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# Long-term survival of Parkinson's disease

## A population-based study

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**Abstract** In a set of a population-based study, long-term survival of 59 prevalent PD patients was compared with that of individuals free of neurological diseases matched 1:2 by sex and age of enrolment. PD individuals, compared with reference subjects, showed a two-fold increased risk of death (OR 2.1; 95 % CI 1.4, 3.1). Among causes of death, pneumonia and cachexia were significantly more frequent among PD patients than among individuals free of neurological diseases. We confirmed in a long-term follow-up study an increased mortality among PD individuals compared with that of the general population.

**Key words** Parkinson's disease · mortality · prognosis · population-based study

## Introduction

Survival of individuals with Parkinson's disease (PD) has been extensively investigated using different methods. Most of the studies were based on case series or used routine mortality statistics to compare survival of PD individuals with that of the general population. These study designs are characterized by an incomplete case ascertainment. Few population-based studies compared mortality of PD patients with that of the general population [1, 2, 5–8]. However, only a few of them estimated long-term survival of individuals with Parkinson's disease [5, 7]. In the present study we compared, after an extended follow-up of 13.5 years, the survival of a cohort of PD patients with the survival of referent subjects identified from the same population in a previous door-to-door prevalence survey [8].

## Patients and methods

Survival, after an extend follow-up (30 April 2001), was determined in a cohort of patients identified during a large scale door-to-door prevalence survey (the Sicilian Neuroepidemiologic Study – SNES) [8]. The SNES study, through means of a two phase door-to-door approach, estimated the prevalence of Parkinson's disease (PD) among residents of three municipalities (Riposto, Catania province; Santa Teresa Riva, Messina province; Terrasini, Palermo province) at prevalence day (1 November 1987). During the first phase, a structured questionnaire, including some simple tasks, was administered by medically trained interviewers to the population. In the second phase, study neurologists, using specific diagnostic criteria, evaluated individuals who screened positive in the first phase. PD diagnosis required, in individuals who were not receiving any antiparkinsonian drug, the presence of at least 2 of 4 cardinal signs (rigidity, resting tremor, bradykinesia, and impaired postural reflexes), while only one sign was necessary to confirm the diagnosis in individuals with documented positive responsiveness to treatment with levodopa or dopaminomimetics.

At the end of the prevalence survey, each PD subject was matched by age (± 1 year), gender, and municipality of residence to two individuals free of neurological diseases, randomly selected from all residents included in the Sicilian survey. When more than two potential

reference subjects were available for a given case, 2 of them were selected by means of a table of random numbers.

Vital status data were obtained from the public record office of the municipalities of residence of PD individuals and referent subjects. For deceased individuals death certificates with causes of death were obtained from the Local Health District. Mean length of follow-up was estimated as the mean time elapsed from date of interview to date of death, or the end of the study.

### Statistical analysis

When vital status or date of death of a component of the triplet (the case or one of the two corresponding referent subjects) were not determined, the individual was not included in the analysis requiring the missing information.

Relative risk was used to compare the risk of death among cases and referent subjects. Kaplan-Meier estimates were used to construct long-term (13.5 years) survival curves. Estimates were calculated including only those who were still alive at last follow-up or if dead, whose date of death was known. The statistical difference between groups was tested with the log-rank test. Influence on survival was evaluated stratifying PD and reference subjects by: gender, age at enrolment (categorized as ≤ 75 years and > 75 years), age at PD onset, duration of PD, stage of the disease according to the Hoen-Yahr scale (≤ 2 and > 2 score points), and PD duration. Age at PD onset, defined as the age at which the patient first noted one of the cardinal signs (tremor at rest, rigidity, bradykinesia, and impaired postural reflexes), was categorized as < 68 years and ≥ 68 years, in accordance with the median distribution of cases. Duration of PD was defined as the lag time between the onset of symptoms and the age of enrolment and categorized as ≤ 5.5 years and > 5.5 years, according to the median distribution of PD individuals.

As information regarding Hoen-Yahr scores after 1 November 1987 were not updated, data regarding the stage of the disease were those at prevalence day. The use of levodopa was not included in the analyses. We could not in fact assume that the drug was continuously taken by the patients during the period 1987–2001 and therefore inferences about the results would have been unreliable. Causes of death reported in the death certificates were classified in the following groups: heart disease, cerebrovascular disease, cancer, pneumonia, and cachexia. The group "other causes" is a miscellaneous group, including all other causes mentioned in the death certificates.

