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RESEARCH PAPER

Ten year survival and outcomes in a prospective cohort of new onset Chinese Parkinson's disease patients

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ABSTRACT

Objective The 10 year outcomes and impact of motor and non-motor features on survival of a cohort of new onset Chinese Parkinson's disease (PD) patients were prospectively studied.

Method A cohort of new onset PD patients from 1995 to 2002 was recruited from a regional hospital based movement disorder clinic. Subjects were classified into postural instability gait disorder (PIGD), tremor predominant type or mixed subtypes at presentation. All were evaluated yearly for development of sensory complaints, first significant fall, hallucinations, dementia, postural hypotension, speech disturbances, dysphagia and postural instability persisted during 'on' medication state (PIPon). Mortality and predictors of death were determined.

Results 171 new onset PD patients were recruited. After a mean follow-up of 11.3±2.6 years, 50 (29%) patients died. The standardised mortality ratio was 1.1 (CI 0.8 to 1.5, p=0.34). 83 (49%) developed dementia, 81 (47%) had psychosis and 103 (60%) had sensory complaints. Postural hypotension was found in 58 (34%) patients, 108 (63%) had PIPon, 101 (59%) had falls, 102 (60%) had dysphagia, 148 (87%) had freezing of gait and 117 (68%) had speech disturbances. 46 (27%) were institutionalised whereas 54 (32%) lived independently. Dementia (HR 5.0, 95% CI 2.1 to 13.0), PIPon (HR 2.8, 95% CI 1.2 to 6.8), older onset (HR 1.05, 1 year increase in age, 95% CI 1.0 to 1.1) and PIGD type (HR 2.1, 95% CI 1.2 to 3.7) were independent predictors of death.

Conclusions 10 years into PD, a significant proportion of patients developed dopa resistant motor and non-motor features. Older onset, PIGD type, PIPon and dementia had a negative impact on survival. Standardised mortality ratio was 1.1.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide. Hoehn and Yahr reported a standardised mortality ratio (SMR) of about 3 in the pre-levodopa era.[1] Most Caucasian studies in the post-levodopa era have found reduced excess mortality, with mortality ratios ranging from 1.5 to 2.5.[2–10] To the best of our knowledge, survival analysis in Chinese PD patients is lacking. Although PD is defined by motor symptoms, non-motor symptoms have attracted increasing attention in recent years. The progression of non-motor features and their associations with PD survival have not been extensively studied in a dedicated longitudinal study with yearly clinical examinations. Such information will be invaluable in our understanding of the natural course of the disease and for health resources planning in an ageing society. A cohort of new onset PD patients without dementia or psychosis can give a better estimation of survival in idiopathic PD. We therefore studied longitudinally a prospective cohort of new onset Chinese PD patients who were first diagnosed and followed in a hospital based movement disorder clinic. Our primary objective was to study the SMR of the cohort, with the secondary aims of monitoring annual progression, along with the appearance of late motor and non-motor features, and their association with survival.

METHODS

Subjects

All new onset PD patients who were diagnosed and followed in our hospital based movement disorder clinic from 1995 to 2002 were recruited into the study. This movement disorder clinic is the only secondary referral centre for PD in the eastern area of Hong Kong Island with a population of approximately half a million. Patients were referred from general practitioners, family physicians and emergency department doctors. A few patients were noted to have parkinsonism during admission to our hospital and were referred to the clinic for further management. A diagnosis of idiopathic PD was made by a single movement disorder specialist (MA) based on the UK Parkinson's Disease Society Brain Bank's clinical diagnostic criteria.[11] All PD patients who were diagnosed and treated elsewhere for more than 1 year and were subsequently referred to us for opinions and management were excluded. Those who became demented or developed hallucinations within 1 year of onset of disease, developed features leading to a diagnosis other than idiopathic PD (eg, Parkinson plus syndrome) or who had incomplete clinical information were excluded from the study. Ethics approval was obtained from the ethics committee of the institution.

