Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

Case-Fatality Rate in Parkinson's Disease: A Nationwide Registry Study

Jussi O.T. Sipilä, MD, PhD,[1,2,*] Valtteri Kaasinen, MD, PhD,[2,3] Päivi Rautava, MD, PhD,[4,5] and Ville Kytö, MD, PhD[5,6]

Abstract: Background: Patients with Parkinson's disease (PD) may have an increased risk of mortality, but robust estimates are lacking.
Objective: To compare mortality rates nationally between patients with PD and controls.
Methods: The case-fatality rates of Finnish PD patients diagnosed in 2004–2018 (n = 23,688; 57% male, mean age at diagnosis = 71 years) and randomly selected sex- and age-matched control subjects (n = 94,752) were compared using data from national registries. The median follow-up duration was 5.8 years (max 17 years).
Results: The case-fatality rate in patients with PD was higher than that in matched controls (HR 2.29; 95% CI 2.24–2.33; P < 0.0001). Excess fatality among PD patients was already present at 1 year from diagnosis and then plateaued at 29% at 12 years after diagnosis. The long-term relative hazard of death in PD patients vs. matched controls did not differ based on sex. Patients with early-onset PD (age at diagnosis <50 years old) had the highest relative hazard of death (HR 3.36) compared to matched control subjects, and the relative hazard decreased with higher age at diagnosis. The seven-year excess risk of death decreased during the study period, especially in men. In patients with PD, male sex, increasing age, and increasing comorbidity burden were associated with an increased risk of death.
Conclusions: An increased risk of death among PD patients was evident from early on. The increase in risk was greatest among young-onset patients. The excess risk in early PD declined during the study period, particularly in men. The reasons for this are unknown.

Introduction

"One dies with Parkinson's disease (PD), not from it", is a phrase sometimes used by clinicians to describe the risk of death among PD patients.[1] Indeed, although PD is seldomly the primary cause of death, there is a body of evidence indicating that patients with PD have higher mortality rates than controls. However, the risk estimates are heterogeneous, and data from community-based inception cohorts in which experts have confirmed the diagnosis are necessary. Relevant studies should have no exclusion criteria (other than those relating to accuracy of diagnosis), conduct prospective follow-up, measure long-term outcomes, and use the time of diagnosis as a baseline for measurements.[2] We therefore conducted such a study using nationwide Finnish data from multiple registries covering patients diagnosed with PD in 2004–2018.

Methods

Study Patients and Design

Patients with new-onset PD in Finland during 2004–2018 were identified from a national Social Security Institution of Finland (SSIF) database of entitlements to special reimbursements for prescription medication expenses (entitlement code 110). Medications for PD are available only by prescription in Finland, and patients receive these state-sponsored medications based on their entitlement. Entitlement for PD and related dopamine-responsive movement disorders requires an appropriate diagnosis verified clinically by a neurologist, and all applications are reviewed by a medical specialist at SSIF. Virtually all patients with PD in Finland apply for and are granted the entitlement after appropriate diagnosis is made, and a

[1]Department of Neurology, Siun Sote North Karelia Central Hospital, Joensuu, Finland; [2]Clinical Neurosciences, University of Turku, Turku, Finland; [3]Neurocenter, Turku University Hospital, Turku, Finland; [4]Department of Public Health, University of Turku, Turku, Finland; [5]Turku Clinical Research Center, Turku University Hospital, Turku, Finland; [6]Heart Center, Turku University Hospital and University of Turku, Turku, Finland

***Correspondence to:** Dr. Jussi Sipilä, Neurology, North Karelia Central Hospital, Tikkamäentie 16, FI-80210 Joensuu, Finland; E-mail: jussi.sipila@utu.fi
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previous study reported that "Of the originally identified Parkinson's disease cases reviewed, 80% met criteria for Parkinson's disease".[3] Our search included all patients who received specialist medical care (any specialty or contact type) or presented to emergency rooms during the study period, covering 99.8% of all patients given the entitlement (https://www.kela.fi/kelasto). The exclusion criteria were previous PD entitlement, ICD-10 diagnosis code of parkinsonism other than PD (G20) in the reimbursement application, diagnosis of secondary parkinsonism (ICD-10 code G21-G22 $n = 71$), other degenerative diseases of the basal ganglia (G23 n = 382), dystonia (G24 $n = 2$), or other extrapyramidal and movement disorders (G25-G26 $n = 26$) as any cause of death during follow-up, age <18 years, missing baseline data ($n = 3$), or missing follow-up data ($n = 4$). Early-onset PD (EOPD) was defined as diagnosis before 50 years of age.[4] Patient baseline comorbidities were recognized from the Care Register for Health Care in Finland (CRHC), which covers all hospital admissions and public outpatient and emergency room visits of specialist medical care in Finland, from the national Finnish Cancer registry, and from the national database of special reimbursements for prescription medications as previously described.[5] Date of reimbursement approval was used as a proxy for the diagnosis. Comorbidity burden at the time of diagnosis was studied by calculating the Charlson comorbidity index.[6] The controls included age- and sex-matched subjects without PD who were randomly selected from the Finnish population at a 4:1 ratio for each patient with PD. The controls were selected from the archives of the national census bureau and did not need to have any contact with health care. Subgroup analyses were performed for men and women and for study subjects aged 18–49, 50–64, 65–79, and ≥80 years at baseline. The outcome of interest was death. Follow-up started at PD diagnosis/entitlement and ended on Dec 31, 2020. The median follow-up was 5.7 years (IQR 3.5–8.8, max 17.0 years).

