

Cumulative Incidence of Milestone Events in Parkinson's Disease: A Retrospective survey-based cohort study with Landmark Analysis

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Article

Keywords: Parkinson's disease, milestone events, disease progression, Kaplan-Meier analysis, landmark analysis, left truncation, prognosis

Posted Date: October 18th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11196018/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

Parkinson's disease (PD) progression is marked by milestone events, but retrospective data on their timing are scarce, and left truncation may distort estimates.

Methods

In this single-center retrospective cohort of 126 patients with PD, six milestone events were assessed: severe urinary incontinence/retention, severe dysphagia, dysarthria, recurrent falls, need for walking assistance, and wheelchair dependence. Kaplan-Meier analysis estimated cumulative incidence at 5, 10, and 15 years, and Cox regression identified predictors. A landmark analysis at 5 years was performed to address left truncation and survival bias.

Results

Median disease duration was 5.0 years (IQR 2.0–8.8), and 39 patients (31.0%) had experienced at least one milestone event. In the primary analysis, 10-year cumulative incidence ranged from 7.7% (dysarthria) to 25.2% (walking assistance); median times were not reached. Age at onset (HR 1.070, 95% CI 1.046–1.094), H-Y stage (HR 1.455, 95% CI 1.154–1.834), and disease duration (HR 0.851, 95% CI 0.742–0.977) were independent predictors. In the landmark analysis ($n = 73$), 10-year conditional cumulative incidence ranged from 4.8% to 20.5%, consistently lower than the primary analysis. Age at onset and H-Y stage remained robust predictors, whereas the inverse association between disease duration and milestone events disappeared, confirming it was driven by left truncation and survival bias.

Conclusions

Primary estimates should be considered upper bounds. Age at onset and H-Y stage were robust predictors, whereas the apparent protective effect of longer disease duration was a statistical artifact of left truncation.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting approximately 1% of adults over 60 years of age [1, 2]. While motor symptoms remain the clinical hallmark, disease progression is characterized by the sequential emergence of milestone events—including motor complications such as recurrent falls, need for walking assistance, and wheelchair dependence, as well as non-motor complications such as severe urinary incontinence/retention, severe dysphagia, and dysarthria. These events not only signify transition to advanced disease stages but also have profound

implications for quality of life, caregiver burden, and healthcare resource utilization [4, 5, 6]. A recent systematic review highlighted the importance of clinical milestones in PD progression [7]. Quantifying the timing of milestone events is therefore essential for prognostic counseling and care planning.

Previous studies, primarily from large prospective cohorts such as DATATOP and ELLDOPA, have provided valuable longitudinal data on motor and non-motor progression [8, 9]. However, prospective studies require decades of follow-up, are costly, and may suffer from selection bias. Previous studies have reported variable rates of clinical progression, with some patients experiencing rapid deterioration while others remain stable for years [10, 11]. Retrospective surveys, despite inherent limitations such as recall bias, can capture disease course information within a shorter timeframe and are particularly suitable for single-center settings [12, 13]. A recent population-based study from Norway reported that the median time from disease onset to visual hallucinations was 3.3 years, to recurrent falls 3.8 years, to dementia 4.0 years, and to nursing home placement 5.4 years [14]. The Parkinson's Progression Markers Initiative (PPMI) cohort has provided valuable longitudinal data [15], and a recent analysis identified distinct progression subtypes based on milestone events, with 42.9% of patients experiencing at least one milestone within 6 years [16]. Despite these advances, systematic analyses of milestone event timing in PD based on retrospective survey data remain scarce.

A critical methodological challenge in retrospective cohort studies is left truncation and survival bias: patients are included only if they survive to the survey, and those who experience milestone events or die before the survey may be systematically excluded. This can distort cumulative incidence estimates and produce spurious associations, particularly between disease duration and outcomes. The conditions under which differential left truncation produces bias have been formally characterized, and survival analysis approaches have been shown to correct for this bias more effectively than logistic regression [17]. Landmark analysis is a well-established approach to partially address this bias by conditioning on event-free survival at a pre-specified time point [18, 19].

Therefore, we conducted this retrospective survey-based cohort study to: (1) estimate the cumulative incidence of six milestone events at 5, 10, and 15 years using Kaplan-Meier survival analysis; (2) identify independent predictors of milestone events; and (3) perform a landmark analysis at 5 years to assess the impact of left truncation and survival bias on the primary estimates.

2. Methods

2.1 Study design and participants

This was a single-center retrospective survey-based cohort study conducted at the Department of Neurology, Aerospace Center Hospital. Consecutive patients with PD were enrolled between September 2019 and June 2021. Data were collected through medical record review and telephone or outpatient survey. Each patient was surveyed once at the time of enrollment. The time origin was the date of PD

onset, and the observation period extended from disease onset to the survey date. For each milestone event, the time from disease onset to first occurrence was recorded based on patient or caregiver recall.