Clinical assessments

A single movement disorder specialist (MA) performed the Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr Scale and Schwab and England activities of daily living (ADL) rating scale for all subjects at baseline and at yearly intervals. Mini-Mental State Examinations were

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also performed at baseline and at approximately 2 year intervals, or at least yearly if cognitive function showed a trend towards decline. All patients were also evaluated yearly for time to development of sensory complaints, freezing of gait (FOG), first significant fall requiring medical attention, any fall complications leading to fractures or intracranial haemorrhages, psychosis, postural hypotension, postural instability persisted during 'on' medication state (PIPon), swallowing and speech difficulty. All assessments were prospectively entered into a database at every clinic visit. Patients were classified as either postural instability gait disorder (PIGD) subtype or tremor predominant subtype. Tremor predominant PD was classified as presence of tremor without gait or postural reflex impairment. Those without tremor but with gait or postural reflex impairment were classified as PIGD type. All other combinations were classified as mixed type. Sensory complaints were regarded as parkinsonian if these symptoms fluctuated with drug effects. FOG was present if patients had sudden and transient inhibitions of movements while walking, especially during gait initiation or when an obstacle or a narrow hallway was encountered. Psychosis was diagnosed according to the UPDRS part I subscore, item 2 (thought disorder). Psychosis was documented if scoring of thought disorder item was ≥2. Dementia was diagnosed according to the DSMIV criteria[12] when functional difficulties could be attributed to cognitive, rather than physical, disability. PIPon was defined as reaching Hoehn and Yahr staging 3 when patients were in the medication 'on' state. Postural hypotension was diagnosed if patients had more than a 20 mm Hg decrease in systolic blood pressure on 3 min of standing from a supine position. Swallowing difficulty was present if patients reported choking on swallowing. A speech problem was registered when patients first complained of hypophonia. Changes in type and dosing of medications were updated at each clinic visit at intervals of 3–6 months. Selegiline and dopamine agonist exposure was documented. First occurrence of dyskinesia and motor fluctuation due to chronic dopaminergic replacement were also recorded. Information about where the subject was living (home or nursing home) was enquired. All patients who failed to turn up at the scheduled appointment were rescheduled, as far as possible. For those residing in nursing homes such that follow-up could no longer be arranged, consultation notes from outreach teams were sought in the clinical database, and telephone interviews with patients and carers were arranged.

Ascertainment of vital status

In August 2011, we looked up the vital status of all patients in a clinical database which contained electronic clinical records of all public hospital patients in Hong Kong. By computerised linkage to the death registry in the Census and Statistics Department of Hong Kong, the clinical database also contains the latest information on the vital status of all Hong Kong people. Death information was obtained from patient hospital records, the clinical database, death certificates and autopsy reports. In Hong Kong, almost all people die in hospital for social and cultural reasons.

Outcome variables

As of August 2011, the following variables were systemically evaluated and recorded. Non-motor features included presence and time to first occurrence of dementia, psychosis, sensory compliant and postural hypotension. Motor features included presence and time to onset of speech and swallowing disturbances, PIPon, FOG and first significant fall requiring medical attention. Time to onset of dyskinesia and motor fluctuations were recorded. Level of dependence was measured by the Schwab and England ADL scale in the 'on' medication state. Those scoring ≥80% were classified as independent living. Subjects were regarded as totally dependent when the Schwab and England score was ≤30. Whether patients were institutionalised was also accounted for in each visit.

Statistics

The ratio of observed deaths to expected deaths compared with people of the same age and sex in the same calendar years in the general population of Hong Kong gives rise to the SMR. Assuming deaths in different categories followed a Poisson distribution, 95% CI were obtained.[13] Kaplan–Meier plots were used to calculate the cumulative survival and median time to various outcome variables specified above.

To identify the independent associations of putative predictors and mortality during the entire study period, we used Cox proportional hazards models with time dependent covariates. In these models, chronological age, UPDRS part III motor score and presence of dementia, psychosis, FOG, PIPon, first significant fall, postural hypotension, swallowing, and sensory and speech disturbances were entered as time dependent covariates whereas non-time independent variables included age of onset, PIGD subtype and sex. HRs and 95% CIs were obtained. In the first step of Cox modelling, all the time dependent covariates were entered in a forward stepwise manner. The log rank tests are used to measure how well the model performed. In the next step, non-time dependent covariates were also entered in a forward stepwise manner. The significant covariates generated were reported. A supplementary model was performed by adding exposure of dopamine agonist and exposure of selegiline to the model, to see if exposure to these two drugs had any effect on survival.

With Cox modelling, one missing value in one annual visit would lead to a loss of the whole case for analysis. To prevent this, we carried over information on a categorical variable (eg, hallucination) from the previous visit to the visit with missing information. For continuous variables (eg, UPDRS motor score), we inputted the mean of the previous and subsequent visits' missing value. For each time dependent covariate, the proportion of missing data ranged from 0.3% to 4.7% of the total number of 1878 assessments for all patients in the cohort.

