

# “Frailty” in patients with Parkinsonian Spectrum Disorders: an observation from a tertiary care teaching hospital

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**Abstract:** Patients with movement disorders are in a pre-frail state due to the physical limitation or reduction in tolerance to physical stress. The study was conducted in the Department of Neurology of a tertiary care teaching hospital in Northern-east Rajasthan with 50 patients. Inclusion criteria: (1) patients with parkinsonian features aged >18 years; and (2) willing to give consent regarding participation in the study. Exclusion criteria: (1) patients with age <18 years; (2) not willing to participate in the study; and (3) exclusion of alternative diagnosis. Frailty and pre-frailty states were assessed using the Fried’s criteria. Modified Frailty Index (MFI) was used to classify it as mild, moderate, and severe. Unified Parkinson's Disease Rating Scale (UPDRS), Multisystem Atrophy Rating Scale (MSARS), and Progressive Supranuclear Palsy Rating Scale (PSPRS) were used for respective disorders. The data was compiled using an MS Excel sheet, and SPSS 20 was used for statistical analysis. Thirty-nine patients fulfilled the criteria for “frailty-phenotype”; only 9 were “pre-frail”, and 2 were non-frail. On the MFI, patients with atypical parkinsonism had severe frailty with a mean index score of 0.54, where the mean scores were higher in the progressive supranuclear palsy (PSP) group (0.57) than in the multisystem atrophy (MSA) group (0.5). Patients with idiopathic Parkinson’s disease (IPD) had mild to moderate frailty with a mean score of 0.29 (Range 0.17-0.51). With a higher UPDRS score, the frailty index score in IPD patients was also higher, as was PSPRS in patients with PSP and UMSARS in patients with MSA. The mean MMSE score was also lower in the group with a higher frailty index. The levodopa dose requirement was higher in the frail group than in the non-frail or prefrail group (125 mg/day vs. 625 mg/day;  $p < 0.05$ ). Frailty is part and parcel of neurodegenerative movement disorders, including movement disorders, and adds to the burden of disease.

**Keywords:** Frailty; Modified frailty index; Idiopathic Parkinson's disease; Multisystem atrophy; Progressive supranuclear palsy

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## 1.0 INTRODUCTION

The term “frailty” is often described in the context of increased or heightened vulnerability resulting from ageing and functional decline or decreased functional capacity of the individual related to age. Fried et al. (2001) described frailty and laid a criterion for it. According to the criteria given by Fried et al., the patients meeting 3 out of 5 criteria points are classified as being “frail”. The five components that are assessed in an individual or patient for frailty are:

1. low hand grip strength
2. low energy
3. slowed walking speed
4. low physical activity
5. unintentional weight loss

There is a stage before the frail stage, known as the “pre-frail stage”, where 1 or 2 but not more than 2 out of 5 criteria points are met. The patients or individuals fulfilling the criteria for this stage are at an extremely high risk of progressing to frank frailty (Fried et al., 2001; Xue, 2011).

Frailty is quasi-subjective when the term is defined according to criteria laid down by Fried et al. On the other hand, the “frailty index” is a more quantified version to describe this entity. It can be used as a standard measure to assess, quantify, and compare the frailty amongst different groups on a quantified basis. Originally, the frailty index was described for 70 items (Rockwood et al., 2005). The modified frailty index (MFI) includes 11 items (Ebina et al., 2022; Farhat et al., 2012):

1. the presence of diabetes
2. the state of congestive heart failure
3. the presence of hypertension requiring the need for antihypertensive medication(s)
4. a previous history of transient ischemic attack (but no sequelae)
5. dependency on others for activities of daily living
6. the presence or history of acute myocardial infarction
7. history of intermittent vascular claudication or a diagnosis of peripheral vascular disease
8. cerebrovascular accident with definite focal neurological deficit
9. recurrent pneumonia or chronic obstructive pulmonary disease (COPD)
10. positive history of angina and/or history of percutaneous or surgical intervention of the coronaries
11. acute onset/recent delirium/encephalopathy

Frailty in neurological disorders can be an ominous but reversible sign that adds to morbidity and mortality. Identifying frailty and addressing it on time can prevent exponential deterioration in patients with any illness, including neurological disorders. Patients with movement disorders have physical and psychological morbidity along with comorbidities and often there is multisystem involvement, as seen with neurometabolic disorders.

