-COG);[9] quality of life (Parkinson's disease questionnaire [PDQ]-39)[10] and EuroQOL (EQ-5D).[11] Additional outcome measures are collected, including Beck Depression Inventory II (BDI)[12] and Total Functional Capacity (TFC).[13]

### 2.4. Statistical analysis

The primary response variable in our analysis is the mRS score dichotomized at <2 *versus* ≥2. The measures under consideration are UPDRS part I-IV, BDI, TFC, SCOPA-COG, symbol digit modalities, EuroQOL (EQ-5D), and PDQ-39. To reduce the number of measures to be considered in the model, we used an initial screening procedure. We fitted univariate logistic regression models for each of the above measures while adjusting for confounding from the following variables: age, sex, employment, education, race, symptom duration, side of symptom onset (right *versus* left) *versus* handedness. Those measures that indicated a significant association with mRS ($p < 0.2$) after adjusting for confounders, were included in the multivariate analysis model. We then examined the correlation among the selected measures. If the correlation coefficient was larger than 0.9, we fit separate models for each of the two highest correlated measures, including other confounding variables. If both measures remained significant ($p < 0.05$) in the respective models, we included the measure representing the largest contribution to the model in terms of variance explained in the final model. All the measures that were not significant ($p > 0.05$) were dropped and the model was refitted to obtain the final estimates of slopes. We also investigated the interaction between variables.

## 3. Results

Baseline characteristics of the LS-1 cohort are presented in Table 1. There are 1367 subjects with mRS < 2 and 374 subjects with mRS ≥ 2. At baseline, there are significant differences in age, disease duration, age at onset, UPDRS I-IV, TFC, SCOPA-COG, symbol digit modalities, EQ-5D and PDQ-39 between the two groups (Table 2). The differences between the two groups on the PDQ-39 are particularly large and present in all domains.

In the univariate analysis, all interested measures except SCOPA-COG ($p = 0.23$) had significant association with mRS ($p < 0.001$) after controlling for confounders. There were no highly correlated measures (maximum was 0.692), so all measures except SCOPA-COG were included in the multivariate analysis model. In the multivariate model, UPDRS Part II (activities of daily living), UPDRS Part III (motor), BDI, TFC and PDQ-39 were significant at $p < 0.05$ after controlling for confounders (Table 3). In order to explore the impact of mood on the mRS we ran the analysis after dichotomizing BDI scores with two cut off values: <14 *versus* ≥14 as the accepted cut off score for depression, and a lower cut off of <9 *versus* ≥9 as the cut off that increases sensitivity of screening for depression.[14] All variables of interest remained significant at both cut offs (Table 3).

## 4. Discussion

The development of disease-modifying therapies has been one of the most active areas of clinical research in PD. In the absence of validated biomarkers that could link the rate of PD progression with the underlying neurodegenerative process, clinical trials have focused on the development of treatments that would slow progression of clinical disability. Selection of an outcome for such interventional trials is essential for the meaningful assessment of efficacy of intervention. Most studies have focused on the impact of intervention on the rate of progression of motor disability as the best defined sphere of disease-related impairment. However, PD is a multi-dimensional disease characterized by impairment in multiple domains including but not limited to cognitive, neuropsychological, sleep, and autonomic dysfunction. In fact, disease-related quality of life in PD is largely determined by mood dysfunction rather than motor disability,[15] and long term disease-related disability is largely defined by cognitive impairment and postural instability.[16] While there are validated measures to assess impact of intervention on each of the above domains, the global measures of disability have not been routinely used in PD. In this study, we found that the mRS correlates with motor impairment, non-motor dysfunction, and quality of life measures in a large cohort of patients with early PD, characteristics that potentially make it a good measure of global disability in PD.

A number of measures of global disability have been validated in other neurological conditions and specifically in stroke and multiple sclerosis. The two most commonly used measures are the Barthel index and modified Rankin score.[1,17] In order for any of these disability measures to be clinically meaningful, they have to be clinically relevant to the patient, representative of the broad scope of disability, valid, reliable, sensitive to important clinical changes, and analyzed appropriately.

Our exploratory analysis demonstrated that the mRS significantly correlates with the measures of motor (UPDRS parts II-III) and mood (BDI) dysfunction. The mRS also correlates with the PDQ-39 but not EQ-5 quality of life measures. The reason for this dissociation is unclear, though one possible explanation may be that the PDQ-39 is more specific to PD than the EQ-5. These correlations will have to be further explored through analysis of the longitudinal data from LS-1 when they become available at the time of study completion. The same is true for the apparent discrepancy between two measures of cognitive performance, the SCOPA-COG, which did not correlate with the mRS in the univariate analysis, and the symbol digit modalities test, which did. Lack of correlation with the UPDRS Part I is not surprising as it is a very unresponsive measure of cognitive performance and likely was limited by the floor effect in the cohort of participants with early PD. A positive attribute of the mRS which is expected from a measure of global disability based on our data is that it is not weighted heavily by any single domain of disability, as demonstrated by lack of high correlation with any single outcome measure.

Our data demonstrates that mRS is not driven by the degree of depressive symptomatology and the correlations remain the same with the higher *versus* lower BDI scores. This is a potential advantage in using a global disability scale as a measure of efficacy of intervention over quality of life outcome measures, as quality of life measures are heavily affected by the emotional domain[18] and relatively insensitive to change in PD motor symptoms.[19] However, quality of life and disability outcomes are complementary as one measures disability and the other measures handicap, factors which are not congruent. Moreover, the present analysis does not provide any clues as to mRS sensitivity to change, but, given the structure of the instrument, one can expect that it would be most useful in assessing disease progression in the long term rather than for short intervals. Lastly, we have dichotomized mRS scores into ≤2 *versus* >2. We believe that such dichotomy is appropriate for the cohort of patients with early disease. Such a dichotomy is supported by the fact that the cohorts of participants in the two groups separated significantly on all individual disability domain measures (Table 2). The stroke literature also supports such a cut off when seeking best outcomes.[5] We anticipate being able to analyze the longitudinal data, when available with the current mRS cut off as well as a cut off of a ≤ 2 and >2, which may be reflective of a more advanced disease state.