All statistical calculations were performed using SPSS statistical software (V.19). All p values were two tailed and we considered $p<0.05$ as significant.

RESULTS

A total of 208 subjects with suspected new onset PD were initially recruited between 1995 and 2002. Nine had incomplete clinical information and one moved out of Hong Kong and defaulted on follow-up. Twenty-seven subjects had their diagnoses revised after entering into the database. Among these 27 patients, nine had dementia within 1 year of diagnosis and had a revised diagnosis of dementia with Lewy body disease, 10 had progressive supranuclear palsy, multiple system atrophy or cortical basal ganglionic degeneration, three had vascular parkinsonism and five had essential tremor.

One hundred and seventy-one patients were eventually recruited for further analysis. Ninety-three (54%) were men, mean age of disease onset was 62.2±10.6 years (range 38–89 years) and mean disease duration at the end of follow-up was 11.4±2.6 years (range 4–16, median 11, IQR 4 years). As of

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Table 1 Baseline characteristics at diagnosis

	Total (%)
No of patients	171
Age at onset (years) (mean±SD (range))	62.2±10.6 (38–89)
Sex (men (n (%))	93 (54)
Tremor type at onset (n (%))	46 (26.9)
PIGD type at onset (n (%))	62 (36.3)
Symmetry at onset (n (%))	15 (8.8)
Postural instability (H&Y ≥3) (n (%))	6 (3.5)
MMSE (mean±SD (range))	26.8±3 (20–30)

H&Y, Hoehn and Yahr; MMSE, Mini-Mental State Examination; PIGD, postural instability gait disorder.

August 2011, all patients remaining alive were evaluated and those deceased were censored at that point. Mean duration of follow-up was 11.3±2.6 (range 4–16) years; duration of follow-up was counted up to the time of death for those deceased. Baseline characteristics are shown in table 1. A total of 50 patients died, of whom 32 (64%) died of pneumonia, nine (18%) died of malignancy, one died of gastrointestinal bleeding, one died of bleeding aneurysm, two died of stroke, one died of heart failure, two died of cirrhosis and two patients died suddenly with unknown cause. SMR was 1.1 (95% CI 0.8 to 1.5, p=0.3). Figure 1 shows the survival curve of the cohort calculated using the Kaplan–Meier method. Table 2 shows the corresponding mortality data. Levodopa exposure was noted in 169 (99%) patients, of whom 63.9% had motor dyskinesia and 75.1% suffered from motor fluctuation. Table 3 shows the proportion of patients having various motor and non-motor features. Findings of the multivariate Cox regression analysis with time dependent covariates are shown in table 4; the age adjusted HR for each individual variable is provided for reference. Running of the supplementary model by adding exposure to selegiline and dopamine agonist, as mentioned above, did not alter the results. Table 5 shows the progression of Hoehn and Yahr staging from the beginning to the end of the study. The initial mean Hoehn and Yahr score was 1.9±0.4 (range 1–3).

At the end of the study, 54 (32%) patients were still functionally independent during the 'on' state while 48 (28%) were totally dependent for ADL with a Schwab and England score ≤30. One hundred and one (59%) patients had at least one significant fall requiring medical attention, of whom 41 had complications of fractures or intracranial haemorrhages. Forty-six (27%) patients were institutionalised.

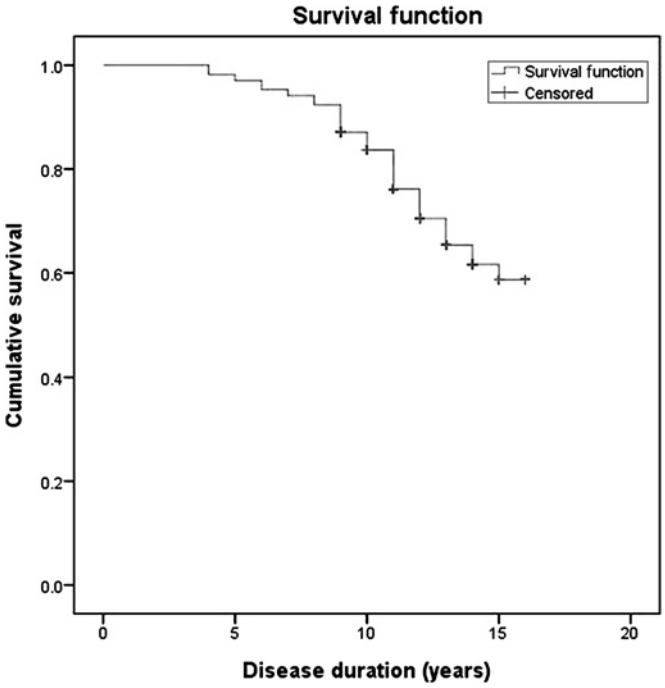

Figure 1 Survival of 171 patients with Parkinson's disease.

