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Research Article

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Posted Date: October 22nd, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11089032/v1>

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Additional Declarations: No competing interests reported.

Survival of patients with Parkinson's disease: a 19-year survey

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Abstract

Objective: Long-term treatment outcomes and prognosis for Parkinson's disease (PD) remain poorly understood. We analyzed the Clalit Health Service (CHS, covering ~50% of the Israeli population) registry data of Parkinson's disease (PD) patients diagnosed in 2002 and followed until 31/12/2021.

Methods: Observed survival was calculated by counting the number of PD patients who were alive, deceased, or censored. Expected survival and relative survival rates (RSR) were calculated by comparing a PD patients cohort to a matched cohort in the general population, in order to estimate survival rates and median survival time (MST).

Results: In total, 3,585 patients with PD were diagnosed in 2002, and their RSRs progressively decreased from 74.6% compared to 84% for the non-PD cohort at 5 years, to 48.6% vs. 61.8% at 10 years, and to 25.1% vs. 37.6% at 19 years, respectively. The RSR were consistently lower in the males vs. females. The MST for the patients with PD ≥ 60 years of age was 10.7 years for males and 13.8 for females.

Conclusion: The outcome of PD is characterized by a poor prognosis in all patients and a shorter MST in patients aged 60–69 years compared to the general population. This low survival likely reflects the limitations of current symptomatic therapy.

Introduction

Levodopa/carbidopa and levodopa/benserazide, like other antiparkinsonian drugs are the mainstays of current symptomatic treatment for Parkinson's disease (PD). There is scarcity of studies that analyzed survival rates of patients with PD in general and even fewer analyses of disease durations exceeding 15 years. Previous studies that addressed this issue relied primarily upon mortality data, with the impact of the pathology on survival ratio having been only indirectly considered. For example, the classic study by Hoehn and Yahr [1], which covered the period from 1949 to 1964 and included 802 cases of PD, preceding to levodopa therapy found a mortality rate of 42.4% among those patients. This percentage was 3 times higher than in the general population matched for age, sex, and race. Those authors concluded that “Parkinsonism substantially shortens life regardless of the age at onset”. According to the research by Hely et al. [2], which began between 1984 and 1987 and lasted 2 decades, the mortality rate among patients with PD was 74%. Mortality trends were characterized by a decline in the first 3 years of levodopa therapy, but subsequently exceeded similar rates in the general population. By the end of their study, levodopa treatment proved ineffective in most participants due to progress of dementia and autonomic impairment.

Since 2000, Clalit Health Services (CHS), Israel's largest health insurance fund, which covers more than one-half of the population, has maintained an anonymous registry of PD patients, which includes dates of diagnosis, types of treatment, dates of last contact, and dates of death. The aim of the present study was to analyze the 19-year relative survival rate (RSR) of patients with PD whose treatment consisted of levodopa and/or other dopaminergic drugs as well as to determine their median survival time (MST). This analysis was conducted from 2002 to 2021

and designed to assess the potential of symptomatic PD therapy in improving patient life expectancy.

Methods

Design and data source

This longitudinal study involved a cohort of patients newly diagnosed with PD whose data were provided by CHS. Identification of the PD cases was based upon ICD-10 diagnostic codes assigned by CHS neurologists, followed by the prescription of dopaminergic therapy. A detailed description of the PD case assignment methodology has been reported elsewhere [3]. Briefly, information was extracted from the CHS main research platform, which is powered by MD Clone (<https://www.mdclone.com>). The CHS Data Science Center at the Kaplan Medical Center extracted anonymized data on age, sex, dates of PD diagnosis, and types of pharmacological treatment from January 1, 2002, to December 31, 2021. Life expectancy data for the general population of Israelis in comparable age and sex groups were obtained from complete life tables published by the Israeli Central Bureau of Statistics.

Methodology and Statistical analysis

The RSR method compares the observed survival of patients with PD with the average life expectancy for the general population with similar demographic characteristics. After adjusting these data for general demographic trends, the method allows estimation of the extent to which survival in PD is reduced compared to expected norms. The RSR assesses survival by assuming PD to be the sole cause of death, making it effective for comparing groups with various background mortality risks unrelated to PD [4]. The use of the RSR does not require information on causes of death, but it does include all deaths among the study participants [5]. The MST

represents the time interval from the diagnosis of PD to the point at which one-half of the study cohort remained alive, thereby incorporating the effectiveness of therapies that were administrated against the background of the biological changes of the disease [6].