Inclusion criteria were: (1) diagnosis of PD according to the Movement Disorder Society (MDS) clinical diagnostic criteria [1]; (2) disease duration ≥ 1 year; (3) complete clinical records and survey data. Exclusion criteria were: (1) secondary parkinsonism; (2) concomitant severe neurological disorders; (3) missing key variables. The study was approved by the Institutional Ethics Committee of Aerospace Center Hospital (approval number: 20190614-SF-06). Written informed consent was obtained from all participants or their legal guardians.

2.2 Data collection

Data were collected through medical record review and telephone/outpatient follow-up. The following variables were recorded: **Demographic characteristics:** sex, age, education level (1 = primary or below, 2 = secondary, 3 = college or above). **Disease characteristics:** age at onset, disease duration at survey, initial symptom (1 = tremor, 2 = bradykinesia/rigidity, 3 = mixed), affected body side (1 = left, 2 = right, 3 = bilateral, 4 = axial), Hoehn and Yahr (H-Y) stage (off-state), UPDRS-III score (on-state). **Cognitive and psychiatric assessments:** MMSE, MoCA, HAMA, HAMD. **Medication:** levodopa equivalent daily dose (LED), initial drug, current drug regimen. **Milestone events:** time from disease onset to each event.

2.3 Milestone events

Six milestone events were assessed: Severe urinary incontinence/retention (persistent urinary incontinence requiring pads or urinary retention requiring catheterization); Severe dysphagia (difficulty swallowing requiring dietary modification or tube feeding); Dysarthria (speech impairment affecting communication); Recurrent falls (≥ 2 falls in the past year); Need for walking assistance (requiring a cane, walker, or assistance from another person for ambulation); Wheelchair dependence (unable to ambulate independently and requiring a wheelchair for mobility).

For each event, the year of occurrence after disease onset was recorded. Patients who had not experienced the event at the time of survey were censored at the survey date.

2.4 Time scale, event ascertainment, and censoring

The time origin was the date of PD onset. For each milestone event, the event time was defined as the interval from disease onset to the first occurrence of that event, as recalled by the patient or caregiver. Patients who had not experienced the event at the time of survey were censored at the survey date; the censoring time was calculated as the interval from disease onset to the survey date, which corresponds to the disease duration at survey.

Because patients were included only if they survived to the survey, left truncation and survivor bias are inherent to this design. To partially address this, we performed a landmark analysis at 5 years (described below).

2.5 Statistical analysis

Continuous variables were expressed as mean $\pm$ SD for normally distributed variables and median (IQR) for non-normally distributed variables. Categorical variables were expressed as frequencies and percentages.

Kaplan-Meier analysis was used to estimate the cumulative incidence of each milestone event at 5, 10, and 15 years [20]. Median times to milestone events were reported as "not reached" when the cumulative incidence did not exceed 50% during the observed time range.

Univariable and multivariable Cox proportional hazards regression models were used to identify independent predictors of milestone events [21]. Variables with $P < 0.10$ in univariable analysis were entered into the multivariable model. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated.

Missing data were handled by complete-case analysis for each specific analysis. All 126 patients had complete data on age at onset, disease duration, and milestone events. Affected body side was missing in 4 patients (3.2%); because this variable was not included in the multivariable model, these patients were retained in all primary analyses. All statistical analyses were performed using R software version 4.2 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided P value < 0.05 was considered statistically significant.

2.6 Handling of censoring and competing risks

In the primary analysis, patients without a milestone event were censored at the survey date. Because mortality data were not systematically recorded, a formal Fine-Gray competing risk model could not be performed. The Fine-Gray proportional subdistribution hazards model is the established method for analyzing competing risks data [22], but its application requires complete mortality data. Given that death is a competing risk for milestone events in older patients with PD, the cumulative incidence estimates reported here should be considered upper bounds of the true incidence. To partially account for the uncertainty in recall-based event timing, a sensitivity analysis using interval midpoint approximation was performed.

2.7 Landmark analysis

To assess the potential impact of left truncation and survival bias, we performed a landmark analysis using disease duration of 5 years as the landmark time point [18, 19]. Patients with disease duration ≤ 5 years at enrollment were excluded. For each milestone event, patients who had already experienced the event before the 5-year landmark were also excluded. Follow-up was restarted at the 5-year landmark, and conditional cumulative incidence was estimated using Kaplan-Meier analysis. Univariable and multivariable Cox proportional hazards regression models were refitted in the landmark cohort. This approach estimates the risk of milestone events among patients who remained event-free at 5 years after disease onset, thereby partially accounting for the selective survival of slower progressors. Estimates at 15 years should be interpreted with caution because fewer than 12 patients remained at risk.

