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ORIGINAL ARTICLE

Relationship between frailty and disease progression in Parkinson's disease: a 3-year longitudinal study

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Abstract Parkinson's disease (PD) shows substantial variability in presentation and progression. Frailty, a multidimensional construct reflecting biological aging, is a determinant of clinical outcomes in several neurodegenerative disorders. While cross-sectional studies suggest that frailty modulates the clinical phenotype of PD, affecting motor and non-motor symptoms, its longitudinal prognostic relevance remains unclear. In this 3-year, single-center cohort study, we investigated whether frailty, measured using a validated 50-item frailty index (FI), predicts clinical progression, motor complications, and mortality in a cohort of 109 PD patients. Clinical assessment included MDS-UPDRS parts III and IV, Non-Motor Symptoms Scale, Hoehn & Yahr stage, Montreal Cognitive Assessment, and levodopa equivalent daily dose (LEDD). Associations between baseline FI and follow-up outcomes were examined using simple and multiple linear regression models. Patients were stratified into three frailty groups at baseline to examine group-level differences in clinical progression and mortality, which were assessed using mixed-effects models and contingency analyses. Higher baseline FI independently predicted greater severity of treatment-related motor complications at follow-up ($\beta=8.3$; $p=0.04$) and greater worsening of these complications over time ($\beta=11.4$; $p=0.017$) and showed trends toward greater non-motor symptom burden and cognitive decline. No significant association was observed between baseline FI and motor progression. Patients classified as frail at baseline displayed greater clinical deterioration across multiple domains, higher LEDD requirements, and had increased mortality ($\chi^2=16.5$, $p<0.001$) compared to less frail counterparts. In conclusion, frailty predicts worse clinical trajectories and increased mortality in PD, supporting its utility as a prognostic biomarker. Incorporating frailty assessment into routine care may improve risk stratification and guide personalized therapeutic approaches in PD patients.

Keywords Parkinson's disease · Frailty · Progression · Longitudinal study

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Introduction

Parkinson's disease (PD), a heterogeneous, multisystem neurodegenerative disorder, is increasingly prevalent in the aging population [1–3]. This seemingly straightforward epidemiological observation sheds light on the intricate, yet not fully understood, interaction between PD and aging-associated changes, which could significantly influence the disease's expression and course [1, 3, 4].

The aging process diminishes the ability to resist damage and stress, resulting in higher levels of disability, an increased incidence of diseases, and mortality [1]. However, the impact of aging varies widely among individuals. Older adults with the same chronological age may exhibit different levels of physical and cognitive function [5–7]. This discrepancy suggests that chronological age is inadequate for disentangling the intricate relationship between ageing-related changes and the phenotypic manifestations or trajectories observed in chronic conditions such as PD.

In contrast to chronological age, which merely counts the years lived, biological age provides a more comprehensive metric that reflects an individual's functional and physiological state. A key indicator of biological aging is frailty, which is defined as a state of increased vulnerability to stressors resulting from a decline in reserve and function across multiple physiological systems [6, 8]. This concept can be quantified through the frailty index (FI), a multidimensional tool that arithmetically measures accumulated biological deficits [9, 10].

Previous cross-sectional studies have shown that frailty, as assessed by the FI, is more prevalent in PD patients than in healthy individuals [11–13]. Furthermore, frailty is associated with higher rates of mortality and hospitalization [14], as well as increased severity of motor and non-motor symptoms [12]. A recent longitudinal study indicated that frailty in newly diagnosed PD patients not only occurs more frequently than in controls but is also significantly associated with an increased risk of developing dementia within a 3-year follow-up period [15]. These findings underscore the need for focused research on the influence of frailty on the progression of PD. Longitudinal studies are indeed pivotal for disentangling the complex relationship between biological aging and the heterogeneous progression patterns observed in PD patients [15, 16].

In this study, we re-evaluated a cohort of patients with PD across different stages of the disease over approximately three years. The primary aim was to investigate whether frailty in PD serves as a predictive factor for increased clinical severity, encompassing both motor and non-motor symptoms, as well as mortality.

Materials and methods

Subjects

In this longitudinal study, we conducted a follow-up assessment of a cohort of patients diagnosed with idiopathic PD, who had been consecutively enrolled and evaluated three years prior at the Department of Human Neuroscience, Sapienza University of Rome [12]. The diagnosis of PD was established based on the International Parkinson and Movement Disorder Society clinical diagnostic criteria [17]. The baseline characteristics of these PD patients were documented in a previously published article [12]. After a 3-year interval, patients were recontacted and provided their written informed consent to participate in the subsequent phase of the study. The protocol was approved by the local ethics committee (n.4734) and conducted according to the principles of the Declaration of Helsinki.

Clinical assessment

The follow-up evaluation was designed to mirror the methodologies employed at baseline [12]. In both evaluations, patients were assessed OFF treatment. Clinical assessments were conducted by a neurologist experienced in movement disorders, while the FI was administered by neurologists trained specifically in its use. The same neurologists who performed the baseline evaluations also conducted the follow-up assessments and FI administration. Follow-up assessments were conducted with raters blinded to baseline data, with no access to baseline scores or study forms prior to or during the clinical evaluation. For each participant, sociodemographic information and medical history were collected, along with details

regarding pharmacological treatments. The levodopa equivalent daily dose (LEDD) was calculated for each patient [18].

Participants underwent a comprehensive clinical evaluation using standardized clinical scales. The stage of disease was evaluated by using the Hoehn & Yahr scale (H&Y) [19]. Motor symptom severity assessment was performed by employing the Italian version of the MDS-UPDRS Part III, whereas evaluation of motor complications was performed through the MDS-UPDRS Part IV [20].