Survival analysis studies the time-to-death by measuring the lifespan of PD patients and processing censored data by measuring life expectancy among patients with PD and allowing for the inclusion of censored data. This approach reveals the proportion of patients still alive after specific time intervals (e.g., 5, 10, or more years), which is an indicator of the disease progression. Because this method measures rates, it allows for a more accurate assessment of the impact of risk factors on lifetime compared to mortality, which is a probabilistic value [7]. We determined the survival status of the patients with PD at monthly intervals from the date of diagnosis to the end of the study period. The annual number of survivors, deaths, and withdrawals for both sexes was calculated. This information along with life expectancy data was imported into the Seer*Stat program (Surveillance Research Program, National Cancer Institute, version 9.0.42.2, USA), whose algorithms used the Ederer II actuarial method. This yielded cumulative observed, expected, and relative survival rates. We also measured the MST for both males and females for age groups in which the RSR decreased to 50% throughout the study. The JoinPoint Regression - Surveillance Research Program (version 5.4.0) was used to analyze annual percentage changes (APCs) for long-term measures of observed and expected survival rates.

Results

In total, 3,585 patients with newly diagnosed PD (53% males) were registered in 2002 of whom 9 were censored at the end of the year. The patient cohort's median age was 77.4 years (IQR¹: 71-82.1), range: 20.4–102.7 for males and 77.2 years (IQR: 71.8-81.9), range: 26.14–100.7 for females. Most of the study participants (2,776 [77.4%]) were taking levodopa-based medications throughout the entire course of treatment. The remaining 809 patients (22.6%) were taking only dopamine receptor agonists, amantadine, and/or anticholinergics. The respective RSRs for the males and females of the entire cohort were 93.1% (95% CI: 91.3–94.5) and 95.4% (95% CI 93.7–96.7) at 1 year; 74.6% (95% CI: 71.3–77.6) and 84% (95% CI: 80.6–86.8) at 5 years; 48.6% (95% CI: 44.5–52.6) and 61.8% (95% CI: 57.1–66) at 10 years; 29.6% (95% CI: 25.7–33.7) and 44.3% (95% CI: 39.2–49.3) at 15 years, and 25.1% (95% CI: 21.2–29.2) and 37.6% (95% CI: 32.1–43) at 19 years. Only 292 patients (8.1%, 44.9% males) remained alive 19 years after PD diagnosis (**Table 1**). The RSR was lower in males than in females throughout the entire study period (**Table 1**).

The observed and expected survival rates (the numerator and denominator used to calculate the RSR) declined at a proportional rate between 2002 and 2020: the APC was -13.6% (95% CI: -13.9–13.2) and -11.9% (95% CI: -12.4–11.4) among the males and -6.3% (95% CI: -6.7–6.0) and -6.9% (95% CI: -7.1–6.8) among the females.

In males, a progressive reduction in mean life expectancy (MST) was observed depending on the age at PD onset. In the 60-69 age group, MST was 12.3 years, in the 70-79 age group, it was shortened to 9.4 years, and in the 80+ age group up to 7.8 years. In females, the

¹ Abbreviations: IQR, interquartile range; CI, confidence interval; APC, annual percent change

MST remained more stable: in the 60-69 group, it was 16.6 years, in the 70-79 group –11.9 years, and in the 80+ age group, it surprisingly was 14 years.

Compared to the life expectancy of the Israeli population, a clear shortening in both sexes was seen only in PD patients aged 60-69 years (Table 2).

The MST in women always exceeded the MST in men, regardless of age (Table 2). The MST for the entire cohort of patients with PD, regardless of age group, was 10.7 years for men and 13.8 years for women (Fig. 1).

Discussion

This study was designed to further our understanding of long-term survival among treated patients with PD by following a cohort for 19 years (from 2002 to 2021), the longest period of time for which the SEER*Stat algorithms are applicable (**Table 1**). The findings showed that the decline in RSR had already begun in the first month of observation and that it was progressive in both sexes and more rapid in males. Five years after PD diagnosis, approximately 75% of the males and 84% of the females had survived compared to the general Israeli population. After 10 years, this rate dropped to just over 50% for the males and 66% for the females. After 15 years, approximately 33% of males and about 50% of females of those expected to survive continued to do so. Finally, after 19 years following the PD diagnosis, only one-quarter of the initial number of surviving males (25.1%) and just over one-third of females (37.6%) of those expected to survive were still alive (**Fig 1**).