Cox proportional hazards model was used in a univariate analysis to estimate RR for the main outcome measure (death) in the different strata. RR was then adjusted for sex, age at enrolment, age at PD onset, and HY score.

## Results

Fifty-nine PD patients and 118 PD free individuals were included in the first study. Because of the rigid matching, the age and sex distributions were similar in reference subjects. Thirty-three (55.9 %) of the 59 patients were female. The median age of PD patients on the day of enrolment (1 November 1987) was 74.2 years for males (75.0 years for referent subjects) and 74.9 years for females (74.0 years for reference subjects). Median PD duration on 1 November 1987, was 5.5 years.

As by the end of the study (30 April 2001) we were not able to determine living status for 1 case and 2 reference subjects, they were excluded from the analyses. The final cohort consisted of 58 PD individuals and 116 PD free individuals. Forty-six cases (79.3 %) and 70 reference subjects (60.3 %) had died at follow-up ($p = 0.01$). Date of death was not identified only for one reference subject. The mean length of follow-up was 92.6 months for 58 cases and 119.8 months for 115 PD free individuals ($p < 0.001$). No significant difference was observed either for mean age at death (82.4 years for 46 cases and 83.7 years for 69 reference subjects; $p = 0.3$). A highly significant difference was observed between the survival of cases and reference subjects (Log-Rank test: chi-square 10.75; df 1; $p < 0.001$). Fifty percent of PD patients survived 81.7 months, while a survival of 89.0 months was observed for the same cumulative percentage of the reference population.

The results of the univariate analyses for the selected variables are shown in Table 1. At multivariate analysis PD individuals had a two fold increased risk of death compared with referent subjects (adjusted OR 2.1; 95 % CI 1.4, 3.1).

Regarding causes of death only pneumonia and cachexia showed a significant difference between individuals with PD and individuals free of neurological diseases (Table 2).

Fig. 1 and Fig. 2 show the cumulative survival probability of PD individuals compared to referent population.

## Discussion

In this study we observed a two-fold increased risk of death in PD individuals over that of the general population.

Our results are consistent with those reported in the previous survey evaluating mortality of the same cohort of patients after 8 years of follow-up [8]. A difference between the two follow-up studies was found in the gender strata. Contrarily to the previous survey carried out in the same population, in the present study we found that women affected by PD had a slightly increased risk of death over men with PD. This discrepancy, consistent with the debate whether gender can be considered a prognostic factor [3, 4, 9], could be, however, due to chance because of the small numbers.

Interestingly, despite the more advanced stage of disease, risk of death for PD individuals calculated in the present study is not different from that obtained in the previous follow-up. This may suggest that in our cohort the progression of the disease is not associated with an increased risk of death. Also, age-dependent pathological conditions might influence in the same way survival of PD and PD free individuals.

Few population based studies compared long-term survival of PD patients with that of the general population. Their results are similar to those observed in our study, the risk of death ranging from 1.6 [5] to 2.5 [7].

