Increased Mortality in Young-Onset Parkinson's Disease

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ABSTRACT

Objective  Few studies have followed Parkinson’s disease (PD) patients from the time of diagnosis to the date of death. This study compared mortality in the Trondheim PD cohort to the general population, investigated causes of death and analyzed the associations between mortality and age at disease onset (AAO) and cognitive decline defined as Montreal Cognitive Assessment (MoCA) score below 26.

Methods  The cohort was followed longitudinally from 1997. By the end of January 2020, 587 patients had died. Comparisons to the Norwegian population were performed by calculating standardized mortality ratios (SMRs). Survival curves were estimated using the standard Kaplan-Meier estimator, and multivariable Cox proportional hazard models were estimated to investigate associations.

Results  SMR was 2.28 [95% confidence interval (CI): 2.13–2.44] for the whole cohort. For participants with AAO 20–39 years, the SMR was 5.55 (95% CI: 3.38–8.61). Median survival was 15 years (95% CI: 14.2–15.5) for the whole cohort. Early-onset PD (EOPD) patients (AAO < 50 years) had the longest median survival time. For all groups, there was a significant shortening in median survival time and an almost 3-fold higher age- and sex-adjusted hazard ratio for death when the MoCA score decreased below 26.

Conclusion  PD patients with an AAO before 40 years had a more than fivefold higher mortality rate compared to a similar general population. EOPD patients had the longest median survival; however, their life expectancy was reduced to a greater degree than that of late-onset PD patients. Cognitive impairment was strongly associated with mortality in PD.

Keywords  Cognitive impairment; genetic; Early-onset Parkinson’s disease; Mortality.

Parkinson’s disease (PD) is the second most common neurodegenerative disorder. The prevalence increases from 0.5%–1% at the age of 65 years to 1%–3% after the age of 80 years. It is a heterogeneous, progressive disorder that is characterized by a variety of motor and nonmotor symptoms (NMSs).¹

The diagnosis of PD is based on the presence of motor symptoms such as bradykinesia, rigidity, and tremor, usually manifesting asymmetrically, and the positive response to dopaminergic therapy. NMSs in PD involve a multitude of functions, including disorders of sleep-wake cycle regulation, disorders of mood and affect, autonomic dysfunction, sensory symptoms, pain, and cognitive impairment.² Several studies have suggested that the impact of NMS on disability and health-related quality of life is higher than that of motor dysfunction, but less is known about the possible influence of NMS on mortality.³

The question of prognosis in terms of progression of motor
symptoms, disability, preservation of cognitive function, and mortality is of particular interest in early-onset PD (EOPD). A better understanding of the factors associated with the risk of mortality would enable a more accurate prognostication of patients, better information, improved health service planning, the identification of relevant outcome measures for clinical trials of putative disease modifying agents and better targeting of treatments.

Despite major advances in the understanding of its pathophysiology and genetics, many aspects of the prognosis of PD remain unclear. Our understanding of the natural history of idiopathic PD remains limited, and surprisingly little has been written about the natural evolution of symptoms and signs in PD late in life.

Recent natural history studies have shown widely varying mortality ratios, ranging from 0.9 to 3.8. Variability in disease duration has been ascribed to differences in study methodology, follow-up duration, patient demographics, and sample size.

According to a recent review and meta-analysis of studies of mortality, 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.

Since studies of mortality have been clinical studies with limited external validity, there is a need for further high-quality studies. Such studies are recommended as a minimum to be inception cohorts, be community based, have expert confirmation of diagnosis using validated diagnostic criteria, have no exclusion criteria other than those relating to accuracy of diagnosis, have prospective follow-up, measure long-term outcomes, and use diagnosis as a baseline for measurements.

Few PD mortality studies have examined large study cohorts with detailed baseline characteristics and prospectively collected data. Although both PD and dementia have separately been associated with increased mortality, few studies have investigated to what extent dementia contributes to the observed shorter survival in patients with PD.

The aims of this study were to compare mortality in the Trondheim PD cohort to the general population, investigate causes of death and analyze the associations between mortality and age at disease onset (AAO) and cognitive impairment.