The Italian version of the Non-Motor Symptoms Scale (NMSS) was used to evaluate the severity of non-motor features, including cardiovascular symptoms, sleep disturbances, autonomic dysfunction, cognitive impairment, neuropsychiatric dysfunction, and pain [21]. The Montreal Cognitive Assessment (MoCA) was employed to evaluate the presence of cognitive impairment and assess global cognitive functioning [22].

Frailty index

Frailty assessment was conducted using the FI administered at the baseline evaluation [12]. This index was developed following a standardized procedure to quantitatively assess frailty by integrating a spectrum of deficits commonly associated with the aging process [10]. The FI encompassed 50 distinct deficits, including a diverse range of clinical symptoms, medical conditions, functional impairments, and abnormalities in laboratory findings. A binary scoring mechanism was employed for each deficit, assigning a score of "0" to indicate the absence of a particular deficit and a score of "1" to denote its presence. The FI score was then calculated by dividing the total number of deficits an individual had by the total number of deficits examined (50 in total), thus potentially ranging from 0 (indicating no deficits) to 1 (indicating all deficits present).

Statistical analysis

Statistical analyses were performed using GraphPad Prism version 10.1.1 (GraphPad Software, Inc., San Diego, CA). Continuous variables were reported as means ± standard deviations. The Shapiro–Wilk test was used to determine whether all variables fit a normal distribution. Both parametric and non-parametric tests were employed to evaluate potential differences between baseline and follow-up measurements in our cohort, as appropriate. Correlation analyses were performed to examine potential associations between variables.

To evaluate the prognostic value of baseline frailty, we used linear regression models with baseline FI as the main independent variable and clinical outcomes at follow-up, including total scores of MDS-UPDRS III and IV, NMSS, H&Y, and MoCA, as dependent variables. We first used simple linear regression models. For those variables that showed significant associations in the simple linear regression models, multiple linear regression models were subsequently applied, to adjust for potential confounders. In these models, follow-up outcomes were adjusted for age, sex, follow-up duration (measured in years between baseline and follow-up evaluations) and the corresponding baseline scores (i.e., follow-up outcome ~ FI + baseline outcome + covariates). To complement the baseline-adjusted approach, we conducted sensitivity analyses using change-scores (Δoutcome = follow-up − baseline) as dependent variable (i.e., Δoutcome ~ baseline FI + age + sex + follow-up duration). To assess the potential impact of incomplete follow-up on our results, we also conducted a sensitivity analysis using stabilized inverse probability weighting (IPW). We modeled the probability of follow-up completion based on baseline variables and re-estimated both baseline-adjusted and change-score models under IPW (Supplementary Materials for full details). All multiple linear regression models were tested for main effects and potential two-way interactions among covariates. Main effect-based and two-way interactions-based models were compared, and model selection was guided by the corrected Akaike information criterion (AICc). Variance inflation factor (VIF) values were used to assess potential multicollinearity among the variables. The final model was selected based on the lowest AICc value and acceptable VIF values (VIF < 1.5).

To further assess the impact of frailty on PD progression, we classified our cohort into the following three categories, based on baseline FI cutoff points that have been validated in the general population: (i) relatively fit: FI ≤ 0.10; (ii) less fit: 0.10 < FI ≤ 0.21; and (iii) frail: FI > 0.21 [23–25]. Because PD-specific FI cutoffs have not yet been established and externally validated, we retained the same categories

based on general population thresholds used in our baseline assessment [12] to ensure methodological consistency and facilitate clinical interpretability. Chi-square tests were applied to evaluate differences in motor complications and mortality rates among these groups. Additionally, a mixed-effects model with restricted maximum likelihood estimation was conducted to assess changes in MDS-UPDRS Parts III and IV, NMSS, MoCA, and LEDDs across the three groups at two time points (baseline and follow-up). TIME (baseline vs. follow-up), GROUP (FI category), and their interaction (TIME × GROUP) were included as fixed effects, and SUBJECT was included as a random effect. Post hoc analyses were performed to further explore significant differences among the groups and time points. We additionally performed an exploratory analysis of NMSS domain-specific scores using a two-way repeated-measures ANOVA with DOMAIN (cardiovascular, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, gastrointestinal or urinary domain) within-subject factor and FI CATEGORY (relatively fit, less fit, frail) as between-subject factor. A p-value < 0.05 was considered statistically significant. Tukey's test or false discovery rate was used to correct for multiple comparisons where appropriate.

Results

Demographic and clinical characteristics of PD patients at follow-up evaluation

One hundred fifty PD patients were enrolled at baseline. By the time of follow-up, the cohort had decreased to 109 participants, with 20 patients having passed away and an additional 21 patients dropping out of the study due to challenges related to traveling to our Department or changes in care centers.

At follow-up, the mean age of participants was 69.6 ± 9.7 years, and the mean interval between the baseline and follow-up assessments was 2.8 ± 0.8 years (33.3 ± 11.6 months). In terms of clinical assessments, the H&Y showed a mean total score of 2.3 ± 0.9. The mean total scores for MDS-UPDRS Parts III and IV were 36.5 ± 13.7 and 4.2 ± 4.8, respectively. Regarding motor complications, dyskinesias were present in 37 of the 109 PD patients, while motor fluctuations were observed in 42 of the 109 PD patients.

Additionally, the mean total score on the NMSS was 65.4 ± 29.5, and the mean MOCA total score was 23.1 ± 3.1. The average LEDD was 587.8 ± 294.8. A comprehensive overview of the demographic and clinical characteristics of the participants at both baseline and follow-up evaluation is detailed in Table 1.