Our study has a number of strengths. First the study

**Table 1** Univariate analysis for the association between PD survival and some disease-related variables

| Sample or stratum | Cases | | | | Referents | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. at risk | No. of deaths (%) | Median length of follow-up (range)* | Mean length of follow-up (± SD)* | No. at risk | No. of deaths (%) | Median length of follow-up (range)* | Mean length of follow-up (± SD)* | Univariate analysis (95% CI) p value |
| Total sample | 58 | 46 (79.3) | 82.2 (8.2, 164.3) | 92.6 (± 50.2) | 116 | 70 (60.3) | 137.7 (12.9, 164.3) | 119.8 (± 48.7) | 1.8 (1.3, 2.7), p = 0.001 |
| By sex | | | | | | | | | |
| Men | 26 | 22 (84.6) | 72.6 (8.2, 164.3) | 83.4 (± 51.6) | 51 | 36 (70.6) | 120.4 (14.1, 164.3) | 112.4 (± 48.3) | 1.8 (1.0, 3.0), p = 0.04 |
| Women | 32 | 24 (75) | 86.0 (33.7, 164.3) | 100.0 (± 48.6) | 65 | 34 (52.3) | 158.9 (12.9, 164.3) | 125.8 (± 48.5) | 1.9 (1.1, 3.2), p = 0.02 |
| By age at enrolment | | | | | | | | | |
| ≤ 75 years | 30 | 19 (63.3) | 122.8 (8.2, 164.3) | 110.7 (± 55.7) | 61 | 25 (41) | 164.3 (14.1, 164.3) | 134.8 (± 46.8) | 1.9 (1.1, 3.5), p = 0.03 |
| > 75 years | 28 | 27 (96.4) | 70.5 (9.6, 164.3) | 73.1 (± 35.1) | 55 | 45 (81.8) | 102.3 (12.9, 164.3) | 102.9 (± 45.5) | 2.3 (1.4, 3.8), p = 0.001 |
| By age at PD onset | | | | | | | | | |
| < 68 years | 27 | 16 (59.3) | 117.4 (8.2, 164.3) | 107.4 (± 56.8) | 54 | 24 (44.4) | 164.3 (29.5, 164.3) | 135.0 (± 41.9) | 1.7 (0.9, 3.3), p = 0.1 |
| ≥ 68 years | 31 | 30 (96.9) | 77.0 (9.6, 164.3) | 79.6 (± 40.4) | 62 | 46 (74.2) | 109.7 (12.9, 164.3) | 105.1 (± 50.4) | 2.0 (1.3, 3.3), p = 0.003 |
| By HY score | | | | | | | | | |
| ≤ 2 | 28 | 20 (71.4) | 121.0 (25.2, 164.3) | 111.6 (± 48.7) | 56 | 32 (57.1) | 151.0 (37.7, 164.3) | 131.5 (± 41.2) | 1.6 (0.9, 2.8), p = 0.1 |
| > 2 | 30 | 26 (86.7) | 68.4 (8.2, 164.3) | 74.8 (± 45.6) | 60 | 38 (63.3) | 119.4 (12.9, 164.3) | 109.1 (± 52.8) | 2.2 (1.3, 3.6), p = 0.002 |
| By PD duration | | | | | | | | | |
| ≤ 5.5 years | 29 | 24 (82.8) | 81.5 (8.2, 164.3) | 91.0 (± 53.4) | 57 | 32 (56.1) | 146.9 (12.9, 164.3) | 123.9 (± 49.5) | 2.1 (1.3, 3.6), p = 0.005 |
| > 5.5 years | 29 | 22 (75.9) | 87.6 (27.2, 164.3) | 94.1 (± 47.8) | 59 | 38 (64.4) | 123.0 (19.7, 164.3) | 116.0 (± 48.0) | 1.6 (0.9, 2.7), p = 0.09 |

* results are expressed in months

**Table 2** Common causes of death among cases and controls

| Causes of death | Cases # of deaths (%) | Controls # of deaths (%) | p* |
|---|---|---|---|
| All causes | 44 | 68 | |
| Heart disease | 12 (27.3) | 24 (35.3) | 0.7 |
| Pneumonia | 12 (27.3) | 5 (7.4) | 0.007 |
| Stroke | 9 (20.5) | 15 (22.1) | 1.00 |
| Cachexia | 4 (9.1) | 1 (1.5) | 0.08 |
| Cancer | 3 (6.8) | 5 (7.4) | 1.0 |
| Others | 4 (9.1) | 11 (16.2) | 0.3 |
| Unknown | – | 7 (10.3) | – |

* Difference was calculated by $\chi^2$ analysis

design allowed the identification of individuals affected by PD, who would not have ever been diagnosed using methodologies different from the door-to-door approach. Second, the diagnosis of PD and PD-free status of referent individuals were confirmed at second visit carried out 8 years after the screening procedure. Finally, the source of information, about living status and causes of death of the cohort was the same in the previous study [8], increasing the comparability of the two surveys.

The above mentioned limited clinical and prognostic significance of HY score is a limitation of our study. A further methodological weakness is represented by the inclusion of prevalent cases. However, the results of the analysis stratified by PD duration (prevalent vs. "quasi incident" cases) do not support the possibility of an overestimation of the risk of death among PD individuals.

In our study, a PD diagnosis was reported only by two death certificates. This further outlines the difficulties in interpreting results of investigations on PD survival, which are based on official mortality statistics.