**MATERIALS & METHODS**

**Study population (The Trondheim PD Cohort)**

Since 1997, we have prospectively collected data on baseline PD characteristics in sequential new referrals, over the age of 22 years, to the Department of Neurology at St. Olav’s Hospital in Trondheim. The main cause for establishing this cohort was to conduct genetic studies in PD. Some of the patients had been followed since 1980. A handful of patients had PD onset before 1980. In these patients, critical information regarding the onset of disease was extracted from the medical records. Eighty percent of the participants resided within Trondheim or within 50 miles. The remainder lived in the surrounding district within a 200-mile radius and less than 5% were from other parts of the country. The clinical diagnosis of PD required the presence of at least two of three cardinal signs (resting tremor, bradykinesia, and rigidity), improvement through adequate dopaminergic therapy and the absence of atypical features or other causes of parkinsonism. Diagnostic re-evaluation was reviewed regularly over the period to ensure diagnostic accuracy, and there were no exclusion criteria other than young age (i.e., 22 years or younger). Patients with atypical disease presentation were excluded, mainly after autopsy.

The autopsy rate was low in regular PD patients. Patients carrying disease-causing mutations in the LRRK2, GBA, PRKN, and PINK1 genes were prioritized for autopsy.

By the end of January 2020, the Trondheim PD cohort contained 1,221 participants (65% males).

**Clinical assessment**

A structured interview on disease and medication history and a general physical examination were performed. All patients were screened for genetic PD mutations (LRRK2, PRKN, PINK1, SCNA, GBA). The patients reported that they had first- and/or second-degree family members with PD in 15% of cases. The majority of the participants came to routine neurological examinations at least once yearly. Assessment of motor symptoms was performed based on the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr rating scale (H&Y). Cognitive function was evaluated according to the Movement Disorder Society level 1 criteria, using the Montreal Cognitive Assessment (MoCA) test with 25 points as a cutoff for cognitive impairment without further distinction between mild cognitive impairment in the context of Parkinson’s disease (PD-MCI) and Parkinson’s disease dementia (PD-D).

We further assumed that there was no reversion back to normal cognition. For those participants who were evaluated with the Mini-Mental State Examination (MMSE), an MMSE-MoCA conversion table was used to convert the scores.

Death certificates for the participants were linked to the Norwegian Cause of Death registry and the Cancer Registry of Norway. We investigated the causes of death for both the entire Trondheim PD cohort and those with EOPD.

**Statistical analysis**

Descriptive statistics are presented using the mean and corresponding standard deviations for continuous variables and absolute and relative frequencies for categorical variables. In the survival analyses, patients were followed from the date of in-
clusion to the date of death or administrative censoring (January 31, 2020). For most patients, the time of inclusion was close to the date of diagnosis, but for some patients, the difference in dates could be up to several years. SMRs, comparing the observed number of deaths in the cohort to the expected number of deaths, were calculated. The expected number of deaths was calculated assuming that the cohort had the same all-cause mortality as the general population, matched by age, sex, and calendar year. Specifically, the person-years in the cohort were calculated separately by five-year age groups, sex, and calendar year (yearly intervals) and multiplied by the corresponding mortality rates in the general Norwegian population, obtained from publicly available statistics from Statistics Norway. The total number of expected deaths was then obtained by summing the expected numbers across all strata. We calculated SMRs stratified by AAO, sex, and MoCA score below 26 at 5, 10, and 15 years of disease duration. We calculated 95% confidence intervals (CIs) for the SMRs assuming a Poisson distribution. Survival was assessed by estimating standard Kaplan-Meier curves, also stratified by AAO, sex, and MoCA score below 26 at 5, 10, and 15 years of disease duration. Log-rank tests were used to assess differences in survival between groups. To investigate potential associations, we estimated multivariable Cox proportional hazard regression models, including age, sex, and MoCA scores as covariates. All statistical analyses were performed using STATA/MP 16.1 (Stata Corp., College Station, TX, USA).

This study was approved by the Ethics Committee of Central Norway (2011/1137), and informed consent was obtained from all participants.

RESULTS

By the end of January 2020, 587 patients had died (61% males). A summary of the 587 participants who died, and their demographic details are presented in Table 1.

The mean AAO was 62.0 ± 10.7 years (range: 25–88 years). The mean age of death was 78.0 ± 8.0 years (range 44.6–98 years), with a median survival of 15 years (95% CI: 14.2–15.5 years) for the whole cohort.