Longitudinal changes in the clinical characteristics of PD patients

The Wilcoxon signed-rank test was employed to evaluate potential differences in the clinical characteristics of PD patients between baseline and follow-up evaluations. The analysis revealed statistically significant differences across various clinical parameters. Specifically, MDS-UPDRS Part III showed a significant change ($W = -5384$; $q < 0.000001$), as did MDS-UPDRS Part IV ($W = -4284$; $q < 0.000001$). Significant changes were also observed in the NMSS ($W = -5973$;

Table 1 Demographic and clinical data at baseline and follow-up evaluation

Variables	Baseline evaluation (n = 150)	Follow-up evaluation (n = 109)
Age	68.8 ± 10.1	69.6 ± 9.7
Sex	96 M, 54 F	71 M, 38 F
Age at onset	62.8 ± 10.7	/
Disease duration at baseline	6 ± 5.4	/
Time interval between baseline-follow-up evaluation (months)	/	33.3 ± 11.6
Time interval between baseline-follow-up evaluation (years)	/	2.8 ± 0.8
Hoehn & Yahr (mean ± SD)	2.1 ± 2.9	2.3 ± 0.9
MDS-UPDRS III (mean ± SD)	22.7 ± 13.6	36.5 ± 13.7
MDS-UPDRS IV (mean ± SD)	1.6 ± 3.3	4.2 ± 4.8
Motor fluctuations (%)	31	42
Dyskinesias (%)	28	37
NMSS	30.1 ± 26.3	65.4 ± 29.5
MoCA	*26 ± 3.5*	*23.1 ± 3.1*
LEDD	*466.5 ± 285.2*	*587.8 ± 294.8*

MDS-UPDRS, International Parkinson and Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; *NMSS*, Non-Motor Symptoms Scale for Parkinson's disease; *MoCA*, Montreal Cognitive Assessment; *LEDD*, levodopa equivalent daily dose

$q<0.000001$), H&Y (W = −4389; $q<0.000001$), MoCA scores (W = 5547; $q<0.000001$), and LEDD (W = −4156; $q<0.000001$). Furthermore, the FI demonstrated significant variations between the two assessments (W = −4372; $q<0.000001$).

Relationship between the FI and the clinical characteristics of PD patients

A non-parametric correlation matrix was utilized to investigate potential associations among various variables, including FI, MDS-UPDRS part III and IV, NMSS, MoCA, H&Y total scores, and LEDDs at follow-up.

Significant correlations were identified between the FI at the follow-up evaluation and the total follow-up scores of MDS-UPDRS Parts III ($r=0.44$; $q=0.000014$) and IV ($r=0.25$; $q=0.019$), H&Y ($r=0.35$; $q=0.0006$), NMSS ($r=0.47$; $q=0.000003$), MoCA ($r=-0.35$; $q=0.0007$), and LEDDs at follow-up ($r=0.27$; $q=0.01$).

In a simple linear regression model, the baseline FI value demonstrated significant association with follow-up scores of MDS-UPDRS parts III ($\beta=25.6$; $p=0.03$) and IV ($\beta=10.6$; $p=0.01$), NMSS ($\beta=68.5$; $p=0.0068$), H&Y ($\beta=3.5$; $p<0.0001$), and MoCA ($\beta=-6.7$; $p=0.0125$). Additionally, the baseline FI value was significantly associated with LEDDs ($\beta=754.9$; $p=0.0032$) at follow-up evaluation. After adjusting for age, sex, follow-up duration, and baseline scores, the baseline FI remained an independent predictor of motor complications severity as measured by MDS-UPDRS part IV ($\beta=8.4$; $p=0.04$). Trends toward significance were also observed for NMSS ($\beta=48.6$; $p=0.059$) and MoCA total score ($\beta=-4.5$; $p=0.059$) at follow-up (see Table 2). Sensitivity analyses using change scores (Δ = follow-up-baseline) were consistent with the primary baseline-adjusted models. The baseline FI was significantly associated with ΔMDS-UPDRS part IV ($\beta=11.4$; $p=0.017$). In contrast, baseline FI was not associated with ΔMDS-UPDRS part III ($\beta=12.4$; $p=0.36$), ΔNMSS ($\beta=42.7$; $p=0.12$), ΔH&Y ($\beta=1.2$; $p=0.14$), with non-significant trends for ΔMoCA ($\beta=4.7$; $p=0.07$) and ΔLEDD ($\beta=430.6$; $p=0.09$) (Table 3). In IPW-weighted sensitivity analyses, effect estimates remained directionally consistent. The association with worsening in treatment-related motor complications (ΔMDS-UPDRS part IV) remained statistically significant (See Supplementary Materials).

Longitudinal trajectories of PD patients classified according to Frailty Index cutoffs

Using FI cutoff points validated in the general population [23–25], PD patients were classified at baseline into three groups: relatively fit ($FI\leq0.10$; $n=51$; 34%), less fit ($0.10<FI\leq0.21$; $n=61$; 40.7%), and frail ($FI>0.21$; $n=38$; 25.3%). At follow-up, 41 out of the initial 51 relatively fit patients (80.4%), 48 of the 61 less fit patients (78.7%), and 20 of the 38 frail patients (52.6%) completed the evaluation. Patients who dropped out at the follow-up evaluation were equally distributed across the three groups, as indicated by the chi-square analysis (relatively fit = 8, less fit = 7, frail = 6; $\chi^2=0.54$; $p=0.76$). Compared with participants who completed the follow-up evaluation, patients who dropped out were older ($U=1251$; $q=0.0003$), had higher age at onset ($U=1449$; $q=0.003$), higher baseline frailty ($U=1472$; $q=0.003$), higher MDS-UPDRS III scores ($U=1686$; $q=0.03$), and lower baseline MoCA total scores ($U=1195$; $q=0.006$). Conversely, no significant differences were observed for disease duration ($U=2052$; $q=0.442$), MDS-UPDRS IV ($U=2161$; $q=0.457$), NMSS ($U=1894$; $q=0.141$), H&Y ($U=1594$; $q=0.141$), or LEDD ($U=2140$; $q=0.457$).