Parkinsonism is classically a complex progressive neurodegenerative hypokinetic movement disorder pathologically characterized by loss of dopaminergic neurons in the substantia nigra. The clinical diagnosis predominates on the motor symptoms of bradykinesia, asymmetric resting tremor, cogwheel rigidity and postural instability (Simon et al., 2020). Parkinsonian disorders are classified as: (1) primary neurodegenerative disorders including typical IPD and atypical parkinsonism, MSA, PSP and corticobasal degeneration (CBD); (2) secondary parkinsonism including drug-induced, post-infectious, toxin-induced, metabolic and systemic disorders such as hepatic failure and trauma; and (3) hereditary neurodegenerative disorders including Huntington disease, spinocerebellar ataxia and dopa-responsive dystonia (Shin et al., 2022).

Patients with movement disorders like parkinsonism qualify in the criteria for a pre-frail state. Reduction in tolerance or response to physical stress and limitation of physical activity are the main contributing factors (Smith et al., 2021). Amongst movement disorders, the syndrome of Parkinsonism, including “atypical Parkinsonism” or “Parkinson-plus”, is of utmost importance concerning frailty for various reasons. In patients with these disorders, patients have both motor and non-motor symptoms, which account for a predisposition for frailty. The motor symptoms include bradykinesia, tremors, postural instability, falls, rigidity, etc. Non-motor symptoms include depression, amotivation syndrome, behavioral issues, multisystem involvement like gastrointestinal, autonomic, genitourinary, cardiovascular, musculoskeletal, and sleep disturbances, in which all culminate in a high vulnerability of the patient for greater functional decline and being frail. Although limited data focused on the relationship between frailty and PD, the prevalence of frailty in PD using the Frailty Phenotype (FP) was 0.38 (0.24–0.55) with  $I^2 = 92.6\%$  ( $p < 0.01$ ) (Ebina et al., 2022; Farhat et al., 2012). A cross-sectional study was conducted in a tertiary care teaching hospital in North-east India to address this.

## 2.0 METHODOLOGY

The current study was conducted in the Department of Neurology of a tertiary care teaching hospital in Northern-east Rajasthan, India, over 2 months (October 2023 to November 2023) after obtaining approval from the Institutional Ethics Committee (MGMC&H/IEC/JPR/2023/1725). The primary aim of the study was to assess frailty among patients with Parkinsonian spectrum disorders. The secondary objectives were to assess the clinical and demographic profiles and compare frailty among various subgroups.

The sample size of 49 was calculated using a 38% population proportion (patient proportion with frailty in previous studies) and an 85% confidence interval with a margin of error of 10%. A total of 50 patients were included in the study. Inclusion criteria were: (1) patients with parkinsonian features (both typical and atypical) fulfilling the diagnostic criteria for disorders like IPD, MSA, PSP, and CBD with age >18 years, and (2) willingness to give consent regarding participation in the study. Exclusion criteria were: (1) patients with age <18 years, (2) unwillingness to participate in the study, and (3) presence of alternative movement disorders, including ataxia, chorea, tremor, athetosis, dystonia, and ballism.

The frailty phenotype was studied in these patients according to the criteria laid out by Fried, known as Fried's Frailty Phenotype. The patients were classified as "pre-frail" and "frail" based on the criteria they fulfilled. They were labeled as "pre-frail" when they had 1 or 2 out of 5 characteristics and "frail" when they had more than 2 out of 5 characteristics, which are as follows: (1) low hand grip strength, (2) low energy, (3) slowed walking speed, (4) low physical activity, and (5) unintentional weight loss. Hand grip was tested using a manual hand grip dynamometer, and the cut-off was taken as per standard hand grip norms for age and weight ([Amaral et al., 2019](#)).

Modified Frailty Index (MFI) was used to classify frailty as mild (0.12-0.23), moderate (0.24-0.35), and severe (0.36 and above) (Clegg et al., 2016). Disease severity was calculated using clinical rating scales for respective Parkinsonian disorders. Unified Parkinson's Disease Rating Scale (UPDRS), Multisystem Atrophy Rating Scale (MSARS), and Progressive Supranuclear Palsy Rating Scale (PSPRS) were used for respective disorders. A pre-validated Hindi version of the Mini Mental State Examination (MMSE) scale was used to assess the overall cognition of the patients. The cut-off was taken according to the education status of the patients. A cut-

off of 18 was used for defining major cognitive decline and 23 for mild cognitive impairment in illiterate patients ([Tiwari et al., 2009](#)).

The clinical profile of these patients was studied. Levodopa responsiveness was defined by at least 30% improvement in the motor component of the UPDRS score (Part-III) from baseline ([Constantinescu et al., 2007](#)). The data were compiled in an MS Excel sheet, and SPSS 20 was used for statistical analysis of the data.