Data Sources, Permissions and Sharing

The data on entitlements to special reimbursements of medication expenses, the CRHC, and the Finnish Cancer Registry were obtained from the Findata (THL/164/14.02.00/2021). The control subjects, mortality data of PD patients and controls, and causes of death of PD patients were obtained from Statistics Finland (permission no: TK/923/07.03.00/2022). Informed consent was waived by the law, and participants were not contacted. Legal grounds for data handling are public interest and scientific research (EU General Data Protection Regulation 2016/679 (GDPR), Article 6 (1)(e) and Article 9 (2)(j); Data Protection Act, Sections 4 and 6). These data are subject to third-party restrictions. Permission can be applied from Findata (www.findata.fi).

Statistical Analysis

Outcomes were studied using the Kaplan–Meier method and Cox regression. Multivariate modeling was used to study the association of baseline features with mortality in PD patients. Stratification by matching was used for case–control regression analyses. Mortality was examined in subgroups of Parkinson's patients diagnosed in 2004–2008, 2009–2013, and 2014–2018 vs. matched controls. Excess mortality due to PD was calculated by subtracting the cumulative mortality of control subjects from the cumulative mortality of PD patients. The impact of unmeasured confounding between PD cases and controls beyond age and sex was estimated by calculating the E-value.[7] The results are presented as the mean, median, percentage, or hazard ratio (HR) with SD, IQR, or 95% CI. Statistical significance was inferred at a P value of <0.05. Analyses were performed using SAS ver. 9.4. (SAS Inc. Cary, NC, USA).

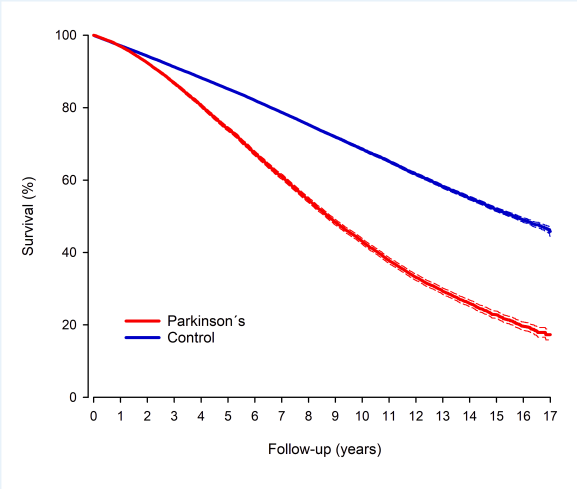

Figure 1. Survival of patients with Parkinson's disease and age-, and sex-matched control subjects. Follow-up started at diagnosis of Parkinson's disease. Dashed lines represent 95% confidence intervals.

Results

The final study population included 23,688 patients with PD and 94,752 matched controls. The majority of PD patients were male (56.7%), and the median age at cohort entry was 72 years (IQR 65–78; range 25–96 years). The median CCI score at cohort entry was 1 (range 0–13). During the 17-year follow-up, 11,580 patients with PD died. Of the control subjects, 27,137 died during follow-up. The case fatality rate was higher in patients with PD than in control subjects after 1 year of follow-up (Fig. 1). The E-value was 4.01 (CI 3.91–4.09). Excess fatality in PD increased between 1 and 12 years after diagnosis and then reached a plateau of 29% (Fig. 2). The long-term risk of death in PD did not differ between men and women when compared to matched controls (Table 1). The risk of death in PD patients compared to matched controls was highest in EOPD patients and decreased stepwise with increasing age at diagnosis (Table 1). The hazard of seven-year fatality in PD patients vs. controls decreased during the study

period with the trend driven by men (Table 2). In patients with PD, male sex, increasing age, higher CCI, and atrial fibrillation were associated with an increased risk of death (Tables 3 and 4).