Kruskal–Wallis tests showed significant differences across FI categories for age ($H=34.61$; $p<0.0001$), age at onset ($H=11.20$; $p=0.0037$), and disease duration ($H=22.11$; $p<0.0001$). Post hoc pairwise comparisons showed that age increased from relatively fit to less fit to frail, with significant differences for relatively fit vs. less fit (mean rank diff = 32.15; $q=0.0001$), relatively fit vs. frail (mean rank diff = 50.69; $q<0.0001$), and less fit vs. frail (mean rank diff = 18.53; $q=0.048$). Age at onset was higher in less fit and frail patients than in relatively fit patients (relatively fit vs. less fit, mean rank diff = 25.45; $q=0.0019$; relatively fit vs. frail, mean rank diff = 21.81; $q=0.0082$), with no difference between less fit and frail (mean rank diff = 3.64; $q=0.243$). Disease duration was longer in frail patients than in relatively fit (mean rank diff = 41.40; $q<0.0001$) and less fit patients (mean rank diff = 32.46; $q=0.0002$), while relatively fit and less fit did not differ (mean rank diff = 8.94; $q=0.095$).

Table 2 Simple and multiple linear regression models evaluating the relationship between frailty index at baseline (independent variable of interest) and MDS-UPDRS part III, MDS-UPDRS part IV, NMSS, H&Y and MoCA (dependent variable of interest). Statistically significant results are reported in bold

Test	Simple linear regression model				Multiple linear regression model			
	Variable	Slope (95%CI)	*p* value	r^2	Variable	Estimate (95%CI)	*p* value	Adj r^2
MDS-UPDRS part III FU	FI baseline	25.6 (1.95 to 49.2)	**0.034**	0.04	*FI baseline*	13.6 (−9.4 to 36.6)	0.24	0.26
					Sex	−1.45 (−6.15 to 3.25)	0.54	
					Age	0.2396 (−0.02 to 0.50)	0.07	
					FU duration	0.004 (−2.93 to 2.93)	0.99	
					MDS-UPDRS part III baseline	0.50 (0.33 to 0.68)	**<0.0001**	
MDS-UPDRS part IV FU	FI baseline	10.6 (2.46 to 18.66)	**0.01**	0.06	*FI baseline*	8.35 (0.43 to 16.26)	**0.039**	0.31
					Sex	0.23 (−1.37 to 1.83)	0.78	
					Age	−0.03 (−0.12 to 0.06)	0.46	
					FU duration	0.17 (0.01 to 0.33)	0.81	
					MDS-UPDRS part IV baseline	0.79 (0.55 to 1.03)	**<0.0001**	
NMSS FU	FI baseline	68.5 (13.3 to 123.8)	**0.0068**	0.07	*FI baseline*	48.6 (−1.92 to 99.2)	0.06	0.26
					Sex	3.7 (−6.7 to 14.01)	0.5	
					Age	0.26 (−0.31 to 0.84)	0.3	
					FU duration	0.48 (−5.9 to 6.87)	0.9	
					NMSS baseline	0.56 (0.35 to 0.77)	**0.0001**	
MoCA FU	FI baseline	−6.7 (−11.9 to −1.46)	**0.01**	0.06	*FI baseline*	−4.5 (−9.19 to 0.18)	0.06	0.42
					Sex	−0.33 (−1.30 to 0.64)	0.50	
					Age	−0.07 (−0.12 to −0.02)	**0.009**	
					FU duration	0.09 (−0.51 to 0.68)	0.77	
					MoCA baseline	0.62 (0.46 to 0.79)	**<0.0001**	
Hoehn & Yahr FU	FI baseline	3.48 (2.1 to 4.9)	**<0.0001**	0.19	FI baseline	0.77 (−0.07 to 2.25)	0.3	0.44
					Sex	0.16 (−0.11 to 0.42)	0.24	
					Age	0.02 (0.0007 to 0.03)	**0.04**	
					FU duration	0.10 (−0.06 to 0.27)	0.31	
					Hoehn & Yahr baseline	0.62 (0.44 to 0.81)	**<0.0001**	
LEDDs FU	FI baseline	754.9 (259.4 to 1250)	**0.0032**	0.08	*FI baseline*	192.4 (−199.3 to 584.1)	0.33	0.54
					Sex	41.58 (−34.81 to 118.0)	0.28	
					Age	−3.33 (−7.52 to 0.86)	0.12	
					FU duration	27.82 (−19.27 to 74.90)	0.24	
					LEDDs baseline	0.73 (0.59 to 0.88)	**<0.0001**	

Adj R^2 adjusted R^2, *CI* confidence interval, *FI* frailty index, *FU* follow-up, *MDS-UPDRS* International Parkinson and Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (Part III: motor examination, *Part IV* motor complications), *NMSS* non-motor symptoms scale for Parkinson's disease, *MoCA* montreal cognitive assessment, *H&Y* Hoehn and Yahr staging scale

Regarding clinical variables, mixed-effects models revealed significant main effects of TIME and GROUP across all outcomes (all $p \leq 0.001$). For MDS-UPDRS Part III, we observed significant effects of TIME ($F=102.8$; $p<0.0001$) and GROUP ($F=17.51$; $p<0.0001$), as well as a significant TIME×GROUP interaction ($F=3.48$; $p=0.034$) (Fig. 1a). For MDS-UPDRS Part IV, TIME ($F=53.27$; $p<0.0001$) and GROUP ($F=8.15$; $p=0.0004$) were significant, whereas the TIME×GROUP interaction was not ($F=0.54$; $p=0.586$) (Fig. 1b). For NMSS,

Table 3 Sensitivity analyses using change scores (Δ) as dependent variables (model: Δoutcome ~ baseline FI + age + sex + follow-up duration). Statistically significant results are reported in bold