3. Results

3.1 Baseline characteristics

The baseline characteristics of the study population are summarized in Table 1. A total of 126 patients with PD were included. The median age was 68.5 years (IQR 61.0–75.8), and the median age at onset was 61.0 years (IQR 52.2–72.4). The median disease duration at survey was 5.0 years (IQR 2.0–8.8). There were 75 males (59.5%) and 51 females (40.5%). The distribution of H-Y stages was: stage 1, 16 patients (12.5%); stage 1.5, 6 (4.7%); stage 2, 29 (22.8%); stage 2.5, 38 (29.9%); stage 3, 26 (20.4%); stage 4, 5 (3.9%); stage 5, 6 (4.7%). The median UPDRS-III score was 29.5 (IQR 21.2–39.8), and the median UPDRS-IV score was 3.0 (IQR 3.0–6.0). The median MMSE score was 27.0 (IQR 23.0–29.0), and the median MoCA score was 24.0 (IQR 19.0–26.0). The median HAMA and HAMD scores were 7.0 (IQR 4.0–11.0) and 7.0 (IQR 3.0–11.0), respectively. The median LED was 481.2 mg/day (IQR 308.6–688.4). Seven patients (5.6%) had undergone DBS. Wearing-off was present in 59 patients (46.8%) and dyskinesia in 27 patients (21.4%).

Table 1
Baseline characteristics of the study population (n = 126).

Characteristic	Value
Demographic	
Male, n (%)	75 (59.5%)
Age, years, median (IQR)	68.5 (61.0, 75.8)
Height, cm, median (IQR)	167.5 (160.0, 172.0)
Weight, kg, median (IQR)	65.5 (58.0, 72.0)
BMI, kg/m ² , median (IQR)	23.4 (21.7, 25.6)
Education, n (%)	
Primary or below	14 (11.1%)
Secondary	57 (45.2%)
College or above	55 (43.7%)
Disease characteristics	
Age at onset, years, median (IQR)	61.0 (52.2, 72.4)
Disease duration, years, median (IQR)	5.0 (2.0, 8.8)
Initial symptom, n (%)	
Tremor	27 (21.4%)
Bradykinesia/rigidity	55 (43.7%)
Mixed	44 (34.9%)
Affected body side, n (%)	
Left	51 (40.5%)
Right	14 (11.1%)
Bilateral	34 (27.0%)
Axial	23 (18.3%)
Missing	4 (3.2%)
H-Y stage (off-state), n (%)	
Affected body side was missing in 4 patients (3.2%); these patients had complete data on age at onset, disease duration, and milestone events, and were therefore retained in the Kaplan-Meier and Cox regression analyses.	

Characteristic	Value
Demographic	
1	16 (12.5%)
1.5	6 (4.7%)
2	29 (22.8%)
2.5	38 (29.9%)
3	26 (20.4%)
4	5 (3.9%)
5	6 (4.7%)
Clinical assessments	
UPDRS-III (on-state), median (IQR)	29.5 (21.2, 39.8)
UPDRS-IV, median (IQR)	3.0 (3.0, 6.0)
MMSE, median (IQR)	27.0 (23.0, 29.0)
MoCA, median (IQR)	24.0 (19.0, 26.0)
HAMA, median (IQR)	7.0 (4.0, 11.0)
HAMD, median (IQR)	7.0 (3.0, 11.0)
Treatment	
LED, mg/day, median (IQR)	481.2 (308.6, 688.4)
DBS, n (%)	7 (5.6%)
Wearing-off, n (%)	59 (46.8%)
Dyskinesia, n (%)	27 (21.4%)
Affected body side was missing in 4 patients (3.2%); these patients had complete data on age at onset, disease duration, and milestone events, and were therefore retained in the Kaplan-Meier and Cox regression analyses.	

3.2 Incidence of milestone events

The incidence of each milestone event is shown in Table 2. At the time of survey, 39 patients (31.0%) had experienced at least one milestone event. The numbers of patients experiencing each event were: severe urinary incontinence/retention, 15 (11.9%); severe dysphagia, 7 (5.6%); dysarthria, 7 (5.6%); recurrent falls, 20 (15.9%); need for walking assistance, 20 (15.9%); wheelchair dependence, 12 (9.5%). Overall, 30 patients (23.8%) experienced at least one motor milestone, and 22 (17.5%) experienced at least one non-motor milestone.

Table 2
Incidence of milestone events (n = 126).