## 3.0 RESULTS

50 patients were recruited in the study. The patients included were IPD (n=27), MSA which included subtypes like MSA-Cerebellar type (MSA-C, n=5) and MSA-Parkinsonian type (MSA-P, n=5), PSP with phenotypes of PSP-Frontotemporal dementia variant (PSP-FTD, n=2), PSP-Oculomotor variant (PSP-OM, n=1), PSP-Parkinsonian variant (PSP-P, n=3), and secondary parkinsonism, including parkinsonism secondary to hepatic failure (n=2), drug-induced parkinsonism (n=3), and vascular parkinsonism (n=2). There were 41 males and 9 females in the study. The mean age of the study population was 61.67 years. The mean age of disease onset was 58.34 years, and the mean disease duration was 2.51 years.

**Table 1** shows the clinico-demographic profile of the patients with parkinsonian features. **Table 2** shows the various characteristics of parkinsonian subgroups. The clinical severity of these disorders was assessed using the rating scales UPDRS, UMSARS, and PSPRS. Of all 50 patients, 39 fulfilled the criteria for "frailty phenotype," having more than 2 out of 5 characteristics. Only 9 were found to be in the category of "pre-frail," and 2 did not meet any criteria. Upon applying the MFI to all patients fulfilling the criteria for frailty, the degree of frailty was estimated as mild (0.12-0.24), moderate (0.24-0.36), and severe (0.36 and above).

Among these patients, those with atypical parkinsonism had severe frailty with a mean index score of 0.54, where the mean scores were higher in the PSP group (0.57) compared to the MSA group (0.5). Patients with IPD had mild to moderate frailty with a mean score of 0.29 (range 0.17-0.51). It was found that with a higher UPDRS score, the frailty index score in IPD patients was also higher, as was PSPRS in patients with PSP and UMSARS in patients with MSA. However, the frailty index was higher in drug-induced and hepatic failure-induced secondary parkinsonism compared to vascular parkinsonism.

The mean MMSE score was lower in the group with a higher frailty index. The frequency of falls (from all causes) was increased in moderate and severe frailty groups. Moreover, falls occurred earlier in atypical parkinsonism compared to IPD, which also constituted the higher frailty index subgroup. The frequency of hospital admissions due to troublesome dyskinesias (seen in IPD), autonomic dysfunction, aspiration pneumonia, and delirium was increased in patients with severe frailty index.

Non-motor symptoms were prominent in patients with frailty, particularly in those with moderate to severe

frailty index scores. The levodopa dose requirement was higher in the frail group than in the non-frail or pre-frail group (125 mg/day vs. 625 mg/day;  $p < 0.05$ ). The response to levodopa was poor in patients with atypical parkinsonism compared to IPD. Also, the mean MMSE score in patients with frailty was lower compared to non-frail or pre-frail states (16.3 vs 25.7;  $p < 0.05$ ). In secondary parkinsonism, the response to levodopa could not be ascertained as the patients could not be followed up. The effect of secondary factors like liver disorders and drugs confounds the assessment of frailty, and these are generally reversible upon treatment of the underlying cause.

**Table 1:** Clinicodemographic profile of the patients with Parkinsonian features

| Parameters  |                       |
|---|-----------------------|
| Total patients, N (%)                             | 50 (100%)             |
| Idiopathic Parkinson disease                      | 27 (54%)              |
| Multisystem atrophy                               | 10 (20%)              |
| Progressive Supranuclear Palsy                    | 6 (12%)               |
| Secondary Parkinsonism                            | 7 (14%)               |
| Gender, N (%)                                     |                       |
| Male  | 41 (82%)              |
| Female  | 9 (18%)               |
| Age (Mean $\pm$ SD)                               | 61.67 $\pm$ 2.3 years |
| Comorbidities, N (%)                              |                       |
| Hypertension                                      | 31 (62%)              |
| Diabetes Mellitus                                 | 27 (54%)              |
| Coronary artery disease                           | 12 (24%)              |
| Anaemia   | 1 (2%)                |
| Liver disease                                     | 2 (4%)                |
| Thyroid disorder                                  | 1 (2%)                |
| Age of onset of disease (Mean $\pm$ SD)           | 58.34 $\pm$ 1.1 years |
| Duration of disease (Mean $\pm$ SD)               | 2.51 $\pm$ 0.8 years  |
| Onset of falls from disease onset (Mean $\pm$ SD) |                       |
| IPD   | 5.6 $\pm$ 1.2 years   |
| Atypical Parkinsonism                             | 1.1 $\pm$ 0.8 years   |
| Gap between onset of falls from onset of disease  | 1.95 $\pm$ 0.3 years  |
| Frequency of hospitalisation per year             | 2.5                   |
| MMSE score (Mean $\pm$ SD)                        | 19.6 $\pm$ 1.4        |
| Frailty, N (%)                                    |                       |
| Non-frail   | 2 (4%)                |
| Pre-frail   | 9 (18%)               |
| Frail   | 39 (78%)              |

