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Prognostic factors for early mortality in Parkinson's disease

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ABSTRACT

Introduction: There are few large studies that have evaluated prognostic factors for mortality in Parkinson's disease (PD). This large study aimed to identify demographic and clinical features associated with early mortality in PD.

Methods: PD patients at the National Neuroscience Institute were identified from the Movement Disorders Database from which demographic information and prospectively collected baseline disease characteristics were obtained. All study patients were linked to the Singapore Registry of Birth and Death to obtain information on vital status through December 31, 2012. The prognostic variables analyzed include patient demographics, baseline disease characteristics, and type of PD medication used. Multivariate Cox regression analysis was carried out to identify factors associated with the risk of mortality in PD.

Results: Of the 1786 PD patients identified, 363 (20.3%) had died during the 11-year study period. Median survival time from diagnosis was 15.8 years (range 0.3–31). Factors associated with higher mortality (HR, 95% CI) were older age at diagnosis (1.06, 1.03–1.08), male gender (2.29, 1.57–3.35), Hoehn & Yahr (HY) stage ≥2.5 (1.54, 1.07–2.22), UPDRS motor score ≥30 (1.63, 1.13–2.35), higher bradykinesia subscores (1.05, 1.01–1.09) and cognitive impairment (2.30, 1.55–3.41).

Conclusions: In the largest study to date evaluating baseline disease characteristics prognostic of mortality risk in PD, we found that male gender, older age at diagnosis, higher baseline HY stage, higher baseline UPDRS motor scores, higher bradykinesia subscores and baseline cognitive impairment were associated with early mortality in PD.

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1. Introduction

Parkinson's disease (PD) has been associated with reduced life expectancy compared to the general population [1]. However, as there is wide variation in the presence and severity of both motor and non-motor symptoms, the survival of PD patients differs considerably across patients. A better understanding of the factors associated with the risk of mortality would enable a more accurate prognostication of patients and better targeting of treatments.

Most studies on mortality and survival in PD patients have found that increased mortality is associated with older age at onset, male gender and presence of dementia. However, the study of other prognostic factors such as disease severity, subtypes and exposure to different types of PD medication has shown inconsistent results [2–6]. A recent meta-analysis showed major heterogeneity in the mean disease duration at death [2]. The variability in disease duration has been ascribed to differences in study methodology, follow-up duration, patient demographics and sample size. Few PD mortality studies have examined large study cohorts [7,8] and none have evaluated a large PD cohort with prospectively collected data on baseline disease characteristics.

We therefore undertook this study to evaluate demographic factors, baseline disease characteristics, and types of PD medications associated with early mortality in a large cohort of PD patients.

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2. Methods

PD patients seen in 2002–2012 were identified using the National Neuroscience Institute Movement Disorders Database. All patients were diagnosed by movement disorders specialists according to the diagnostic criteria for PD defined by the National Institute of Neurological Disorders and Stroke (NINDS). Linkage to the Singapore Registry of Birth and Death provided additional information on the date and cause of death through December 31, 2012. The study was approved and waiver of informed consent was permitted by the Centralized Institution Review Board of the Singapore Health Services.

Baseline clinical assessment was performed by movement disorders specialists using the modified Hoehn and Yahr (HY) stage and the Unified Parkinson's Disease Rating Scale (UPDRS) motor score. During the initial visit, additional demographic and clinical information was recorded which included age, gender, ethnicity, date of diagnosis, years of education and Mini-Mental State Examination (MMSE).

All patients were seen and followed up during the years 2002–2012. In order to obtain reliable information on vital status, only Singapore citizens and permanent residents were included. Patients whose PD diagnosis was revised during the follow-up period were excluded from the study. In addition, patients who had undergone deep brain stimulation (DBS) surgery were excluded, as surgery can influence PD patient survival [9]. 1786 patients fulfilled the inclusion criteria from whom demographic and socio-economic information (age, gender, ethnicity, date of diagnosis and years of education) were obtained. Baseline clinical information was evaluated only if it had been obtained within 2 years of the diagnosis date. Baseline UPDRS motor score, baseline HY stage, and baseline MMSE scores were available for 1134 patients. Use of PD medications from 2002–2012 was also recorded. Additionally, UPDRS motor subscores of the cardinal features of tremor (items 20 and 21), rigidity (item 22), bradykinesia (items 23–26 and 31) and postural instability and gait difficulty (PIGD) (items 27–30) were computed. The primary causes of death in patients dying during the study period were registered and grouped into distinct categories.

Baseline variables investigated as potential predictors of survival were age at diagnosis, gender, ethnicity, years of education (<10, ≥10), baseline cognitive impairment (MMSE < 24), baseline HY stage (<2.5, ≥2.5), baseline UPDRS motor score (<30, ≥30), baseline UPDRS subscores (tremor, rigidity, bradykinesia, PIGD), and type of PD medication (levodopa, dopamine agonist, trihexyfenidyl, amantadine, selegiline) used.