The major limitation of this exploratory analysis is the lack of longitudinal data, though that will become available as the LS-1 study continues. At this point, it is unknown if the mRS is sensitive to change over time. Another important aspect of future research is analysis of mRS performance in advanced PD complicated by motor fluctuations. The LS-1 study provides a unique opportunity to establish sensitivity of the mRS to change in a large cohort of PD patients followed longitudinally for at least 5 years and explore correlation with the multiple domains of PD related impairment as well as the Global Statistical Test used as the primary outcome measure for the study.

## 5. Conclusions

The mRS has a significant association with the wide spectrum of motor and non-motor impairment measures and quality of life measures in early PD and shows good potential to be a global measure of disability in PD. The sensitivity of the mRS to change has yet to be established longitudinally.

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**Table 1**

Descriptive statistics of baseline variables of the longitudinal study of creatine cohort

| Variables | Mean (standard deviation) | Range |
|---|---|---|
| Age | 61.79 (9.64) | 24.00–87.00 |
| Sex, Male:Female% | 64.5:34.5 | |
| Age at onset | 58.53 (9.87) | 17.00–86.00 |
| Disease duration (years) | 1.54 (1.08) | 0–5.50 |

**Table 2**

Comparison of participants with modified Rankin scale scores of <2 *versus* ≥2

| | **Mean (SD) for participants with Rankin <2 (*n* = 1367)** | **Mean (SD) for participants with Rankin ≥2 (*n* = 374)** | ***p* value for *t*-test** |
|---|---|---|---|
| Age | 61.42 (9.55) | 63.15 (9.88) | 0.002 |
| Disease duration (years) | 1.48 (1.06) | 1.76 (1.12) | <0.001 |
| Age at onset | 58.28 (9.79) | 59.43 (10.11) | 0.049 |
| UPDRS I/mental | 1.16 (1.27) | 1.90 (1.57) | <0.001 |
| UPDRS II/ADL | 6.29 (3.38) | 10.34 (4.25) | <0.001 |
| UPDRS III/motor | 16.39 (7.49) | 22.79 (9.45) | <0.001 |
| TFC | 12.38 (1.13) | 10.71 (1.74) | <0.001 |
| SCOPA-COG | 30.45 (5.24) | 29.59 (5.71) | 0.009 |
| Symbol digit modalities | 45.44 (11.46) | 40.79 (12.18) | <0.001 |
| EQ-5D | 0.85 (0.15) | 0.69 (0.21) | <0.001 |
| PDQ-39 | 10.95 (8.59) | 21.58 (13.02) | <0.001 |
| PDQ-39_mobility | 7.60 (11.80) | 25.88 (21.25) | <0.001 |
| PDQ-39_ADL | 11.85 (12.58) | 26.46 (19.60) | <0.001 |
| PDQ-39_emotional | 12.00 (13.27) | 21.62 (17.95) | <0.001 |
| PDQ-39_stigma | 11.83 (15.31) | 16.98 (19.30) | <0.001 |
| PDQ-39_social | 4.25 (10.10) | 8.95 (15.15) | <0.001 |
| PDQ-39_cognition | 12.75 (13.41) | 23.43 (17.84) | <0.001 |
| PDQ-39 communication | 9.04 (12.38) | 19.50 (18.50) | <0.001 |
| PDQ-39_discomfort | 18.26 (17.01) | 30.21 (22.89) | <0.001 |
| Use of antidepressants,% | 22.68 | 30.21 | .004 |

ADL = activities of daily living, PDQ-39 = Parkinson's disease questionnaire, SCOPACOG = Scales for Outcomes in Parkinson's disease – cognition, SD = standard deviation, TFC = Total Functional Capacity, UPDRS = Unified Parkinson Disease Rating Scale.

## Table 3

Association of modified Rankin scale with other measures of Parkinson's disease disability in a multivariate analysis

| Association with modified Rankin score | *p* value for multivariate analysis (BDI continuous) | *p* value for multivariate analysis (BDI dichotomized at ≥9) | *p* value for multivariate analysis (BDI dichotomized at ≥14) |
|---|---|---|---|
| UPDRS I/mental | 0.68 | 0.98 | 0.94 |
| UPDRS II/ADL | <0.001 | <0.001 | <0.001 |
| UPDRS III/motor | 0.01 | 0.02 | 0.02 |
| BDI | 0.01 | 0.04 | 0.08 |
| TFC | <0.001 | <0.001 | <0.001 |
| Symbol digit modalities | 0.06 | 0.05 | 0.05 |
| EQ-5D | 0.22 | 0.18 | 0.12 |
| PDQ-39 | 0.01 | <0.001 | <0.001 |
| S&E* | <0.001 | <0.001 | <0.001 |

ADL = activities of daily living, BDI = Beck Depression Inventory, PDQ-39 = Parkinson's disease questionnaire, S&E = Schwab and England Activities of Daily Living scale, TFC = Total Functional Capacity, UPDRS = Unified Parkinson Disease Rating Scale.

* S&E was dichotomized by <100 (*n* = 1465) *versus* = 100 (*n* = 275).