Seo et al.[8] followed the time to death of more than 10,000 patients with PD for 10 years and found a similar reduction in RSR to our data. Those authors reported that at 5 years after diagnosis, the RSR decreased to 71.9% in the males vs. 80.4%, in the females, and to 52.5% in the males vs. 62.5% in the females after 10 years. As such, both their study and ours agree upon

the 5- and 10-year survival rates for PD, which may serve as benchmarks for comparative analyses across different countries, regions, and periods. However, the predominant decrease in that Korean study occurred in the observed survival rates (averaged APC of 10.5% in males vs. 7.5% in females) compared to the expected survival rates (averaged APC of 4.3% vs. 2.9%, respectively), especially for females, reflecting the survival rates in the general Korean population. These data could indicate a widening “gap” between the life expectancy of those who developed PD and those who remained healthy in this study. In addition, since the RSR is calculated as the ratio of the observed survival of a group of PD patients to the expected survival of the corresponding population, if the decline in the numerator in this fraction was faster than the denominator, or conversely the decline in the denominator was slower than the numerator, the resulting RSR could be underestimated. In contrast to the Korean study, the progressive decrease in the RSR in our study was accompanied by a proportional reduction in both the observed and expected ratios.

Data similar to ours had been published in a study by Uitti et al [9] in which the 5-year survival rate of PD patients seen at the Mayo Clinic was 72%, 42% at 10 years, and 23% at 15 years, measured from the time of the first visit. This was lower than the survival probabilities in the general population, which were 78%, 58%, and 40%, respectively. Their study emphasized that although levodopa treatment significantly improved survival in patients with PD, it did not completely normalize mortality rates. Unlike our current work, their study did not analyze sex differences in survival.

PD is known to shorten survival, and our study more precisely quantified this effect compared to an age-matched control group in the Israeli population. Importantly, survival in PD patients was highly dependent on the age of disease onset. The earlier the onset of PD, the longer

the relative life expectancy of patients. In our study, those who developed the disease before age 60 had a life expectancy longer than the 19-year study period itself, and therefore, we were unable to determine their MST. However, while in the 60-69 age group, we observed significant differences between the MST in PD patients and the life expectancy of the general Israeli population, in the 70-79 and 80+ age groups, the differences between these values disappear (**Table 2**). This may mean that their PD, having begun late, did not have time to develop to a stage that seriously affects life expectancy, or their PD has acquired a more sluggish nature, when the majority of patients die not from PD, but from natural causes of aging or other random factors like people without this disease.

We also confirmed that even with modern therapeutic approaches, survival rates remained relatively low over a long-term follow-up, and were even comparable to those seen in PD patients in the late 1960's. Diamond et al [10] reported that the initiation of levodopa therapy in the early 1960's has resulted in a significant decrease in mortality and concluded that levodopa treatment, especially in the early stages of PD, had a beneficial effect on life expectancy, with survival time from onset of disease increasing by 4–5 years. Although the administration of levodopa early in the disease course prolongs the patient's life span [11], it has not been shown to be effective in slowing or halting neurodegenerative processes. The medications also reportedly had no effect on the progression of cognitive impairment, the development of dysphagia, postural disorders, or the incidence of falls [2, 12-15]. As a result, according to Hely et al [2], mortality among patients again exceeded that of the general population 15–20 years after the start of therapy. Supramaximal doses of levodopa in patients with late-stage PD were able to temporarily reduce the severity of rest tremor, but had no effect on axial disturbances or overall

motor improvement. Furthermore, the therapy was associated with a risk of side effects, such as drowsiness [16].

In the scientific literature, we found no evidence that dopamine receptor agonists, MAO-B inhibitors, COMT inhibitors, amantadine, or anticholinergics can prolong life in patients with PD [17, 18]. Thus, current symptomatic therapy for PD, which has demonstrated significant success in controlling motor symptoms, is limited in its effectiveness due to the progressive nature of the disease and the limited mechanisms of action of existing medications. These medications do not slow the death of dopaminergic neurons or inhibit the progression of PD, and eventually, according to our results, have no significant effect on the RSR and the MST in patients with PD.

Another issue of interest is the clear survival advantage in females with PD. This finding should stimulate further research into the neuroprotective effects of estrogens on the dopaminergic system, potentially slowing the progression of PD and explaining why the disease is more rapid in males. It has been suggested that declining estrogens levels during menopause can worsen PD symptoms, while hormone replacement therapy may help manage motor symptoms and reduce dementia [19]. Estrogen replacement therapy was reportedly safe and well-tolerated over 8 weeks in postmenopausal women with advanced PD and may be associated with improvement in motor symptoms [20-22]. Despite the possible effect of testosterone in PD progression, androgens have received less attention than estrogens [23]. A recent study found a lower risk of developing PD in patients undergoing androgen deprivation therapy for prostate cancer, which may indicate a neuroprotective effect of this therapy. [24]. Holmes et al.'s [25] experiments with a female rat dopaminergic neuronal cell line observed that adding testosterone exacerbated the damage to dopamine neurons exposed to oxidative stress. Their data showed that testosterone increased the expression of COX2 and apoptosis in dopamine neurons. Inhibiting

the NF- κ B and COX2 pathway with CAPE and ibuprofen, respectively, blocked testosterone's negative effects on cellular viability, indicating that the NF- κ B/COX2 cascade plays a role in the negative interaction between testosterone and oxidative stress on neuroinflammation in their murine model.