DISCUSSION

The SMR of this cohort was 1.1, and the 95% CI crossed 1.0, implying that the 10 year mortality ratio of the cohort was not significantly different from the general population of Hong Kong. Although most of the studies had a 10 year mortality ratio ranging from 1.5 to 1.8,[5–8 14 15] significantly higher than the general population or control groups, one clinic based study reported a 10 year mortality ratio of 0.9.[16] Survival analysis of the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) study[17] 13 years after enrolment showed an SMR of 1.04 (95% CI 0.52 to 1.86). We believe that there are several reasons why our cohort had a better survival. Firstly, those with dementia or psychosis in the first year of diagnosis and patients with 'atypical' features developing during the follow-up period were excluded. We believe that those with idiopathic PD enjoy better survival. Indeed, previous studies showed that clinically definite PD patients had a much better prognosis than clinically probable or clinically possible PD.[8] Secondly, clinic based patients might have less comorbidities

Table 2 Mortality of 171 patients with Parkinson's disease

Interval (start–end)	No at risk at start of interval	No censored during interval	No at risk at end of interval	No of subjects who died at end of interval	Proportion surviving during this interval	Cumulative survival at end of interval	CI (upper level)	CI (lower level)
0–4	171	0	171	3	0.982	0.982	0.963	1.002
4–5	168	0	168	2	0.988	0.971	0.945	0.996
5–6	166	0	166	3	0.982	0.953	0.922	0.985
6–7	163	0	163	2	0.988	0.942	0.906	0.977
7–8	161	0	161	3	0.981	0.924	0.885	0.963
8–9	158	23	158	9	0.943	0.871	0.820	0.922
9–10	126	10	126	5	0.960	0.837	0.778	0.896
10–11	111	20	111	10	0.910	0.761	0.766	0.832
11–12	81	20	81	6	0.926	0.705	0.627	0.783
12–13	55	16	55	4	0.927	0.654	0.567	0.740
13–14	35	12	35	2	0.943	0.616	0.526	0.707
14–16	21	20	21	1	0.952	0.587	0.483	0.691

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Table 3 Clinical outcomes and drug profiles at a mean of 11 years after disease onset

	Total (%)	Median time to outcome (years)	Alive (n)	Death (n)
Dementia (n (%))	83 (49)	13	40	43
Psychosis (n (%))	81 (47)	13	50	31
Sensory compliant (n (%))	103 (60)	9	75	28
Postural hypotension (n (%))	58 (34)	16	45	13
Postural instability (PIPon) (n (%))	108 (63)	11	66	42
Freezing of gait (n (%))	148 (87)	6	105	43
Falls (n (%))	101 (59)	11	70	31
Swallowing problem (n (%))	102 (60)	11	65	37
Speech disturbance (n (%))	117 (68)	10	87	37
Institutionalised (n (%))	46 (27)	—	17	29
Dopamine exposure (n (%))	83 (49)	—	70	13
Selegiline exposure (n (%))	28 (16)	—	24	4

PIPon, postural instability persisted during 'on' medication state.

compared with community patients. As shown in the DATATOP study, selected patients with less comorbidities had better survival. Thirdly, PD patients receiving quality care from movement disorder specialists have better survival, which echoes previous studies.[16 17] Finally, all of our patients were diagnosed with PD early in the course of their disease. Documentation of symptom onset at an early stage could improve the accuracy of the reported disease duration; therefore, mortality would appear to be less than those with late diagnoses when symptom onset might be mistakenly recalled to be shorter. Other cohort studies have noted increasing SMRs over time, suggesting that advanced PD has a more negative effect on survival than early PD.[6 9 16] Hence those with actual duration of disease longer than 10 years would have a higher SMR.