As presented in Figure 1 and Table 2, median survival differed between AAO groups. The median survival times in the AAO 20–39 group vs. AAO 80 plus groups were 32.5 years (95% CI: 23.5–36.5 years) and 7.0 years (95% CI: 5.0–8.5 years), respectively. Kaplan-Meier survival estimates stratified by AAO categories, show statistically significant difference in the median survival time ($p < 0.001$). AAO: age at disease onset.

Table 1. Demographic and clinical baseline characteristics in Parkinson’s disease patients who died ($n = 587$)

| Variable                  | Value   |
|---------------------------|---------|
| Male                      | 356 (61) |
| Age at disease onset, years | 62.0 ± 10.7 |
| Disease duration, years    | 15.6 ± 7.4 |
| Age at death, years        | 78.0 ± 8.0 |
| UPDRS motor score          | 33.4 ± 9.9 |
| Hoehn & Yahr stage         | 3.4 ± 0.8 |
| LEDD, mg                   | 584.5 ± 303.3 |

Values are presented as $n$ (%) or mean ± standard deviation. UPDRS: Unified Parkinson’s Disease Rating Scale, LEDD: levodopa equivalent dose.

Table 2. Median survival in Parkinson’s disease in relation to sex, AAO, and MoCA scores at 5, 10, and 15 years of disease duration

| Variable                  | No. subjects | Median survival (50%) | Standard error | 95% CI       |
|---------------------------|--------------|-----------------------|----------------|--------------|
| Sex                       |              |                       |                |              |
| Female                    | 231          | 15.4                  | 0.715172       | 14.1–16.7    |
| Male                      | 356          | 14.7                  | 0.391162       | 13.8–15.5    |
| Total                     | 587          | 15.0                  | 0.352951       | 14.2–15.5    |
| AAO, years                |              |                       |                |              |
| 20–39                     | 17           | 32.5                  | 2.195182       | 23.5–36.5    |
| 40–49                     | 53           | 25.4                  | 1.299788       | 20.2–26.2    |
| 50–59                     | 124          | 19.7                  | 0.661172       | 18.1–21.1    |
| 60–69                     | 225          | 14.7                  | 0.358565       | 13.7–15.2    |
| 70–79                     | 155          | 11.0                  | 0.323044       | 10.0–11.4    |
| ≥80                       | 13           | 7.0                   | 0.778888       | 5.0–8.5      |
| Total                     | 587          | 15.0                  | 0.352951       | 14.2–15.5    |
| MoCA at 5 years           |              |                       |                |              |
| ≥26                       | 212          | 13.8                  | 0.562305       | 12.3–14.5    |
| < 26                      | 133          | 5.1                   | 0.578612       | 4.4–6.4      |
| Total                     | 345          | 10.7                  | 0.415459       | 9.8–11.5     |
| MoCA at 10 years          |              |                       |                |              |
| ≥26                       | 98           | 13.5                  | 1.286934       | 11.4–15.9    |
| < 26                      | 114          | 5.2                   | 0.492788       | 3.9–5.8      |
| Total                     | 212          | 7.0                   | 0.633053       | 6.3–8.8      |
| MoCA at 15 years          |              |                       |                |              |
| ≥26                       | 60           | 11.2                  | 0.663940       | 9.5–13.6     |
| < 26                      | 101          | 4.5                   | 0.639255       | 3.6–5.6      |
| Total                     | 161          | 6.6                   | 0.783691       | 5.2–8.5      |

AAO: age at disease onset, MoCA: Montreal Cognitive Assessment, CI: confidence interval.
23.5–36.5 years) vs. 7 years (95% CI: 5–8.5 years) (p < 0.001), respectively. However, the differences were not statistically significant between the AAO 20–39 and AAO 40–49 groups or between the AAO 40–49 and AAO 50–59 groups.

A total of 87% (511/587) of the participants had available MoCA scores to assess whether there was a decrease in MoCA scores below 26 within the first 20 years of disease duration.