In the PD cohort, the underlying cause of death was classified as PD in 38.5%, cardiac or cardio/peripheral vascular in 20.1%, dementia (incl. Alzheimer's disease) in 11.9%, malignancy or tumor in 10.7%, cerebrovascular in 6.3%, external cause in 4.5%, infection in 2.1%, gastrointestinal in 2.1%, other neurological disease in 1.1%, and other (endocrinological, congenital abnormality, hematological, genito-urological, psychiatric, musculoskeletal or connective tissue, respiratory, or nonspecified) in 2.7% of deceased PD patients. PD was the underlying cause of death more frequently in PD patients who died within the first seven years of diagnosis than in PD patients who died later during follow-up (54.4% vs. 45.6%; $P < 0.0001$).

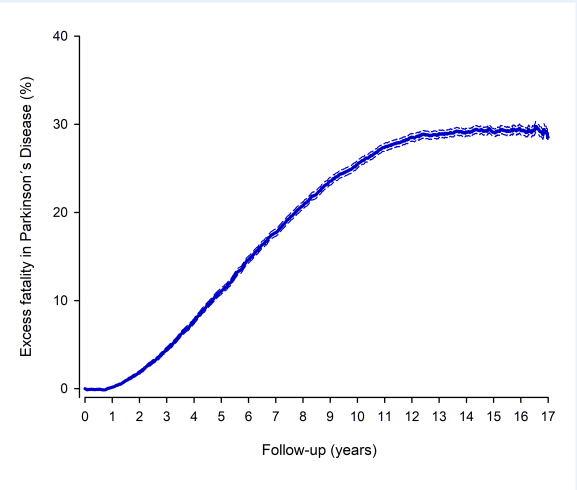

Figure 2. Excess fatality of patients with Parkinson's disease vs. age-, and sex-matched control subjects. Follow-up started at diagnosis of Parkinson's disease. Dashed lines represent 95% confidence intervals.

Discussion

In this population-based nationwide study utilizing multiple registries and covering almost 20 years, we observed an over two-fold higher risk of death in both women and men with PD than in non-PD control subjects. Age at PD diagnosis was inversely correlated with excess risk of death. Increased risk was already present at early motor stages of the disease, at 1 year after diagnosis, and then further increased until plateauing at 12 years after diagnosis. The hazard ratio for death during the first 7 years after diagnosis decreased during the study period with the trend particularly evident in men.

Mortality data using only population-based death records have often been used to estimate the epidemiology of PD. However, this approach is problematic due to inaccuracies in death certificate data.[8–11] Naturally, this also concerns the death certificate data at our disposal. Moreover, there is major heterogeneity in studies using cohort data to estimate survival and mortality in PD. The most accurate data seem to be derived from community-based studies with validated inception cohorts. The current data correspond almost exactly to the seven requirements previously laid out for studies investigating mortality in PD,[2] with only post hoc validation of the drug reimbursement data missing. However, the approval process ensures that the diagnoses of parkinsonism are expertly confirmed at the time of diagnosis. Furthermore, we also excluded deceased patients who died from or had atypical parkinsonism, further ensuring that only patients with idiopathic PD were examined. Nevertheless, the preliminary validity data of the reimbursement registry

TABLE 1 *Cumulative fatality and hazard ratio (HR) for death in patients with Parkinson's Disease compared to age- and sex matched control subjects during 17-year follow-up*

	Cumulative fatality (17-year follow-up)			
	Parkinson's	**Controls**	**HR (95% CI)***	***P* value**
All	82.7%	54.2%	2.29 (2.24–2.33)	<0.0001
Sex				
Men	84.3%	56.0%	2.30 (2.24–2.36)	<0.0001
Women	80.7%	52.1%	2.27 (2.20–2.34)	<0.0001
Age (years)				
18–49	15.0%	5.1%	3.36 (2.43–4.64)	<0.0001
50–64	53.9%	19.3%	3.03 (2.85–3.23)	<0.0001
65–79	93.0%	60.6%	2.42 (2.36–2.49)	<0.0001
≥80	99.4%	84.6%	1.88 (1.81–1.94)	<0.0001

Results of total study cohort and sex- and age- based subgroups.
*Parkinson's Disease vs. controls.