Test	Multiple linear regression model			
	Variable	Estimate (95%CI)	***p*** value	Adj r^2
Δ MDS-UPDRS part III	*FI baseline*	12.36 (−14.28 to 39.00)	0.36	0.025
	Sex	−2.34 (−7.74 to 3.06)	0.39	
	Age	0.24 (−0.06 to 0.54)	0.12	
	FU duration	−0.07 (−3.44 to 3.30)	0.97	
Δ MDS-UPDRS part IV	*FI baseline*	11.36 (2.03 to 20.68)	**0.02**	0.030
	Sex	0.59 (−1.30 to 2.48)	0.54	
	Age	−0.01 (−0.12 to 0.10)	0.85	
	FU duration	0.18 (−0.99 to 1.36)	0.76	
Δ NMSS	*FI baseline*	42.71 (−11.74 to 97.16)	0.12	0.005
	Sex	0.63 (−10.43 to 11.69)	0.91	
	Age	0.17 (−0.44 to 0.79)	0.58	
	FU duration	0.04 (−6.84 to 6.92)	0.99	
Δ MoCA	*FI baseline*	4.69 (−0.42 to 9.80)	0.07	0.116
	Sex	−0.17 (−1.20 to 0.87)	0.75	
	Age	0.071 (0.01 to 0.13)	**0.02**	
	FU duration	−0.039 (−0.69 to 0.61)	0.90	
Δ Hoehn & Yahr	*FI baseline*	1.20 (−0.41 to 2.80)	0.14	0.045
	Sex	0.31 (−0.02 to 0.64)	0.06	
	Age	0.005 (−0.01 to 0.02)	0.62	
	FU duration	0.12 (−0.082 to 0.32)	0.24	
Δ LEDDs	*FI baseline*	430.6 (−66.93 to 928.2)	0.09	0.020
	Sex	48.69 (−52.54 to 149.9)	0.34	
	Age	−5.83 (−11.45 to −0.21)	**0.04**	
	FU duration	22.98 (−40.56 to 86.52)	0.48	

Adj R^2, adjusted R^2; *CI*, confidence interval; *FI*, frailty index; *FU*, follow-up; *MDS-UPDRS*, International Parkinson and Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (Part III: motor examination; Part IV: motor complications); *NMSS*, Non-Motor Symptoms Scale; *MoCA*, Montreal Cognitive Assessment; *H&Y*, Hoehn & Yahr staging scale; *LEDD*, levodopa equivalent daily dose; Δ, change score (follow-up—baseline)

TIME ($F=145.1$; $p<0.0001$) and GROUP ($F=20.40$; $p<0.0001$) were significant, with no interaction ($F=1.74$; $p=0.180$) (Fig. 1c). Exploratory analyses on NMSS domain-specific scores showed significant main effects of DOMAIN ($F=34.6$; $p<0.0001$) and FI CATEGORY ($F=3.6$; $p=0.03$), as well as a significant DOMAIN×FI CATEGORY interaction ($F=2.1$; $p=0.04$). Post hoc comparisons indicated between-category differences in the cardiovascular domain (relatively fit vs. less fit, mean diff = −1.8; $p^{adj}=0.04$; relatively fit vs. frail, mean diff = −3.1; $p^{adj}=0.02$) and in the mood/cognition domain (less fit vs. frail, mean diff = −9.5; $p^{adj}=0.04$) (Fig. 2). Conversely, no significant differences emerged for sleep/fatigue, hallucinations/perceptual problems, attention/memory, gastrointestinal, or urinary domains (Fig. 2).

For MoCA, TIME ($F=79.26$; $p<0.0001$) and GROUP ($F=17.79$; $p<0.0001$) were significant, with a significant TIME×GROUP interaction ($F=4.90$; $p=0.009$) (Fig. 1d). Finally, for LEDD, TIME ($F=49.45$; $p<0.0001$) and GROUP ($F=7.88$; $p=0.0006$) were significant, with no interaction ($F=0.24$; $p=0.790$) (Fig. 1e). Post hoc analyses at follow-up indicated higher MDS-UPDRS IV scores in frail patients than in both less fit (LS = −2.5; 95% CI = −4.8 to −0.2; $p^{adj}=0.03$) and relatively fit patients (LS = −2.867; 95% CI = −5.2 to −0.5; $p^{adj}=0.01$), higher NMSS scores versus less fit (LS = −19.9; −35.6 to −4.2; $p^{adj}=0.008$) and relatively fit patients (LS = −23.4; 95% CI = −39.4 to −7.3; $p^{adj}=0.002$), lower MoCA scores versus less fit (LS = 2.3; 95% CI = 0.4 to 4.1;