As presented in Table 2, median survival significantly differed in the patients with MoCA scores < 26 compared to those with normal scores at 5, 10, and 15 years of disease duration: 5.1 years vs. 13.8 years, 5.2 years vs. 13.5 years, and 4.5 years vs. 11.2 years (p < 0.001), respectively. Median survival did not significantly differ between females and males: 15.4 years vs. 14.7 years, respectively.

As presented in Table 3, multivariable analyses showed that participants with MoCA scores < 26 at 5, 10, and 15 years of disease duration had age- and sex-adjusted hazard ratios (HRs) for death of 2.60 (95% CI: 2.01–3.36), 2.95 (95% CI: 2.07–4.70), and 2.53 (95% CI: 1.71–3.74) (p < 0.001, respectively), compared to participants with MoCA scores ≥ 26 with the same disease duration. MoCA: Montreal Cognitive Assessment, HR: hazard ratio, CI: confidence interval.

Table 3. MoCA score as a clinical predictor of mortality in Parkinson’s disease

| Risk factor                  | Unadjusted HR (95% CI) | p-value | Adjusted for age and sex HR (95% CI) | p-value |
|------------------------------|------------------------|---------|-------------------------------------|---------|
| MoCA < 26 at 5 years         | 3.84 (3.03–4.88)       | < 0.001 | 2.60 (2.01–3.36)                    | < 0.001 |
| MoCA < 26 at 10 years        | 4.78 (3.42–6.67)       | < 0.001 | 2.95 (2.07–4.70)                    | < 0.001 |
| MoCA < 26 at 15 years        | 3.21 (2.21–4.66)       | < 0.001 | 2.53 (1.71–3.74)                    | < 0.001 |

Participants with MoCA < 26 at 5, 10, and 15 years of disease duration had an age- and sex-adjusted HR for death of 2.60 (95% CI: 2.01–3.36), p < 0.001, 2.95 (95% CI: 2.07–4.70), p < 0.001, and 2.53 (95% CI: 1.71–3.74), p < 0.001, respectively, compared to participants with MoCA score ≥ 26 and the same disease duration. MoCA: Montreal Cognitive Assessment, HR: hazard ratio, CI: confidence interval.

Table 4. SMRs in PD in relation to sex, AAO, and MoCA scores at 5, 10, and 15 years of disease duration

| Variable | Observed no. of deaths | Expected no. of deaths | SMR (95% CI) |
|----------|------------------------|------------------------|--------------|
| Sex      |                        |                        |              |
| Female   | 231                    | 89.87                  | 2.57 (2.30–2.86) |
| Male     | 356                    | 167.63                 | 2.12 (1.95–2.31) |
| Total    | 587                    | 257.50                 | 2.28 (2.13–2.44) |
| AAO, years |                      |                        |              |
| 20–39    | 17                     | 3.06                   | 5.55 (3.38–8.61) |
| 40–59    | 177                    | 46.71                  | 3.79 (3.38–4.23) |
| 60–69    | 225                    | 95.54                  | 2.36 (2.12–2.61) |
| 70–79    | 155                    | 100.95                 | 1.54 (1.39–1.69) |
| ≥ 80     | 13                     | 11.23                  | 1.16 (0.95–1.40) |
| MoCA at 5 years |                  |                        |              |
| ≥ 26     | 214                    | 93.62                  | 2.29 (2.04–2.55) |
| < 26     | 149                    | 59.25                  | 2.19 (2.19–2.87) |
| MoCA at 10 years |                 |                        |              |
| ≥ 26     | 99                     | 42.57                  | 2.33 (1.94–2.77) |
| < 26     | 133                    | 61.56                  | 2.16 (1.92–2.43) |
| MoCA at 15 years |               |                        |              |
| ≥ 26     | 60                     | 28.39                  | 2.11 (1.67–2.63) |
| < 26     | 129                    | 64.36                  | 2.00 (1.75–2.28) |