Recent genomic studies have highlighted the critical role of sex-linked genetic mutations on the X and Y-chromosomes in the pathogenesis of PD. Several genes located on the X chromosome are directly involved in the development of parkinsonian phenotypes, often affecting lysosomal degradation pathways and vesicular transport. One such gene is RAB39B (Xq28), which regulates intracellular vesicular transport. Mutations in this gene lead to loss of protein function, which causes impaired autophagy and subsequent accumulation of α -synuclein. Clinically, this mutation manifests as X-linked juvenile parkinsonism in males and, less commonly, in females, often accompanied by intellectual disability and severe Lewy body pathology [26-27]. A mutation in the ATP6AP2 gene (Xp11.4) leads to impaired lysosomal function and autophagy, and because the substantia nigra is highly sensitive to disruption of protein proteostasis, this leads to the death of dopaminergic neurons. The clinical phenotype of this condition is X-linked parkinsonism with spasticity [28]. A recent study suggested that the sex-determining region Y (SRY) gene, located on the Y chromosome, might play a direct role in the male brain. Overexpression or dysregulation of the SRY gene may increase the vulnerability of dopaminergic neurons to oxidative stress, potentially explaining why the male midbrain is more susceptible to PD triggers [29].

The main limitations of this study are that we could not account for the definiteness of the diagnosis of idiopathic PD based only upon the diagnosis of PD according to the ICD 10 CM code (G20) and the drug-tracing approach. Thus, it is possible that the inclusion of a number of

patients who, at the time of or before the diagnosis of PD, were diagnosed with vascular parkinsonism due to cerebrovascular stroke, traumatic brain injury, or a psychiatric illness previously treated with neuroleptic drugs, may have distorted the obtained results. The data we used were collected from various sources (specialized medical centers and outpatient settings across the country) and may vary in quality and completeness. Therefore, our conclusions based upon CHS-reported diagnoses may contain inaccuracies due to differences in healthcare practices and coding across different healthcare facilities. Our data did not include genetic information on mutations in the LRRK 2 gene and the GBA1 gene (the most common causes of hereditary PD in Israel), which may have different survival rates than those of patients with idiopathic PD. Our register-based study lacked specific clinical markers, such as PD stage although such omission is often acceptable in large population-based epidemiological survival studies of PD. Although our CSH database was extensive, it is possible that some PD patients had been missed when the diagnosis was not formally established or when patients were not receiving standard pharmacological therapy. We also did not have data on the actual date of PD onset, and we used the date of first registration of the disease in patients' medical records as a surrogate.

Conclusion

This study presents one of the longest reported follow-ups of patients with PD treated by standard symptomatic therapy. Its findings showed that 19 years after diagnosis, only 25.1% of those expected to live according to the life expectancy of the general population did survive among the males, as did 37.6% among the females. PD has had and continues to have a significant impact on survival rates and in reducing survival time. Therefore, since the life

expectancy of a healthy young person in Israel is 84-86 years [30], the difference between this figure and actual life expectancy (i.e., time lost by PD patient) is the greatest [31].

We suggest that this finding indicates that current symptomatic therapy has reached its limits of effectiveness, offering temporary relief of the disease's symptoms but not slowing its progression. This necessitates the search for new approaches to treating PD, based upon neuroprotection, neurorestoration, immunotherapy, and genetic engineering. The goal of these methods should considerably improve patient survival rates beyond compared to the results of the current study.

Author Contributions:

Yacov Balash: study concept and design; analysis and interpretation of data; drafting/revision of the manuscript for content. **Ronit Gilad:** revision of the manuscript for content.

Anda Eilam: revision of the manuscript for content. **Amos D. Korczyn:** analysis and interpretation of data; drafting/revision of the manuscript for content.

Acknowledgments

We would like to thank personnel of the Kaplan Medical Center's CHS Data Research Center and personally Tamar Zohar, for providing the primary data on Parkinson's disease patients. The authors are grateful to Esther Eshkol, MA, for editorial assistance.

Funding None.

Conflict of Interest

The authors have no conflicts of interest to declare.