Milestone event	n (%)
Severe urinary incontinence/retention	15 (11.9%)
Severe dysphagia	7 (5.6%)
Dysarthria	7 (5.6%)
Recurrent falls	20 (15.9%)
Need for walking assistance	20 (15.9%)
Wheelchair dependence	12 (9.5%)
At least one milestone event	39 (31.0%)
Motor milestone (falls, walking assistance, or wheelchair dependence)	30 (23.8%)
Non-motor milestone (urinary incontinence/retention, dysphagia, or dysarthria)	22 (17.5%)

3.3 Time to milestone events (primary analysis)

Kaplan-Meier analysis estimated the cumulative incidence of each milestone event at 5, 10, and 15 years (Table 3 and Fig. 1). Median times to all milestone events were not reached, because the cumulative incidence remained below 50% for all events throughout the observed time range. At 10 years, the highest cumulative incidence was observed for need for walking assistance (25.2%, 95% CI 11.9–36.5), followed by recurrent falls (23.9%, 95% CI 11.6–34.4) and severe urinary incontinence/retention (21.0%, 95% CI 8.1–32.0). Dysarthria showed the lowest cumulative incidence at 10 years (7.7%, 95% CI 0.3–14.5). At 15 years, need for walking assistance remained the most common milestone (36.6%, 95% CI 15.8–52.2). The cumulative incidence curves for non-motor and motor milestone events are shown in Fig. 1A and Fig. 1B, respectively.

Table 3
Cumulative incidence of milestone events at 5, 10, and 15 years (primary analysis)

Milestone event	5-year % (95% CI)	10-year % (95% CI)	15-year % (95% CI)
Severe urinary incontinence/retention	6.7 (1.7–11.4)	21.0 (8.1–32.0)	27.5 (9.0–42.3)
Severe dysphagia	0.9 (0.0–2.7)	8.6 (0.0–16.9)	16.2 (0.0–31.1)
Dysarthria	3.0 (0.0–6.4)	7.7 (0.3–14.5)	7.7 (0.3–14.5)
Recurrent falls	9.9 (3.4–15.9)	23.9 (11.6–34.4)	27.9 (13.4–39.9)
Need for walking assistance	6.0 (1.1–10.6)	25.2 (11.9–36.5)	36.6 (15.8–52.2)
Wheelchair dependence	0.8 (0.0–2.3)	14.2 (3.3–23.8)	20.3 (3.8–34.0)
Cumulative incidence was estimated using Kaplan-Meier analysis. Because the cumulative incidence remained below 50% for all events, median times to milestone events were not reached. Estimates at 15 years should be interpreted with caution because fewer than 10 patients remained at risk beyond 13 years.			

3.4 Predictors of milestone events (primary analysis)

The univariable and multivariable Cox regression results are shown in Fig. 2. In univariable Cox regression analysis, age at onset (HR 1.083, 95% CI 1.048–1.119, $P < 0.001$), H-Y stage (HR 1.596, 95% CI 1.186–2.148, $P = 0.002$), and disease duration (HR 0.797, 95% CI 0.698–0.910, $P < 0.001$) were significantly associated with milestone events. In the multivariable model including age at onset, sex, and H-Y stage, both age at onset (HR 1.070, 95% CI 1.046–1.094, $P < 0.001$) and H-Y stage (HR 1.455, 95% CI 1.154–1.834, $P = 0.002$) remained independently associated with milestone events, whereas sex was not significant (HR 0.690, 95% CI 0.400–1.191, $P = 0.183$). When disease duration was added to the multivariable model, it was independently associated with a lower hazard of milestone events (HR 0.851, 95% CI 0.742–0.977, $P = 0.022$), an association that is biologically implausible as a protective effect and suggestive of left truncation bias.

3.5 Sensitivity analysis (interval midpoint approximation)

In the interval midpoint sensitivity analysis, cumulative incidence estimates were consistent with the primary Kaplan-Meier estimates (Supplementary Table S1). At 10 years, the cumulative incidence was 24.6% for need for walking assistance, 23.7% for recurrent falls, and 20.9% for severe urinary incontinence/retention. All estimates differed from the primary analysis by less than 1 percentage point.

3.6 Landmark analysis

In the landmark analysis, patients with disease duration ≤ 5 years at enrollment were excluded, leaving 73 patients (357 observations) for analysis. The 10-year conditional cumulative incidence was 20.5% for need for walking assistance, 15.5% for recurrent falls, 15.3% for severe urinary incontinence/retention,

13.8% for wheelchair dependence, 7.8% for severe dysphagia, and 4.8% for dysarthria (Table 4 and Fig. 3). At 15 years, the conditional cumulative incidence was 32.5% for need for walking assistance, 22.4% for severe urinary incontinence/retention, 20.4% for wheelchair dependence, 20.0% for recurrent falls, 15.5% for severe dysphagia, and 4.8% for dysarthria. These estimates were consistently lower than those from the primary analysis, with the largest differences observed for recurrent falls (– 8.4%) and need for walking assistance (– 4.7%). A direct comparison of cumulative incidence between the primary and landmark analyses is provided in Supplementary Table S2.