Mortality in the PD cohort was more than two times higher than expected, given the mortality in the whole population, with an SMR of 2.28 (95% CI: 2.13–2.44). Mortality in the PD cohort for the AAO 20–39 years group was more than five times higher than expected, given the mortality in the whole population, with an SMR of 5.55 (95% CI: 3.38–8.61). Mortality in the PD cohort was slightly higher in females (SMR: 2.57; 95% CI: 2.30–2.86) than in males (SMR: 2.12; 95% CI: 1.95–2.31); however, the difference was not statistically significant. SMR: standardized mortality ratio, PD: Parkinson’s disease, AAO: age at disease onset, MoCA: Montreal Cognitive Assessment, CI: confidence interval.
pants defined as EOPD, death records were available for 73% (51/70). PD was identified as the underlying cause of death for 39% (20/51), 16% (8/51) of deaths were attributable to cardiovascular disease, 10% (5/51) were due to malignant neoplasms, 6% (3/51) were due to pneumonia, and 4% (2/51) were due to cerebrovascular diseases. The remaining 25% (13/51) of deaths occurred due to other causes, including degenerative diseases in the central nervous system, hypertension, benign neoplasm, volvulus, external causes of morbidity and mortality, diseases of the urinary system, inflammatory polyarthritis and systemic connective tissue disorders.

The autopsy results confirmed that patients carrying disease-causing mutations in the PRKN and PINK1 genes had less cognitive impairment and a longer survival time than sporadic PD cases.14,15 Most patients with an LRRK2 G2019S mutation also had a better prognosis.

**DISCUSSION**

In this population-based observational PD study, we report follow-up data from more than 20 years on two key irreversible milestones: cognitive impairment and death. Based on our results, the SMR in the whole cohort was two times higher than that in the normal population.

To date, only a limited number of studies have followed the clinical features of PD patients with a disease duration of 20 years or more.16,17 As PD is a slowly progressive disorder, disease-related mortality would be expected to be highest in later stages reached after 15 or 20 years.18 Our results are consistent with the results from a systematic review by Macleod et al.19 from 2014 that included a meta-analysis of nine inception cohorts with a median follow-up duration of 9 years, which reported a mortality ratio of approximately 1.5 when compared to the general population. A cohort study of 237 patients over 38 years reported a similar SMR of 2.0, suggesting that the mortality ratio does not increase further beyond the 20-year horizon of observation.19

In contrast to Diamond et al.20 who found that a youthful age at onset was possibly associated with a more favorable prognosis than an older presentation, we found that patients with PD onset before 40 years had a mortality ratio of more than five when compared to the general population. The patients who developed PD at a young age lived for a longer period of time in absolute terms than older patients (Figure 1); however, their life expectancy was reduced to a greater degree than that of late-onset PD patients (Table 4). Our results are in line with Schrag et al.,4 who found that mortality in young-onset PD patients was increased twofold compared with the normal population.

In a recent study by Hoogland et al.21 looking at data from a cohort of newly diagnosed PD patients followed for at least 13 years, a significantly increased hazard of PD-related mortality was associated with early onset of PD and the presence of PD-MCI at baseline.

A total of 80% (409/511) of the participants developed MoCA scores below 26 within the first 15 years of disease duration and 85% (436/511) within the first 20 years of disease duration. Our results are consistent with the results of Skovnæk et al.14 reporting cumulative prevalence rates of dementia up to 80% after 20 years of disease duration, Hely et al.21 reporting dementia in 83% of PD patients after 20 years and Buter et al.23 reporting dementia in 60% during a 12-year study period. There are similar findings from other longitudinal studies.23,24 Marder et al.26 found that incidence is a much better measure of dementia in PD than prevalence because shortened disease duration makes it less likely to detect dementia in prevalence surveys.

The average age when MoCA scores dropped below 26 was 72.9 years, which is in line with results from the Sydney Multipurpose Older Australian Community Health Study.22,27,28 One of the participants developed cognitive impairment (MoCA scores below 26) in his 40s, while 26 developed cognitive impairment in their fifties.

With an almost threefold higher age- and sex-adjusted HR for death in participants with MoCA scores below 26, cognitive impairment and PD-D are associated with increased mortality (Table 3).