Table 1
Demographic and baseline disease characteristics.

	n	
Age at diagnosis, mean (SD)	1786	64.40 (11.23)
No. of males (%)	1786	1021 (57.17)
Ethnicity, n (%)	1786	
Chinese		1553 (86.95)
Other (Malay, Indian, others)		233 (13.05)
Years of Education, n (%)	1272	
<10		793 (62.34)
≥10		479 (37.66)
mean (SD)		6.75 (4.89)
MMSE, n (%)	926	
Non-cognitively impaired (nCI, ≥24)		601 (64.90)
Cognitively impaired (CI, <24)		325 (35.10)
mean (SD)		24.33 (4.74)
HY stage, n (%)	1134	
<2.5		708 (62.43)
≥2.5		426 (37.57)
mean (SD)		2.21 (0.76)
UPDRS motor score, n (%)	1134	
<30		813 (71.69)
≥30		321 (28.31)
mean total motor score (SD)		24.39 (11.60)
UPDRS subscores, mean (SD)	1134	
Tremor subscore (range 0–28)		2.54 (2.45)
Rigidity subscore (range 0–20)		5.03 (3.20)
Bradykinesia subscore (range 0–36)		11.22 (6.19)
PIGD subscore (range 0–12)		3.28 (2.68)
Medication, n (%)	1134	
Levodopa		1023 (90.21)
Amantadine		20 (1.76)
Trihexyphenidyl		193 (17.02)
Dopamine agonist		389 (34.30)
Selegiline		362 (31.92)

Abbreviations: SD, standard deviation; MMSE, Mini-Mental State Examination; CI, cognitive impairment; HY, Hoehn and Yahr; UPDRS, Unified Parkinson's Disease Rating Scale; PIGD, postural instability and gait difficulty.

Kaplan–Meier analysis was used to estimate an overall survival curve for all cause mortality and to compare survival rates among strata of baseline variables. Univariate Cox regression survival analysis was performed on all baseline variables. Multivariate Cox regression analysis was run with age at diagnosis, gender, ethnicity, years of education, MMSE, UPDRS motor score and the use of different types of medication as independent variables. Hazard ratios were calculated with 95% confidence intervals. Owing to co-linearity between baseline HY stage and UPDRS motor scores, UPDRS motor score was included in the model in lieu of HY stage. A second multivariate Cox regression model was run to further elucidate the association of UPDRS subscores with risk of mortality. In this model the subscores for the domains of tremor, rigidity, bradykinesia and PIGD were entered in lieu of UPDRS motor score. Statistical significance was set at $p < 0.05$. Data extraction and statistical analyses were performed using SAS, version 9.3 (SAS Inc., Cary, NC, USA).

3. Results

The inclusion and exclusion criteria for this study were met for 1786 PD patients. The average age at diagnosis was 64.4 years, with the majority being males (57%) and ethnic Chinese (87%). In the 11-year study period, almost all patients were exposed to levodopa (90%). The demographic and clinical baseline characteristics are given in Table 1. Of the 1786 PD patients, 363 (20.3%) died during the study period. Median survival from time of diagnosis was 15.8 years with a range of 0.3–31 years (Fig. 1). From the deceased patients, a HY stage (in the ON-state) assessed within one year before death was available from 202 patients. The mean HY stage was 3.6 and median HY stage was 4 (range 2–5). The number of patients in HY stage 2, 2.5, 3, 4 and 5 in the year before they died were 41, 21, 32, 51, and 57 respectively. The most common primary causes of death were infection or sepsis (n = 197, 54.3%), cardiac disease (n = 63, 17.4%), malignancy (n = 35, 9.6%), and stroke (n = 29, 8.0%).

Univariate Kaplan–Meier survival analysis and univariate Cox regression indicated significantly higher risk of mortality (hazard ratio) for older age at diagnosis, education <10 years, baseline cognitive impairment, baseline HY stage ≥2.5, baseline UPDRS motor score ≥30, higher subscores of rigidity, bradykinesia and PIGD, use of levodopa, and patients who were not on trihexyfenidyl, dopamine agonist, or selegiline (Table 2).

In the Cox multivariate regression models, older age at diagnosis, male gender, baseline cognitive impairment, baseline UPDRS motor score ≥30, and higher bradykinesia subscores were associated with higher mortality. When analyzing HY stage in lieu of UPDRS motor score, HY stage ≥2.5 was significantly associated with higher mortality risk (HR 1.544; 95% CI 1.072–2.223; p = 0.0195). Ethnicity, years of education, subscores of tremor, rigidity and PIGD and type of medication used showed no significant association with mortality in the Cox multivariate regression analysis (Table 2).

4. Discussion

In this large cohort of PD patients, we found that older age at diagnosis, male gender, baseline cognitive impairment, higher baseline HY stage, higher baseline UPDRS motor score and higher bradykinesia subscores were associated with higher mortality risk. These results are consistent with previous mortality studies which also found that older age at diagnosis [3–6,8,10–14] and male gender [4,7,8,13–15] predicted higher mortality risk. These demographic variables reflect the generally lower life expectancy in males and older people.

In this study, baseline cognitive impairment was a strong predictor of mortality (HR 2.30), a finding consistent with previous studies on mortality in PD [4–7,10,11,14,16–20]. Cognitive impairment and dementia are associated with higher mortality in the general population [21–23] as well as in renal dialysis patients, stroke and post hip fracture surgery patients [24–26]. The

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