Table 4
Cumulative incidence of milestone events at 10 and 15 years (landmark analysis)

Milestone event	10-year % (95% CI)	15-year % (95% CI)
Severe urinary incontinence/retention	15.3 (2.5–26.5)	22.4 (3.1–37.8)
Severe dysphagia	7.8 (0.0–15.9)	15.5 (0.0–30.4)
Dysarthria	4.8 (0.0–11.1)	4.8 (0.0–11.1)
Recurrent falls	15.5 (3.6–26.0)	20.0 (5.2–32.5)
Need for walking assistance	20.5 (7.1–31.9)	32.5 (10.9–48.9)
Wheelchair dependence	13.8 (2.7–23.7)	20.4 (3.0–34.8)
Conditional cumulative incidence was estimated from the 5-year landmark among patients who remained event-free at 5 years (n = 73). Estimates at 15 years should be interpreted with caution because fewer than 12 patients remained at risk		

In the landmark cohort, multivariable Cox regression identified age at onset (HR 1.081, 95% CI 1.049–1.114, $P < 0.001$) and H-Y stage (HR 1.645, 95% CI 1.189–2.276, $P = 0.003$) as independent predictors of milestone events, whereas sex was not significant (HR 0.927, 95% CI 0.459–1.872, $P = 0.832$). Notably, disease duration was not included in this model because it was no longer associated with milestone events after conditioning on the 5-year landmark. A comparison of Cox regression models between the primary and landmark analyses is provided in Supplementary Table S3.

4. Discussion

4.1 Main findings

In this retrospective survey-based cohort study of 126 patients with PD, we quantified the cumulative incidence of six milestone events and performed a landmark analysis to address left truncation and survival bias. The key findings were: (1) in the primary analysis, cumulative incidence at 10 years ranged from 7.7% to 25.2%, and median times to all milestone events were not reached; (2) in the landmark analysis, 10-year conditional cumulative incidence ranged from 4.8% to 20.5%, consistently lower than the primary analysis, indicating that the primary estimates should be considered upper bounds; (3) age at onset and H-Y stage were robust independent predictors in both the primary and landmark analyses;

and (4) the inverse association between disease duration and milestone events in the primary analysis was no longer present in the landmark analysis, providing direct evidence that this association was driven by left truncation and survival bias.

4.2 Comparison with previous studies

A recent population-based study from Norway reported that the median time from disease onset to recurrent falls was 3.8 years, to dementia 4.0 years, and to nursing home placement 5.4 years [14]. In the PPMI cohort, 42.9% of patients experienced at least one milestone event within 6 years, and latent class analysis identified distinct progression subtypes [16]. Our estimates are broadly consistent with these observations, although direct comparison is limited by differences in milestone definitions and follow-up duration.

Falls are among the most disabling motor milestones in PD, with a meta-analysis of six prospective studies reporting that approximately 60% of patients experience at least one fall annually [23, 24]. Previous studies using Kaplan-Meier analysis have reported median H-Y transition times: 20 months from stage 1 to 2, 62 months from stage 2 to 2.5, and 25 months from stage 2.5 to 3 [25]. These early-stage transitions occur within the first few years after disease onset, whereas the milestone events assessed in our study represent more advanced functional milestones and occurred much later. In a large cohort of 3,343 patients, approximately 35.0% developed motor fluctuations and 18.5% developed dyskinesia at 4–6 years after disease onset [26]. The Sydney Multicenter Study reported that among 20-year survivors, 87% had experienced falls, 71% had urinary incontinence, and 81% had moderate dysarthria [27]. Non-motor symptoms, including dysphagia and urinary dysfunction, have been shown to significantly impair health-related quality of life and increase caregiver burden [28, 29]. Dysphagia, in particular, has been associated with aspiration pneumonia and increased mortality in advanced PD [30], and bladder and bowel dysfunction are prevalent and disabling in advanced disease [31]. Our study extends these observations by quantifying the cumulative incidence of clinically meaningful milestone events and by demonstrating the importance of addressing survival bias in retrospective designs.

4.3 Interpretation of disease duration and the impact of left truncation

In the primary analysis, disease duration was associated with a lower hazard of milestone events (HR 0.851, 95% CI 0.742–0.977, $P = 0.022$), which is biologically implausible as a protective effect. The landmark analysis provided direct evidence that this inverse association was driven by left truncation and survival bias. In the landmark cohort restricted to patients who remained event-free at 5 years, the association between disease duration and milestone events was no longer present, whereas age at onset and H-Y stage remained robust predictors.

This finding supports the interpretation that patients with longer disease duration in the primary analysis represent a selected subgroup of slower progressors who survived without events to the survey date, whereas rapidly progressive patients may have already experienced events, died, or been unavailable for

inclusion. The conditions under which left truncation produces bias of this magnitude have been formally described: when exposed and unexposed groups enter observation at systematically different times, hazard ratios can be biased toward or away from the null depending on the direction of differential entry [17]. In our cohort, patients with longer disease duration entered the observation period (survey) later relative to their disease onset, and those who had already experienced events before enrollment were not represented. The consistency of age at onset and H-Y stage across both models, in contrast to the instability of disease duration, further supports this interpretation. Therefore, the inverse association between disease duration and milestone events should be regarded as a statistical artifact of the retrospective survey design rather than a true clinical phenomenon.