Similar results were reported by Forsaa et al.,29 who studied independent predictors of mortality in their population-based study of 230 participants (211 died) followed for 12 years. They found that in addition to AAO, chronological age, and motor severity, dementia was a major independent predictor of mortality with an almost twofold higher HR than patients without dementia. Limitations to this study included the relatively high age at baseline (73.5 years) and the relatively short follow-up time (12 years), both of which are factors that could have affected the results. In a recent study by Bäckström et al.30 studying 143 patients diagnosed with PD (77 died) and followed prospectively for up to 13.5 years, increased mortality in PD correlated with core parkinsonian symptoms (except tremor), olfactory dysfunction, and severity of striatal DAT imaging deficits, both in the putamen and in the caudate. However, mortality was not increased in patients with PD who did not have cognitive impairment at study entry, which led to the conclusion that patients with PD presenting with normal cognitive function seem to have a largely normal life expectancy.30 This is in contrast to our findings showing that participants with an AAO of 20–39 years had an SMR of more than five when compared to the general population. The distribution of the underlying causes of death was the same for participants with EOPD as for the whole cohort, with the exception of a higher percentage of cardiovascular disease in the participants with EOPD. Similar to the previously mentioned study by Forsaa et
Identifying factors predictive of cognitive impairment and PD-D is important to identify high-risk patients for clinical prognostication and stratification of participants in clinical trials. Finding the earliest features of cognitive involvement may provide insights into the underlying mechanisms of disease progression, ultimately leading to the identification of novel therapeutic targets.

Our best predictor for cognitive function was the results of the genetic tests. Being a homozygous or compound heterozygous carrier of autosomal recessive mutations, PRKN or PINK1 implied a low risk of cognitive impairment. In LRRK2 G2019S carriers, there was a clear correlation with the presence of Lewy bodies in the brain and intellectual performance, while GBA mutation carriers had a shorter time from onset of disease to the development of severe dementia.

The ability to predict outcomes in PD patients has many benefits, including individualized risk prediction with improved information for patients, personalizing treatments according to prognosis, and improving the design of clinical trials.

De Pablo-Fernández et al. performed a retrospective cohort study with clinical subtyping of 111 autopsy-confirmed patients with PD based on motor symptoms, RBD, and autonomic and cognitive dysfunction at diagnosis. The subtypes were diffuse malignant, mainly motor—slow progression and intermediate, corresponding to the criteria made by Ferenshtehnejad et al. They showed that subtypes clearly stratify the survival curves for time from diagnosis to particular outcomes, survival and different disease milestones such as regular falls, wheelchair use, dementia, and care placement. Based on their conclusion, clinical subtyping in PD is feasible in clinical practice and provides accurate estimation of disease progression and survival. McGhee et al. developed the outcome “dead or dependent,” where dependent refers to a score below 80 on the modified Schwab and England assessment and demonstrated its potential efficacy as a clinical trial outcome. Macleod et al. developed some survival models for predicting this outcome. However, before these models can be used for individualized or personalized medicine, they need further validation, improved prediction by, for example, adding biomarkers such as genetic or imaging factors, implementation for use in clinical practice, and evaluation of benefit versus harm.

Many of the prospective studies on survival in PD are limited by small study cohorts and a relatively short duration of follow-up, resulting in small numbers of observed deaths. Our study has several strengths, including a well-defined population-based study cohort followed prospectively for more than 20 years at one center, with diagnostic re-evaluation made regularly over the period to ensure diagnostic accuracy and diminish the possibility of including, in particular, parkinsonian plus syndromes, which are associated with worse prognosis and higher mortality rates. A retrospective design may cause biased effect size estimates and misleading association results. Studies in which the diagnosis of PD is based on death certification have low sensitivity for detecting PD. Within our cohort, PD was the most common cause of death (41%). The results are in line with Phillips et al., who found that in a group of patients, all diagnosed during life as having idiopathic PD, only 37% had PD coded as the underlying cause of death.

One limitation in our study was the lack of annual assessment of MoCA scores, which would have enabled us to make a more accurate determination of when MoCA scores decreased below 26 as well as determine the rate of reversion back to normal cognition.

Conclusion
The present study shows that patients with PD onset before 40 years had a more than fivefold higher mortality rate compared to a similar general population. Patients who develop PD at a young age will live for a longer period of time in absolute terms than older patients; however, their life expectancy is reduced to a greater degree than that of late-onset PD patients. For all groups, there was a significant shortening in median survival and an almost threefold higher age- and sex-adjusted HR for death when the MoCA score decreased to below 26, confirming that cognitive impairment is strongly associated with mortality in PD.

Conflicts of Interest
The authors have no financial conflicts of interest.

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