**Table 2:** Characteristics of various disorders

| Characteristics   | IPD              | MSA               | PSP              |
|---|------------------|-------------------|------------------|
| Age of onset (Mean ± SD)                                | 56.7 ± 2.3 years | 59.83 ± 2.5 years | 61.2 ± 2.6 years |
| Duration of disease (Mean ± SD)                         | 3.89 ± 1.2 years | 1.65 ± 0.6 years  | 1.21 ± 0.3 years |
| Duration of falls from the onset of disease (Mean ± SD) | 2.8 ± 0.9 years  | 0.94 ± 0.2 years  | 0.67 ± 0.1 years |
| Levodopa responsiveness                                 | Good             | Poor              | Poor             |
| MMSE score (Mean ± SD)                                  | 21.6 ± 1.1       | 25.3 ± 1.7        | 16.8 ± 1.4       |
| Rating scale score (Mean ± SD)                          | UPDRS : 58.9     | MSARS: 45.6       | PSPRS: 68.4      |
| Overall Frequency of hospitalization per year           | < 2              | < 2               | ≥ 3              |
| Modified Frailty Index Score (Mean ± SD)                | 0.29 ± 0.12      | 0.5 ± 0.11        | 0.57 ± 0.14      |

#### 4.0 DISCUSSION

The results of the present study were comparable with the available literature. In their study, Belvisi et al. (2022) found greater motor symptom severity, motor complications, and non-motor symptom burden in frail patients (Belvisi et al., 2022). The findings of the current study were consistent with these results. Ahmed and colleagues found that patients with PD who were frail had higher UPDRS scores compared to those without frailty (44.8±15.8 vs. 31.4±12.7; P<0.002). Other factors, like weekly caloric expenditure, predicted frailty status in these patients (Ahmed et al., 2008). However, in the present study, caloric expenditure was not calculated.

The findings of the current study are also supported by a systematic review and meta-analysis, which found that frailty in patients with Parkinsonism was associated with recurrent falls, cognitive impairment, dementia, orthostatic hypotension, fatigue, hallucinations, nursing home placement, dependency in activities of daily living, and in-patient mortality (McMillan et al., 2021). The daily levodopa dose requirement was also found to be higher. The present study similarly found that the mean levodopa dose was higher in Parkinsonian patients with frailty compared to those in pre-frail and non-frail states. Within the frail group, the subgroups of mild, moderate, and severe frailty had almost comparable doses, while moderate to severe subgroups had higher dose requirements and poor response to levodopa.

The present study found that levodopa responsiveness decreases as one moves from IPD to the atypical parkinsonism spectrum. This finding is again consistent with studies from the past (Acharya et al., 2021; Mitra et al., 2003). Cognitive decline is integral to both frailty assessment and vice versa. It is also established that patients with atypical parkinsonism have earlier

cognitive involvement compared to IPD. Conversely, cognitive impairment is a feature of advanced PD when compared with the early stages of the disease (Degirmenci et al., 2023; Raimo et al., 2022).

Patients with parkinsonism who fall into the frail category are at risk of earlier cognitive decline. The mean MMSE score in patients with frailty was lower than in non-frail or pre-frail states. These findings were similar to those of the study by Lin et al. (2019). They also found that frontal lobe dysfunction in the form of dysexecutive syndrome (or executive dysfunction) was independently associated with frailty.

The major strength of the present study is that it is one of its kind from the region. To the best of our knowledge, there are very limited data on frailty in patients with Parkinsonian spectrum disorders from India. This study adds to the existing literature on frailty in patients with parkinsonism. Moreover, an attempt was made to compare different disorders of the Parkinsonian spectrum. The study's limitations included its small sample size and cross-sectional nature. The socio-demographic profile did not include educational status, including years of schooling, profession, and economic status. The results cannot be projected or generalized to a larger population.

#### 5.0 CONCLUSIONS

Patients with Parkinsonism spectrum disorders can be classified as either pre-frail or frail. There is ongoing debate about whether these disorders worsen the condition of already frail individuals or whether individuals with these disorders become frail over time. Nonetheless, frailty is an integral part of neurodegenerative disorders and adds significantly to the disease burden.

For future studies, it is recommended that a large-scale study from this region of the country is needed to better assess the implications of frailty in patients with the Parkinsonian spectrum. Several factors need to be explored, including bone health and osteoporosis, comorbidities, immune status, cardiovascular health, diabetes, and hypertension. The mechanisms by which these conditions contribute to frailty, and conversely, how frailty influences the progression of these disorders, require further investigation. Treatment

interventions should be specifically designed for frail individuals to achieve better clinical outcomes.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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