4.4 Clinical implications

The quantified cumulative incidence of milestone events has several clinical implications. First, it provides clinicians with estimates for prognostic counseling. Based on the landmark analysis, approximately 1 in 5 patients may require walking assistance within 10 years of disease onset, and approximately 1 in 6 may experience recurrent falls. These estimates are more conservative than those from the primary analysis and should be considered more reliable for counseling purposes. Second, age at onset and H-Y stage are robust predictors that can be used to identify patients at higher risk of milestone events. Third, the findings may inform the planning of rehabilitation resources and caregiver support, which is particularly relevant given the substantial economic burden of PD [32]. Fourth, the landmark approach provides a practical framework for addressing survival bias in future retrospective PD studies.

4.5 Limitations

Several limitations should be acknowledged. First, the retrospective survey-based design is subject to recall bias. Second, left truncation and survival bias were present because patients were included only if they survived to the survey. We partially addressed this by performing a landmark analysis at 5 years, which showed that the inverse association between disease duration and milestone events disappeared after conditioning on event-free survival at 5 years. However, residual bias may persist, and the cumulative incidence estimates from the primary analysis should be considered upper bounds of the true incidence. Third, the competing risk of death was not formally modeled because mortality data were not systematically recorded; the cumulative incidence estimates reported here should therefore be considered upper bounds of the true incidence. Fourth, the single-center design and the relatively small sample size ($n = 126$; $n = 73$ in the landmark analysis) limit generalizability and the power of subgroup analyses. Fifth, the median disease duration at survey was only 5.0 years, so estimates beyond 10–15 years should be interpreted with caution.

4.6 Future directions

Future prospective, multicenter cohort studies with long-term follow-up are needed to validate our findings and to explore biomarkers that predict milestone event timing [33, 34]. Additionally, the development of a clinical prediction model incorporating baseline characteristics to estimate individual-

level milestone event timing would be valuable, and recent work has begun to address this need [35]. Motor complications such as wearing-off and dyskinesia, which were prevalent in our cohort, may also serve as early indicators of subsequent milestone events [26]. Finally, the landmark approach used in this study can be adapted for other retrospective PD cohorts to facilitate more reliable comparisons across studies.

5. Conclusions

In this retrospective cohort study of 126 patients with PD, we quantified the cumulative incidence of six milestone events using Kaplan-Meier analysis and performed a landmark analysis to address left truncation and survival bias. In the primary analysis, 10-year cumulative incidence ranged from 7.7% to 25.2%; in the landmark analysis, 10-year conditional cumulative incidence ranged from 4.8% to 20.5%, with the primary estimates considered upper bounds. Age at onset and H-Y stage were robust independent predictors in both models, whereas the inverse association between disease duration and milestone events was no longer present in the landmark analysis, confirming that it was driven by left truncation and survival bias. These real-world estimates may inform prognostic counseling and care planning, and the landmark approach provides a practical framework for addressing survival bias in retrospective PD studies.

Declarations

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

The authors reported that there is no funding associated with the work featured in this article.

Notes on contributor

LZ, ZW and JD conceived the study, participated in the design, performed statistical analyses and drafted the manuscript. LZ, YT, YL, HS, ZH and ZW collected the data, and drafted the manuscript. JY and JL analyzed and interpreted the data results. ZW and JD participated in the design and helped to revise the manuscript critically for important intellectual content. All authors read and approved the final manuscript and reviewed this manuscript.

Data availability statement

The raw data supporting the conclusions of this article will be available from the corresponding author upon reasonable request.

Ethics statement

Our study was approved by the Ethics Committee of the Aerospace Center Hospital (approval number: 20190614-SF-06). We obtained a written informed consent from all participants.