Data Availability The primary data for the findings of this study are unavailable due to the CHS restrictions and requirements for anonymity.

Ethics approval

The Kaplan Medical Center Institutional Review Board in accordance with the Declaration of Helsinki approved this study (protocol number: KMC-0071-22). It was based upon anonymous databases and involved no direct interaction with patients. Informed consent was not required for this study, which used anonymized data.

Consent to publish: Not Applicable.

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Table 1 Observed, expected, and relative^a survival rates of patients with PD during a 19-year period of observation after diagnosis

Year	Number of cases at beginning of the calendar year		Number of deaths at the end of the calendar year		Number of deaths of the censored cases at the end of the calendar year		Survival rate at the end of the calendar year, %		Expected survival rate at the end of the calendar year, %		Relative survival rate at the end of the calendar year, % 95% CI	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
2002	1893	1683	242	159	0	0	87.2	90.6	93.9	94.9	93.1(93.3-94.5)	95.4(93.7-96.7)
2003	1651	1524	182	112	0	0	77.6	83.9	87.7	89.9	88.5(86.2-90.4)	93.3(91.1-95)
2004	1469	1412	167	103	0	0	68.8	77.8	81.9	84.8	84(81.3-86.4)	91.7(89-93.7)
2005	1302	1309	140	121	0	0	61.4	70.6	76.4	79.8	83(77.3-83)	88.5(85.4-90.9)
2006*	1162	1188	156	131	0	0	53.1	62.8	71.3	74.8	74.6(71.3-77.6)	84(80.6-86.8)
2007	1006	1057	117	100	1	2	47.0	56.9	66.5	70.0	70.6 (67.1-73.9)	81.2 (77.6-84.3)
2008	888	955	133	91	1	0	39.9	51.4	62.0	65.4	64.4(60.7-67.8)	78.7(74.7-82)
2009	754	864	95	82	1	1	34.8	46.5	57.8	61	60.1(56.3-63.7)	76.3(72.1-80)
2010	656	781	81	99	0	0	30.5	40.6	54	56.8	56.5(52.6-60.2)	71.6(67.2-75.5)
2011**	575	682	71	90	1	3	26.7	35.3	50.4	52.9	53(49-56.9)	66.6(62.1-70.8)
2012	503	589	72	80	0	1	22.9	30.5	47.1	49.3	48.6(44.5-52.6)	61.8(57.1-66)
2013	431	508	61	68	2	1	19.6	26.4	44.1	45.8	44.6(40.5-48.6)	57.6(52.8-62)
2014	368	439	68	50	0	1	16.0	23.4	41.1	42.4	38.9(34.9-43)	55.1(50.2-59.8)
2015	300	388	50	71	0	2	13.3	19.1	38.5	39.2	34.6(30.7-38.6)	48.7(43.8-53.4)
2016***	250	315	36	38	2	1	11.4	16.8	36.2	36.2	31.5(27.6-35.5)	46.3 (41.3-51.2)
2017	212	276	25	30	0	2	10.1	14.9	33.9	33.5	29.6(25.7-33.7)	44.3(39.2-49.3)
2018	187	244	19	28	0	2	9.0	13.2	38.1	31	28.4(24.4-32.6)	42.6(37.3-47.8)
2019	168	214	25	26	0	0	7.7	11.6	29.8	28.6	25.8(21.9-30)	40.5(35.1-45.9)
2020	143	188	11	27	1	0	7.1	9.9	27.9	26.4	25.1(21.2-29.2)	37.6(32.1-43)
Remainder	131	161	-	-	-	-	-	-	-	-	-	-

Abbreviation: CI, confidence interval.

^aThe relative survival rate is the quotient of the observed survival rate divided by the expected survival rate.

*5-year survival

**10-year survival

***15-year survival

Table 2. Median survival time of patients with PD according to the age groups at PD onset compared with life expectancy among healthy individuals (2002–2021).

Age at PD onset, years	Number of patients, (M/F)	Median survival time (MST), years		Life expectancy in the general Israeli population ²	
		Males	Females	Males	Females
60-69	500 (274/226)	12.3	16.6	18.5-19.3	24-26
70-79	1519 (769/750)	9.4	11.9	9-14.2	10-14.5
80+	1347 (722/625)	7.8	14	9.1	10
Total	3576 (1893/1683)	10.7	13.8	NA	NA

Abbreviations: NA, not applicable; MST, median survival time; PD, Parkinson's disease

² Data obtained from bulletins published by the Israel Central Bureau of Statistics

Figure 1. Decline in relative survival rate and median survival time in males and females at the end of each calendar year over 19 years.