Whether Chinese PD patients have a different survival compared with Caucasians has yet to be determined, as there are few data on Chinese and Asian parkinsonian patients. A study with multiple ethnicities did not reveal a difference in mortality among White, Hispanic, Asian or Black patients but the proportion of Chinese patients in this report was only 6%.[18]

Similar to Sydney's multicentred study,[9] a substantial proportion of patients developed non-dopa responsive motor features and non-motor features 10 years into PD (table 3). Among these, dementia and PIPon both predicted mortality independently. Concerning baseline demographic features, we were able to reaffirm previous findings that PD patients with the PIGD subtype and older age of onset had worse survival. The risk of mortality within the study period was increased by 1.05 for each year increase in age at entry to the study, which was in accordance with other reports.[16 19]

Table 4 Association of outcome variables with mortality risk using Cox proportional hazards model with time dependent covariates

	Mutually adjusted HR (95% CI)	Age adjusted HR (95% CI)
Age onset, 1 year increase in age	1.05 (1.01 to 1.10)	1.08 (1.04 to 1.12)
PIGD subtype	2.1 (1.2 to 3.7)	2.6 (1.4 to 4.7)
Dementia	5.0 (2.1 to 13.0)	7.9 (3.2 to 19.5)
Postural instability in 'on' state	2.8 (1.2 to 6.8)	4.8 (2.1 to 11.1)

PIGD, postural instability gait disorder.

Table 5 Hoehn and Yahr staging at baseline and at the end of the study

H&Y staging	Study start (n)	Study end (n)
1	21	0
1.5	23	1
2	113	45
2.5	8	21
3	6	43
4	0	19
5	0	42
Total	171	171

H&Y, Hoehn and Yahr.

We found that PIPon developing during the course of PD was a risk factor for death. To the best of our knowledge, it has not been reported previously in the literature. Since we defined PIPon, it seems that when postural instability becomes dopa resistant it is associated with worse survival. Postural instability is one of the four cardinal features of PD yet it should not be prominent in the early phase of disease and is commonly dopa responsive. However, as the disease progresses, postural instability becomes increasingly dopa resistant and therefore persists in the 'on' state. Our study found that both PIGD at presentation and PIPon at a later stage of PD worsened survival.

PIGD subtype at onset was shown to have 2.1 times higher mortality, which was in line with many other studies.[18 20] To date, the pathophysiology of maintenance of postural stability is not well understood. The dopamine axis and basal ganglion are involved, which explains the initial response of postural instability to dopamine replacement in the early phase of PD.[21] Mounting evidence suggests the important role of the pedunculopontine nucleus and its cholinergic projections in maintaining postural balance.[22 23] Cholinergic deficits from the nucleus basalis of Meynert to the basal forebrain also lead to cognitive decline and dementia.[24 25] As both dementia and PIPon were found to independently increase the risk of death in this longitudinal PD cohort, this may suggest that widespread extradopaminergic involvement, especially cholinergic deficit at a later phase of PD, has an important survival implication.

Evidence shows that the PIGD subtype of PD at presentation not only confers worse survival[18 20] but also an increased risk of dementia.[26] Could this imply an earlier cholinergic deficit, apart from the dopaminergic deficit in this subtype, resulting in earlier dopa resistant postural instability and dementia, subsequently threatening survival in these patients? Prospective longitudinal clinicopathological studies to better understand the underlying pathophysiology should deliver more clues, which might form the basis for devising treatment strategies targeting dopa resistant motor and non-motor features of PD. Indeed, it was recently shown that central cholinesterase inhibitors might reduce falls in PD patients,[27] further supporting the relationship between cholinergic deficit and postural instability in PD patients.

While this dedicated longitudinal study with interval repeated clinical examinations provided both mortality data and the various predicaments that advance PD patients suffered, we understand that a clinic based study would lead to selection bias and the problem of generalisability, as community patients are different from those seeing specialists. Further to this, we do not know the clinical profiles and proportions of PD patients who are looked after by primary physicians. Moreover, PD patients in Hong Kong might not be representative of patients in other areas of China. Factors such as differential socioeconomic environment

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and standard of medical care between different areas might have an impact on survival. Finally, the cohort may not be large enough to detect weaker independent factors of survival.

Nevertheless, to the best of our knowledge, this is the first longitudinal mortality study in Chinese PD patients. The SMR at approximately 10 years was 1.1 and was not significantly higher than the general population. However, a large proportion of PD patients were suffering from both dopa resistant motor and non-motor features at a later phase of their disease. Among these, dementia and postural instability were associated with mortality. Health resources should be directed towards developing new lines of treatment to combat many of the dopa resistant features, so as to improve the morbidities of PD patients.

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Contributors Acquisition of the data: MA, CMC, CNL, RL and EY; analysis and interpretation of the data: MA, THT, VM, CMC, CNL, RL and EY; drafting of the manuscript: MA and THT; and critical revision of the manuscript: MA, THT and VM.

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