TABLE 2 *Total and sex-stratified cumulative fatality in patients with Parkinson's Disease (PD) compared to age- and sex matched control subjects during the first seven from the PD diagnosis according to time of diagnosis*

	Seven-year fatality in PD patients vs. controls according to the time of diagnosis			
	Parkinson's	**Controls**	**HR (95% CI)***	***P* value**
2004–2008				
Total	39.3%	21.9%	2.05 (1.97–2.13)	<0.0001
Men	42.2%	23.2%	2.08 (1.98–2.19)	<0.0001
Women	35.8%	20.3%	2.00 (1.88–2.13)	<0.0001
2009–2013				
Total	39.9%	21.7%	2.12 (2.04–2.19)	<0.0001
Men	42.6%	22.8%	2.17 (2.07–2.17)	<0.0001
Women	36.3%	20.2%	2.03 (1.92–2.16)	<0.0001
2014–2018				
Total	37.4%	20.1%	1.84 (1.76–1.93)	<0.0001
Men	39.8%	21.7%	1.85 (1.74–1.97)	<0.0001
Women	34.2%	17.9%	1.83 (1.69–1.98)	<0.0001

HR, Hazard ratio.
*Parkinson's Disease vs. controls.

TABLE 3 *Association of baseline features with fatality during 17-year follow-up of patients with Parkinson's Disease*

	Baseline	**Univariable**		**Multivariable**	
	%	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Male sex	56.6%	1.18 (1.14–1.23)	<0.0001	1.38 (1.32–1.43)	<0.0001
Age (years)			<0.0001		<0.0001
18–49	2.7%	Reference	Ref.	Reference	Ref.
50–64	20.6%	3.92 (2.92–5.27)	<0.0001	3.69 (2.74–4.96)	<0.0001
65–79	57.2%	13.57 (10.14–18.16)	<0.0001	11.94 (8.91–16.00)	<0.0001
≥80	19.5%	36.25 (27.04–48.61)	<0.0001	31.14 (23.19–41.81)	<0.0001
CCI			<0.0001		<0.0001
0	43.4%	Reference	Ref.	Reference	Ref.
1	27.1%	1.77 (1.69–1.85)	<0.0001	1.48 (1.41–1.54)	<0.0001
2	16.7%	2.21 (2.10–2.33)	<0.0001	1.71 (1.62–1.80)	<0.0001
3	7.6%	3.11 (2.89–3.33)	<0.0001	2.17 (2.02–2.33)	<0.0001
≥4	5.1%	4.13 (3.80–4.49)	<0.0001	2.70 (2.47–2.95)	<0.0001
Atrial fibrillation	13.3%	1.46 (1.38–1.54)	<0.0001	1.07 (1.01–1.13)	0.018

Baseline features at the time of diagnosis and results of univariable and multivariable analyses.

suggests that some patients who did not actually have PD may have been included in the analyses. The suboptimal accuracy of the clinical diagnosis is an international problem,[12] although recent data overlapping our study period suggest improvement after the adoption of MDS-PD diagnostic criteria.[13] Case validity clearly below 100% is not uncommon in even most the recent studies comparable to ours.[8,14] Unfortunately, we were unable to control for place of residence and socioeconomic status which are associated with mortality. Using the date of reimbursement approval as proxy for the date of diagnosis may slightly

TABLE 4 *Prevalence of Charlson co-morbidity index components and atrial fibrillation in PD patients (n = 23,688) at the time of cohort entry*

Comorbidity	Prevalence (%)
Diabetes	15.9%
No complication	13.6%
With complication	2.3%
Dementia	13.7%
Atrial fibrillation	13.3%
Malignancy	12.5%
Non-metastatic	12.2%
Metastatic	0.3%
Cerebrovascular disease	11.1%
Chronic pulmonary disease	10.9%
Heart Failure	7.6%
Myocardial infarction	5.0%
Rheumatic disease	4.8%
Peripheral vascular disease	2.9%
Renal disease	1.3%
Peptic ulcer disease	1.2%
Hemi-/paraplegia	0.9%
Liver disease	0.9%
Mild	0.8%
Severe	0.1%
AIDS/HIV	0.03%

overestimate the mortality especially during the first year since there is a period of a couple of weeks between the doctor's appointment and when the approval is granted. Moreover, in some milder cases the initiation of medication (and therefore also seeking for the reimbursement) may be postponed. Immortal time bias therefore affects the mortality ratios towards an underestimate of the mortality risk in PD when compared with controls, further emphasizing the survival difference between patients and controls. On the other hand, misdiagnosis of atypical parkinsonism as PD has likely resulted in an overestimate of the relative mortality in PD, therefore somewhat balancing the immortal time bias. E-value suggested that the observed HR of 2.29 in long-term case fatality could be explained by an unmeasured co-founding associated with PD and death by a risk ratio of ≥4.0-fold each, above and beyond age- and sex, but weaker confounding could not do so.[7]