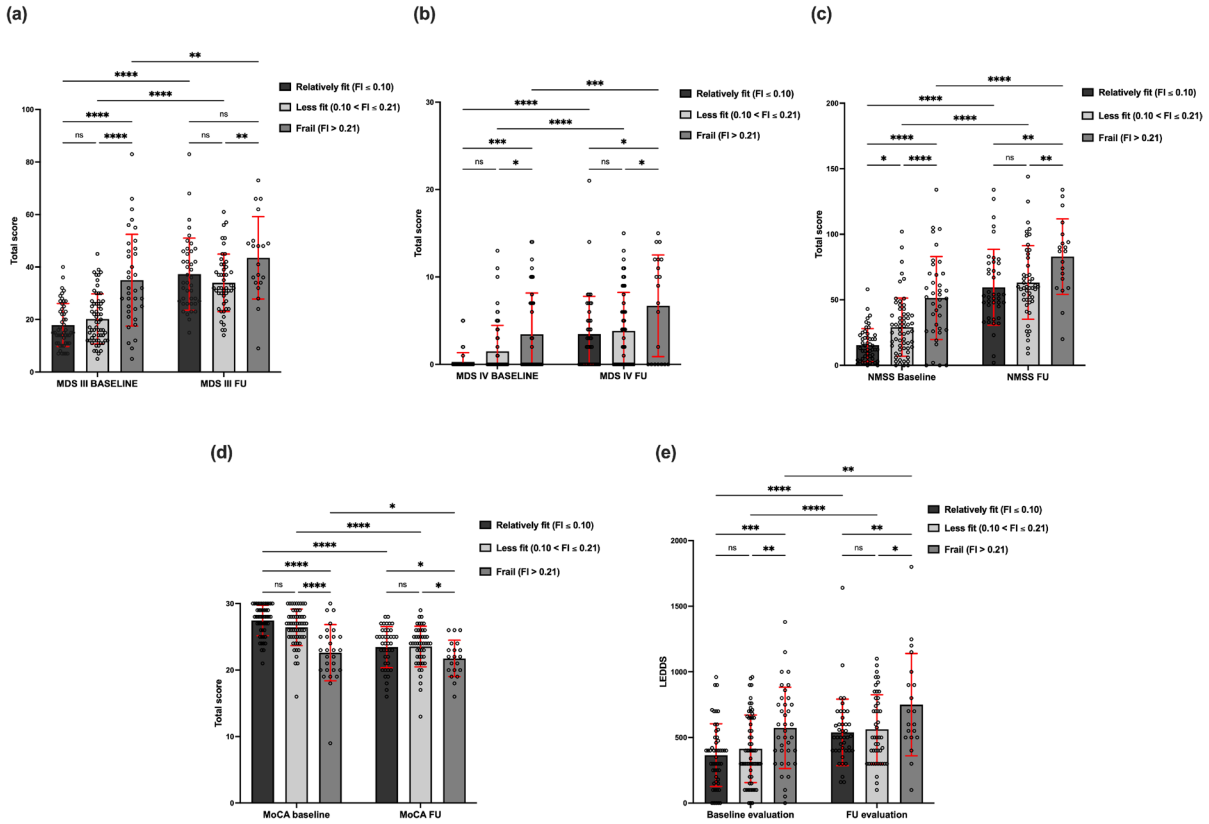

Fig. 1 Comparison among groups of PD patients, classified according to validated FI cutoff points, in terms of MDS-UPDRS part III (**a**), MDS-UPDRS part IV (**b**), NMSS (**c**), MoCA (**d**), and LEDDs (**e**). Error bars represent mean ± SD. Abbreviations: FI, frailty index; FU, follow-up evaluation; *MDS III*, International Parkinson and Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale, part III; *MDS IV*, International Parkinson and Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale, part IV; *NMSS*, Non-Motor Symptoms Scale for Parkinson's disease; *MoCA*, Montreal Cognitive Assessment; *H&Y*, Hoehn and Yahr staging scale; LEDDs, levodopa equivalent daily dose

$p^{adj}=0.0106$) and relatively fit patients (LS = 2.2; 95% CI = 0.4 to 4.1; $p^{adj}=0.01$), and higher LEDD versus less fit (LS = −188.4; 95% CI = −343.6 to −33.3; $p^{adj}=0.01$) and relatively fit patients (LS = −208; 95% CI = −367.5 to −48.5; $p^{adj}=0.006$) (Fig. 1b–e). For MDS-UPDRS III, frail patients had higher scores than less fit patients (LS = −10.4; 95% CI = −17.9 to −2.8; $p^{adj}=0.004$), while the comparison with relatively fit patients did not reach significance but showed a trend in the same direction (LS = −7.4; 95% CI = −15.1 to 0.35; $p^{adj}=0.06$) (Fig. 1a).

Wearing off periods were reported in 29.3% (12/41) of relatively fit and 39.6% (19/48) of less fit patients, compared to 55% (11/20) in the frail category. Similarly, dyskinesias were observed in 29.3% (12/41) of relatively fit and 31.3% (15/48) of less fit patients, compared to 50% (10/20) in the frail group. However, these differences did not result as statistically significant. In contrast, the Chi-square test results showed significant differences in terms of mortality among the three groups ($\chi^2 = 16.5$; $p = 0.0003$). Mortality rates (calculated excluding dropouts) were 4.7% (2/43) in the relatively fit group, 11.1% (6/54) in the less fit group, and 37.5% (12/32) in the frail group. Post hoc pairwise comparisons with FDR correction indicated that frail patients exhibited significantly higher mortality compared to both relatively fit ($\chi^2 = 13.04$; $q = 0.0009$) and less fit patients ($\chi^2 = 8.45$; $q = 0.0054$) (Fig. 3). No significant differences in mortality rates were observed between relatively fit and less fit patients.