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Figures

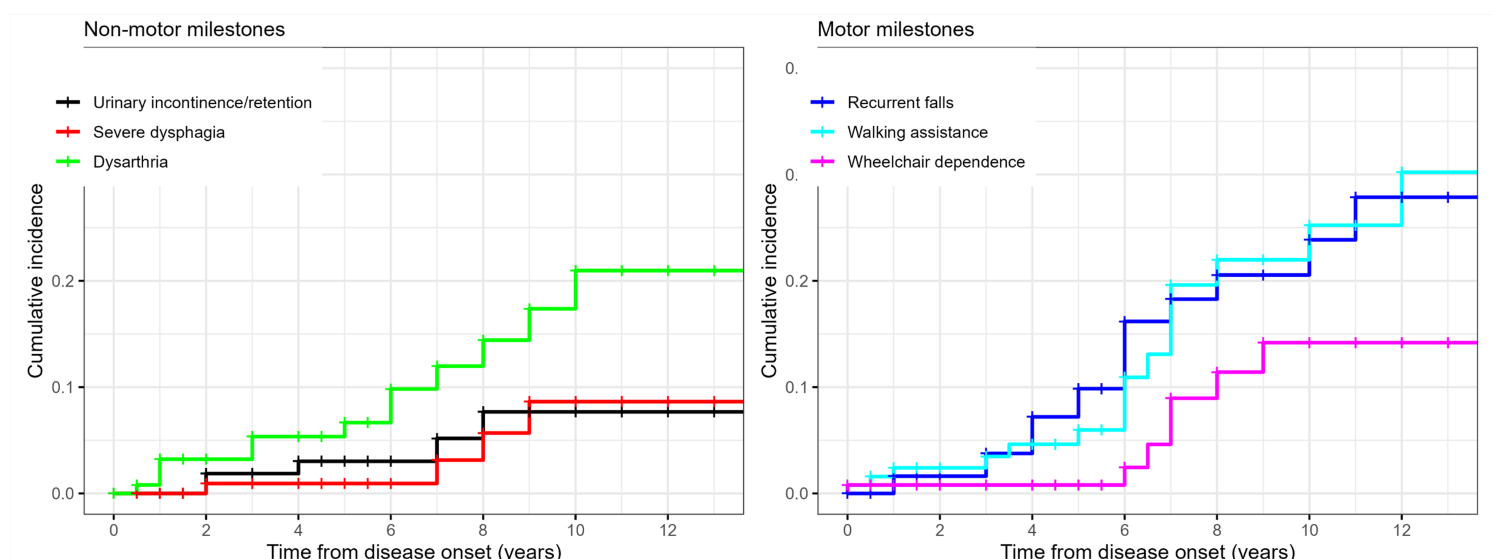


Figure 1

Cumulative incidence of milestone events (primary analysis). (A) Non-motor milestones: severe urinary incontinence/retention, severe dysphagia, and dysarthria. (B) Motor milestones: recurrent falls, need for walking assistance, and wheelchair dependence. The time origin was the date of Parkinson's disease onset. Patients who had not experienced the event at the time of survey were censored at the survey date. Curves were truncated at 13 years because fewer than 10 patients remained at risk beyond 13 years. Median times were not reached for all events because the cumulative incidence remained below 50% throughout the observed time range. Corresponding 95% confidence intervals are reported in Table 3.