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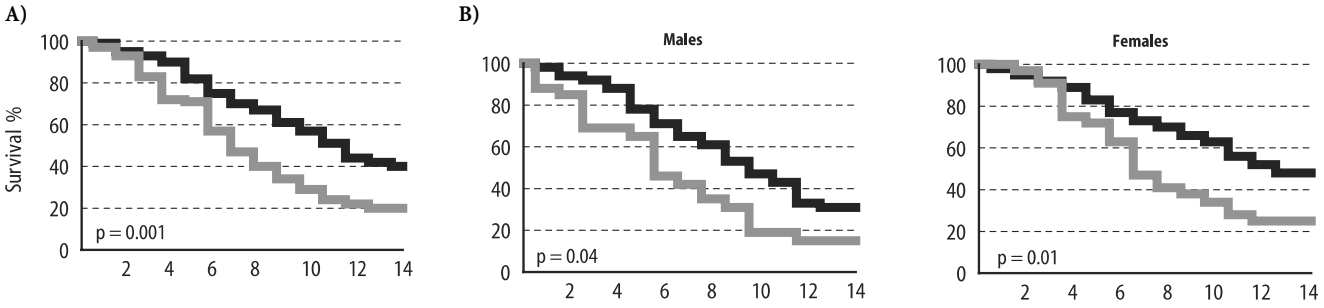
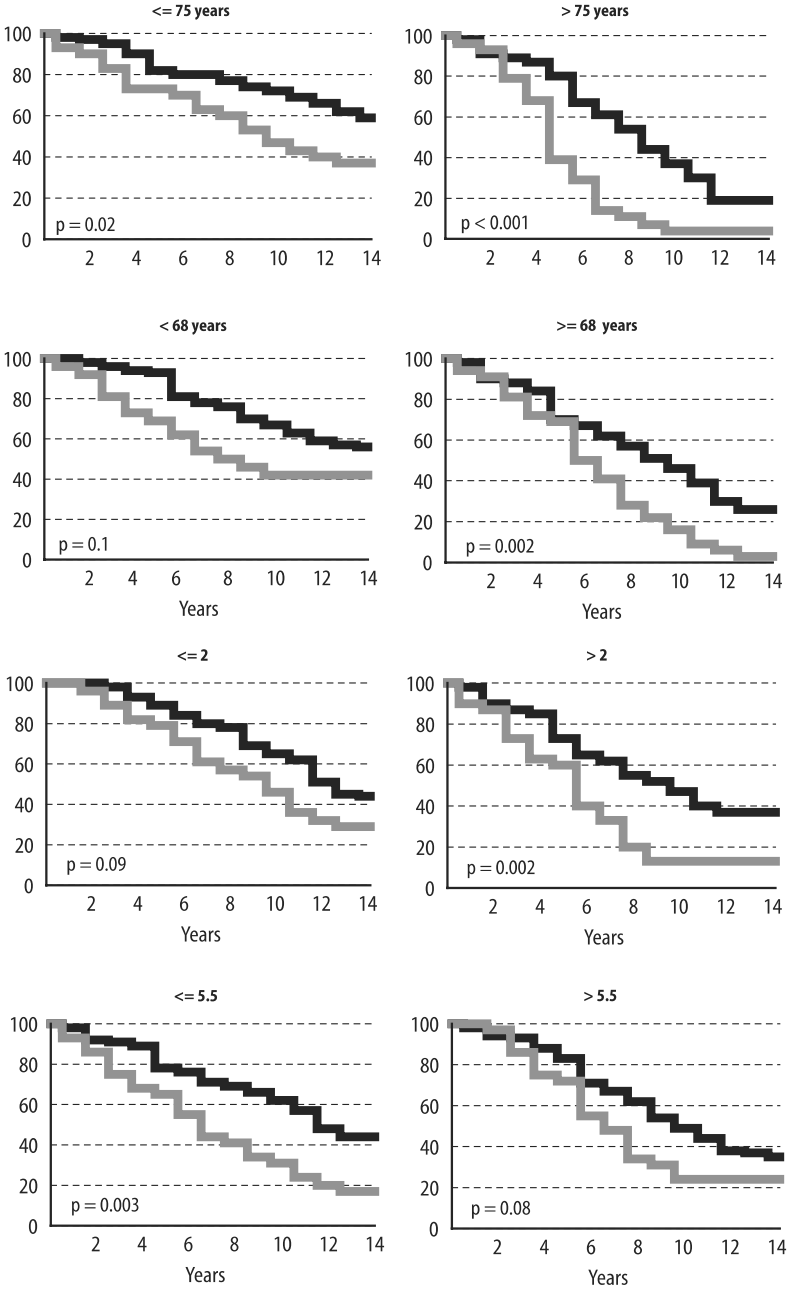



**Fig. 1** Cumulative survival probability for PD individuals and reference subjects. **A)** whole cohort; **B)** stratified by gender

**Fig. 2** Cumulative survival probability for PD individuals and reference subjects. **A)** by age at 1 November 1987; **B)** by age at PD onset; **C)** by HY score; **D)** by PD duration



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