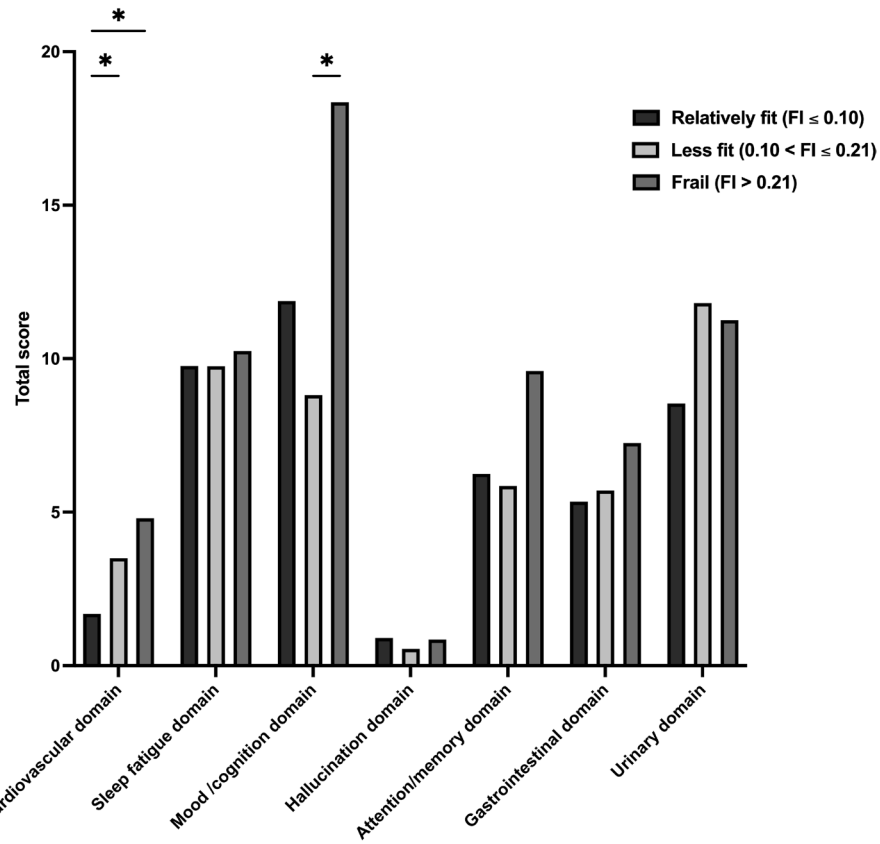

Fig. 2 Exploratory analysis comparing Non-Motor Symptoms Scale (NMSS) domain scores among groups of patients with Parkinson's disease stratified according to validated Frailty Index (FI) cutoff points

Discussion

In this 3-year, single-center, prospective cohort study, we investigated the relationship between frailty, assessed using a frailty index, and clinical progression in 109 patients with idiopathic PD. Our findings confirmed the reliability of the FI in terms of clinometric properties in PD patients, as it maintained its association with both motor and non-motor features, the severity of motor complications, disease stage, and LEDDs throughout the longitudinal evaluation. Simple and multiple linear regression models showed that baseline frailty predicted more severe treatment-related motor complications, as measured by MDS-UPDRS Part IV, at follow-up, with consistent findings in baseline-adjusted follow-up models and change-score sensitivity analyses. By contrast, we did not observe a significant association between baseline frailty status and worsening of motor impairment from baseline to follow-up, as measured by MDS-UPDRS Part III. Additionally, a trend toward an association between frailty and both non-motor symptoms

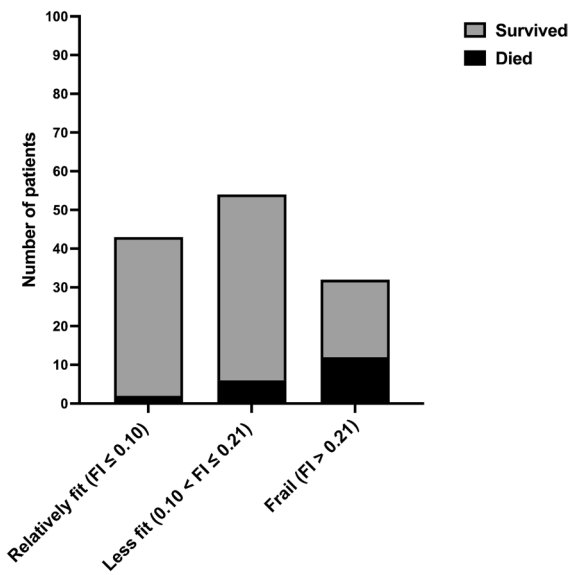

Fig. 3 Comparison of mortality rates among groups of PD patients stratified according to validated Frailty index (FI) cutoff points

burden and cognitive decline was observed at follow-up. Finally, stratification of patients at baseline using validated FI cutoff points revealed that frail participants had worse clinical progression, dopaminergic treatment requirements, and mortality rates compared to their relatively fit and less fit counterparts.

Several precautions were taken to mitigate potential confounding factors. To minimize misclassification bias, we confirmed the diagnosis of PD during follow-up evaluations by ensuring adherence to current diagnostic criteria [17] and by excluding any clinical signs of atypical parkinsonism in patients with shorter disease duration at baseline. Measurement biases were addressed through two key strategies. First, the same examiners conducted both baseline and follow-up evaluations, which helped minimize variability in scoring sensitivity for clinical scales. Second, follow-up evaluations were blinded to baseline scores, reducing the risk of expectation bias. Third, the items incorporated in the FI were carefully selected to minimize overlap with PD characteristics, thereby reducing the likelihood that predictor variables reflect intrinsic aspects of the adopted clinical outcome measures [12]. Finally, we performed sensitivity analyses using change-scores defined as follow-up minus baseline to assess the robustness of our findings.

In this study, we observed that, similar to baseline observations, the FI at follow-up was correlated not only with age but also with various clinical aspects, including the severity of motor and non-motor symptoms. This finding underscores the excellent test–retest reliability of the FI, demonstrating its consistency in terms of clinometric properties over time when applied to the same cohort. Importantly, it reaffirms the strong relationship between frailty and the clinical expression of PD. Indeed, frailty in PD has already been associated with recurrent falls, orthostatic hypotension, fatigue, hallucinations, dependency in activities of daily living, and delirium [26–28]. Although the underlying mechanisms behind this association remain to be clarified, one possibility is that the factors contributing to frailty may directly modulate the pathophysiological mechanisms of PD. Alternatively, frailty might represent a marker of reduced resilience, reflecting the organism's diminished ability to adapt to PD-related changes [29].

The strength and novelty of our study lie in its longitudinal design, enabling us to explore the predictive effect of frailty on PD clinical progression over time. We found that a higher baseline FI predicted more severe motor complications at follow-up and greater worsening from baseline. Unlike previous studies that primarily focused on the risk of developing or not developing dyskinesias or fluctuations [30–33], our study investigated whether baseline biological frailty predicts the eventual severity of motor complications, rather than simply their occurrence. The detrimental role of frailty that emerged from the analysis may be biologically plausible. Indeed, frailty encompasses several vulnerability factors, including sarcopenia, systemic inflammation, and altered synaptic function, which can influence the pharmacokinetics and pharmacodynamics of dopaminergic therapies [34–37]. Alternatively, the higher LEDD requirements observed in frail participants may point to a vicious circle in which biological aging leads to increased medication needs and greater susceptibility to medication-related side effects, thereby amplifying motor complications.