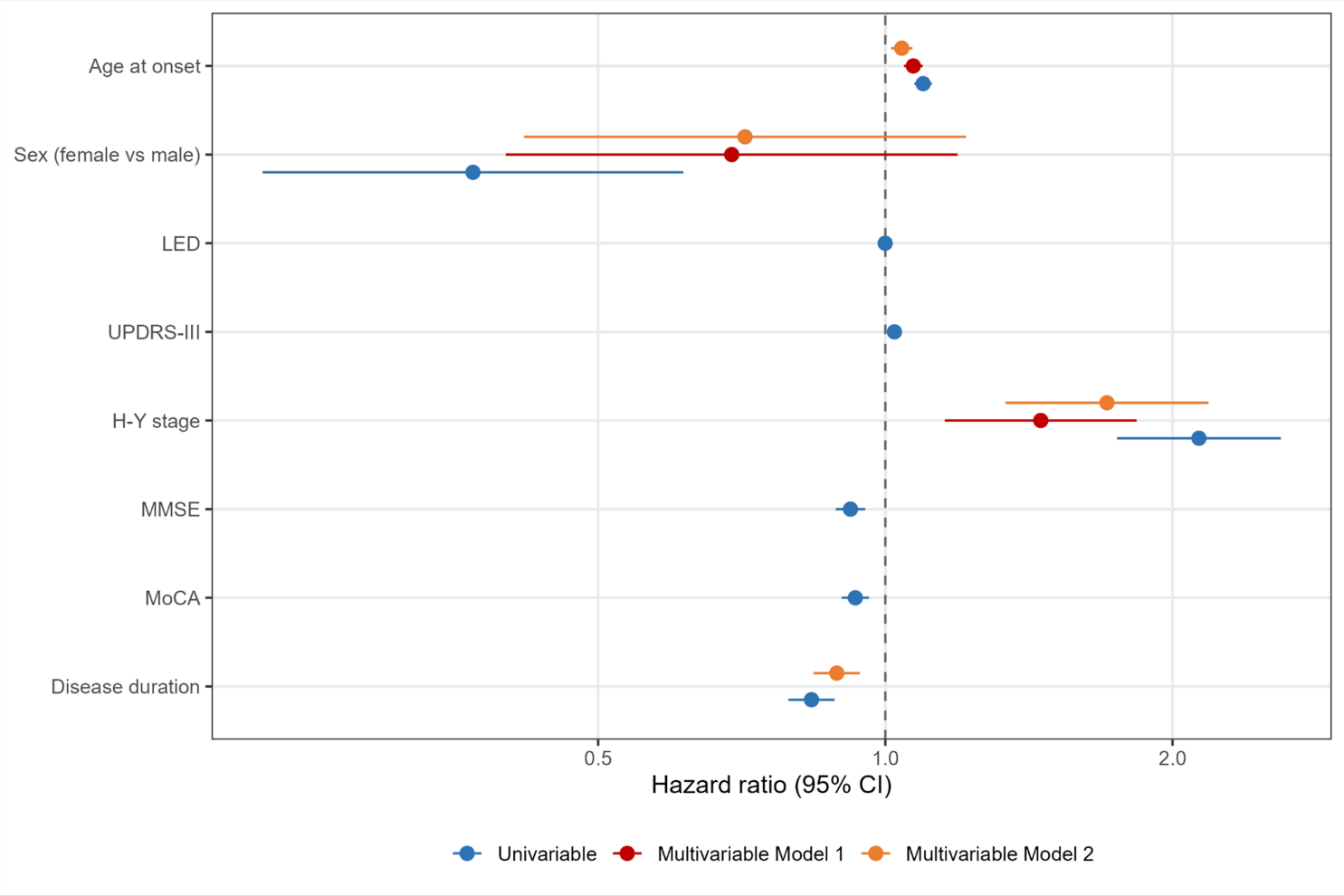


Figure 2

Univariable and multivariable Cox regression analyses of predictors of milestone events (primary analysis). Blue points indicate univariable hazard ratios; red points indicate multivariable Model 1 (age at onset + sex + H-Y stage); orange points indicate multivariable Model 2 (Model 1 + disease duration). The dashed line indicates a hazard ratio of 1.0.

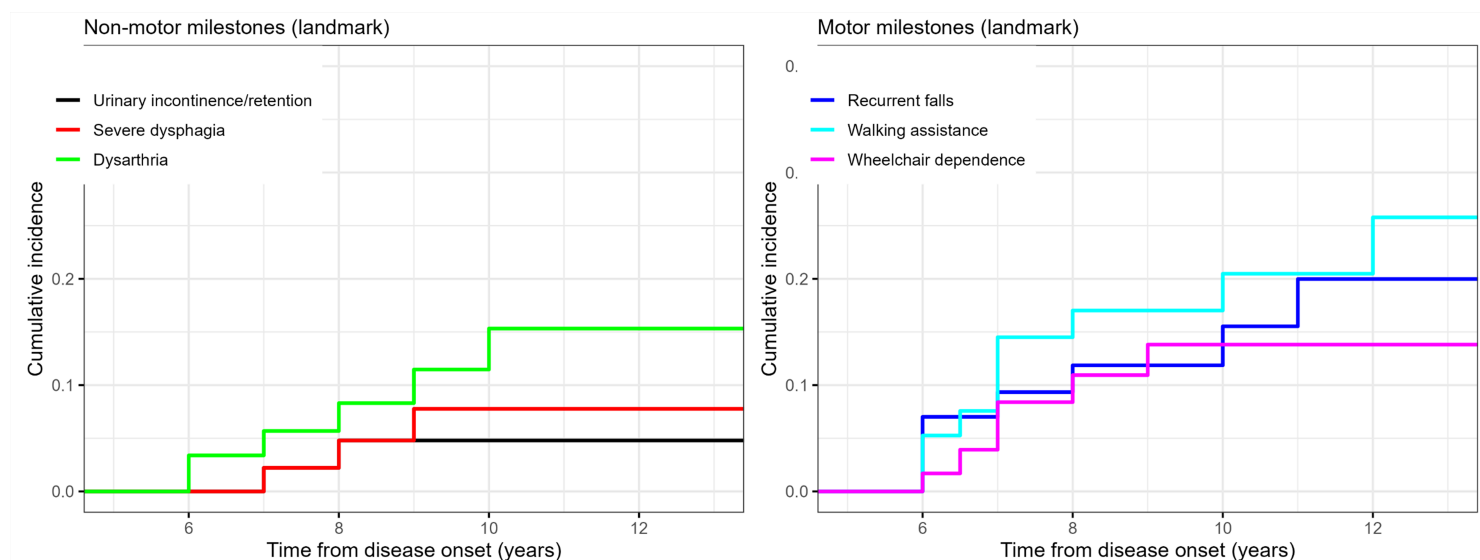


Figure 3

Cumulative incidence of milestone events in the landmark analysis. Conditional cumulative incidence was estimated from the 5-year landmark among patients who remained event-free at 5 years ($n = 73$; 357 observations). (A) Non-motor milestones: severe urinary incontinence/retention, severe dysphagia, and dysarthria. (B) Motor milestones: recurrent falls, need for walking assistance, and wheelchair dependence. The x-axis starts at the 5-year landmark. Curves were truncated at 13 years. Corresponding 95% confidence intervals are reported in Table 4.

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