According to a meta-analysis, PD is associated with increased mortality, approximately 1.5 times the control mortality in inception cohorts, and a decrease in survival of approximately 5% per year of follow-up.[2] However, as it was noted that poor study quality and heterogeneity in study methods and patients studied hampered the analysis these results should be considered preliminary. More recent reports on the possible excess risk of death in patients with PD are also conflicting. Incidence data from Israel are in line with our results, with a greater than two-fold risk of death in both women and men with PD compared to controls.[15] On the other hand, recent inception cohort data from Estonia and China show no difference in mortality between PD patients and controls.[8,16] Interestingly, a population-based registry study covering approximately 6% of the UK population but lacking expert validation of diagnoses reported only a slightly increased mortality compared to non-PD controls (adjusted mortality rate ratio: 1.14; 95% CI: 1.03 to 1.19).[14] They also observed that the risk for people with PD approximately doubled in the 5 years following diagnosis. Our data concur with this observation but not with the modestly increased hazard. On the other hand, the UK study reported that adjusted mortality rates declined more slowly between 2007 and 2016 for people with PD than for people without PD. This is in stark contrast to our result that the hazard ratio of death in the first 5 years from the diagnosis decreased during the study period. Our previous study also reported improved 4-year survival in PD patients in south-western Finland, but population controls were unavailable.[17] Similarly to that study, we now observed that the prognosis had improved particularly in men resulting in the 2014–2018 HR for death in patients with PD being almost equal in men and women. In our earlier study we considered the overall increase in men's life expectancy in Finland a probable partial explanation to our findings. However, this does not seem to be the case since our current data show that the prognosis has particularly improved in male patients with PD. The reasons for the decline in Finnish early PD excess risk of death, and why it happened especially in men, are unknown. A potential (partial) explanation for the falling excess mortality over time is improved identification of atypical parkinsonism over time.

Even when an increased risk of PD mortality has been reported, there are differences between studies in how it develops during PD. Similar to Korean data,[18] our results showed that the excess risk of death was already present during the first year after the PD diagnosis. On the other hand, in a Norwegian inception cohort study, it appears to have taken approximately 2 years after the diagnosis before the difference becomes discernible.[19] Interestingly, a recent UK study found that the mortality rate of patients with PD was even lower than that of controls during the first 2 years, although the lines crossed thereafter.[14]

These differences may result from methodological and/or population-specific factors. Most previous inception cohort studies have reported 1.3- to 1.5-fold higher mortality rates in PD patients, but three previous studies also found no difference.[2] Considerable variation in the nation-specific mortality risk of PD patients appears possible, and this might be due to differences in both environmental factors and the genetic background considering, for example, the often more severe course in *GBA1*-associated PD,[20] the prevalence of which is population specific.[21] Importantly, the UK study only included a population >50 years

of age, and the Israeli study only included people >40 years of age, while the Norwegian study did not report any age cutoffs or an age range.[14,15,19] This is pertinent since the patients with EOPD had the highest hazard ratio in our data and age at diagnosis overall inversely associated with the excess risk of death. Longitudinal data from Trondheim, Norway, also report that patients with PD onset before the age of 40 years have an over fivefold mortality compared to the general population.[22] Highly similar datasets from different populations are therefore needed for comparison before any firm conclusions on the subject can be made.

There are consistent data to show that certain clinical factors, most commonly higher age, cognitive defects and hallucinations, are correlated with increased mortality in PD.[19,23,24] The Clinical Frailty Scale also independently predicts inpatient mortality in older PD patients. In our data, age, male sex and comorbidity burden were associated with an increased risk of death. In PD patients, pneumonia is a common immediate cause of death, whereas cardio- and cerebrovascular insults and cancer are common underlying causes of death in PD. Additionally, in our data, the most common underlying causes of death were PD, cardiac and vascular causes, dementia and malignancies. While the causes of death were unavailable for the controls in the current study, our data are in line with previous reports showing moderate to modest proportions of vascular causes and malignancies, with more than one-third of the deaths attributed solely to PD.

In conclusion, Finnish PD patients were at an increased risk of death already at early stages of the disease, and the risk increase was inversely correlated with age at diagnosis. However, the risk diminished by more than one-third during the study period. International comparisons suggested possible population-specific differences but also remaining methodological challenges, and similar datasets from different populations are needed. The clearly increased early mortality risk in PD patients underlines the need for early neuroprotective interventions that could improve survival across the PD disease course.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

J.S.: 1A-C, 2C, 3A
V.K.: 1A, 2C, 3B
P.R.: 1A, 2C, 3B
V.K: 1B-C, 2A-B, 3B

Disclosures

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