We observed a trend suggesting an association between frailty and the burden of non-motor symptoms at the 3-year follow-up. Conversely, we did not detect a significant association between baseline FI and the trajectory of core motor features. Motor decline in PD is primarily driven by specific neuropathological changes, including misfolded α-synuclein-mediated nigrostriatal dopaminergic degeneration [38]. Non-motor symptoms, in contrast, arise from widespread pathophysiological mechanisms involving not only dopaminergic circuits but also serotonergic, noradrenergic, and cholinergic networks [39–41]. In this context, biological aging may enhance vulnerability to this multisystem involvement, making it an appealing therapeutic target for alleviating the non-motor symptom burden, which is an important source of disability in PD. Additionally, frail PD patients may experience physical deconditioning, reduced daily activity, polypharmacy, and social withdrawal, exacerbating cognitive impairment, mood disorders, sleep disturbance, and other non-motor manifestations such as constipation, autonomic failure, and pain [12, 42–45].

Regarding the assessment of motor progression, the MDS-UPDRS Part III is considered the gold standard [46]. While we minimized examiner bias and inter-rater variability by using the same experienced

rater for both baseline and follow-up evaluations, this scale is coarse-grained and ordinal, which may limit sensitivity to subtle yet biologically relevant longitudinal motor changes [46]. Therefore, the absence of a significant association between frailty and motor progression in our study should be interpreted with caution and does not exclude a true relationship. Future studies should incorporate frailty assessments alongside high-resolution digital or biomarker-based measures of motor decline to better address this issue.

In our study, we detected only a non-statistically significant trend suggesting an association between baseline FI and subsequent cognitive decline at follow-up evaluation. This contrasts with the findings of a recent study [15], which identified the FI as a strong predictor of incident dementia in PD patients. Methodological differences likely explain this discrepancy. Our cohort covered a broad range of disease stages at baseline, while Borda et al. [15] focused exclusively on drug-naïve patients with newly diagnosed PD. The discrepancy may also reflect differences in how cognitive outcomes were operationalized across studies. Moreover, the SARS-CoV-2 outbreak reduced our sample size, which may have led to an underestimation of the true effect. Adequately powered, longitudinal studies with stage-stratified cohorts are needed to confirm the previously reported link between frailty and cognitive decline.

Finally, we conducted a stratified analysis based on baseline FI groups, which revealed that patients with higher FI scores not only experienced greater clinical impairment and increased treatment demand but also had higher mortality rates. This finding provides additional and complementary insights into the prognostic relevance of frailty in PD. The evidence from our analysis, both regression-based and group-oriented, reinforces the notion that frailty is not merely an associated factor but rather a clinically meaningful predictor of poorer long-term outcomes in PD. Moreover, it highlights FI as a simple and rapid tool for identifying PD patients at greater risk of health deterioration.

Several limitations should be acknowledged. First, this single-center study enrolled PD patients at different disease stages in a specialized movement disorders clinic. This may have introduced selection bias and may limit the generalizability to patients managed in primary-care settings. Notably, a relevant number of patients, particularly those within the frailer groups, already exhibited motor complications or cognitive impairment at baseline.

Accordingly, although baseline-adjusted and change-score models were used to mitigate this issue, the FI may still partially capture baseline disease burden in addition to biological aging. Second, loss to follow-up was selective, involving patients who were older, had a later age at onset, a higher FI, greater motor involvement, and worse cognitive performance at baseline. This pattern likely introduced survivor bias, leading to an underestimation of frailty's impact on clinical outcomes. Nevertheless, the association between frailty and worsening of treatment-related motor complications was preserved in IPW-based sensitivity analyses. Additionally, although the 3-year follow-up period provided valuable insights, it may not fully capture the longer-term evolution of PD phenotypes. Future studies should involve larger independent cohorts, extended observation periods, and stage-stratified designs to better clarify the prognostic role of frailty across specific PD trajectories and to enable external validation of these findings. Third, while the FI quantifies accumulated deficits, its underlying biological substrate remains poorly defined, which limits our understanding of the mechanisms determining clinical progression in PD. This underscores the need for future research integrating molecular, neuroimaging, or neurophysiological markers to clarify the pathophysiological processes captured by the FI. Finally, it is important to consider that our follow-up occurred during the SARS-CoV-2 pandemic, which may have influenced both dropout and mortality rates.

In conclusion, our longitudinal study suggests that frailty has a detrimental role in PD, being predictive of more severe motor complications and increased risk of mortality. Incorporating frailty assessments into routine clinical practice could enable the early identification of patients at greater risk of deterioration, thereby facilitating more personalized care planning and therapeutic strategies [47]. Future studies are needed to determine whether intervention targeting frailty can positively influence PD progression and enhance long-term health outcomes.

Author contribution M.C. (Matteo Costanzo) and M.C. (Marco Canevelli) contributed to conceptualization, clinical data collection, methodology, formal analysis, writing—original draft, writing—review and editing, and visualization. M.I.D.B, M.V., and M.T.B. were responsible for data curation, formal analysis and methodology, and writing—original draft; F.M. contributed to writing—original draft, and visualization; G.L. and A.C. contributed to writing—review and editing;

G.B. and G.F. contributed to conceptualization and writing—review and editing; D.B. contributed to conceptualization, supervision, and writing—review and editing. All authors read and approved the final manuscript.

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Data availability The data obtained in this research are available from the corresponding author upon reasonable request.

Declarations

Ethical approval The protocol was approved by the local ethics committee (n.4734) and conducted according to the principles of the Declaration of Helsinki.

Competing interests The authors declare no competing interests.

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