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Subthalamic nucleus deep brain stimulation in Parkinson's disease – survival and long-term results

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Subthalamic nucleus deep brain stimulation in Parkinson's disease – survival and long-term results

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

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Integrity Declaration

Eu, Alexandra Almeida Rodrigues*, abaixo-assinado, com o número mecanográfico* 201904857*, estudante do 6°ano do Mestrado Integrado em Medicina no Instituto de Ciências Biomédicas Abel Salazar, declaro, pela minha honra, absoluta integridade na elaboração desta Dissertação. Assim sendo, confirmo que não recorri à prática de plágio ou falsificação de resultados. Toda a informação retirada de outras fontes foi devidamente citada e referenciada. Ademais, declaro a inexistência de qualquer conflito de interesse pessoal ou financeiro envolvido neste projeto.*

AUTOR

Alexandra Rodrigues

(Alexandra Rodrigues)

Porto, 6 de abril de 2025

Dedicatory Message

Aos meus pais, Paulo e Natalina,

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pelo seu contributo e pela disponibilidade que sempre me ofereceu.

List of Abbreviations

CHUdSA Centro Hospitalar Universitário de Santo António

DRS-2 Dementia Rating Scale-2

EMM Estimated marginal means

GEE Generalized estimating equations

HR Hazard ratio

H&Y Hoehn and Yahr stages

CI Confidence interval

LEDD Levodopa-equivalent daily dose

MDS Movement Disorder Society

PD Parkinson's disease

Preop Preoperative

Postop Postoperative

STN-DBS Subthalamic nucleus deep brain stimulation

S&E Schwab and England activities of daily living scale

UPDRS Unified Parkinson's Disease Rating Scale

Resumo

Introdução: A estimulação cerebral profunda dos núcleos subtalâmicos (STN-DBS) é eficaz na doença de Parkinson (DP) avançada. Existem poucos estudos sobre mortalidade e resultados a longo prazo na DP tratada com STN-DBS.

Objetivos: Estudar a sobrevivência, os preditores pré-operatórios de mortalidade e os efeitos da STN-DBS a longo prazo em doentes com DP tratados no nosso Centro.

Metodologia: Realizámos uma análise retrospetiva dos dados dos doentes com DP submetidos consecutivamente a STN-DBS bilateral. O Kaplan-Meier e a regressão de Cox foram utilizados para estimar a sobrevida pós-cirurgia e para explorar preditores pré-operatórios de mortalidade. As *generalized estimating equations* foram aplicadas para explorar a evolução dos indicadores clínicos a longo prazo (até 15 anos) - *Unified Parkinson's Disease Rating Scale* (UPDRS)-I a IV, pontuação axial, *Schwab and England* (S&E), *Hoehn and Yahr* (H&Y) e dose equivalente de levodopa diária (LEDD).

Resultados: Foram incluídos 101 doentes (34.7% mulheres). Aquando da cirurgia, tinham 60 (52.5-64.5) anos de idade, 11 (9-14) anos de doença e LEDD de 1560 (1290-1875) mg. No seguimento pós-cirurgia faleceram 21 doentes (20.8%). A sobrevivência aos 5, 8 e 10 anos foi 96.6%, 90.5% e 85.1%, respetivamente. O tempo médio de sobrevivência estimado foi 166.1 meses (IC 95%: 154.9, 177.4). Idade mais avançada; pontuações mais elevadas na UPDRS-III em *OFF* e *ON* e axial em *ON*; e pontuação inferior na Dementia Rating Scale-2 foram preditores de mortalidade. Comparando com o *OFF* pré-operatório, verificou-se uma redução significativa das pontuações da UPDRS-III em *ON*-estimulação/*OFF*-medicação e da S&E em *OFF*, demonstrando um benefício sustentado da cirurgia em todo o seguimento, também objetivado na redução da LEDD e da UPDRS-IV. O benefício da cirurgia, comparando com o *OFF* pré-operatório, tende a diminuir para as pontuações da UPDRS-II em *OFF*, score axial e H&Y, em *ON*-estimulação/*OFF*-medicação. Quando realizada a comparação com as pontuações pré-operatórias em *ON*, verificou-se uma deterioração em todos os parâmetros.

Conclusões: A mortalidade encontrada (independente da causa) é relativamente baixa à semelhança de outras coortes. Os resultados são úteis na seleção de doentes para STN-DBS, podendo haver maior benefício em doentes mais jovens, com sintomas motores menos graves, que respondem à levodopa e com menor disfunção cognitiva. A STN-DBS tem impacto positivo a longo prazo no *OFF* no pré-operatório, função motora e independência, permitindo uma redução das complicações motoras e da medicação. Contudo, alguns sintomas, especialmente quando comparados com o *ON* no pré-operatório, agravam-se à medida que a doença continua a progredir.

Palavras-chave: Mortalidade, Estimulação cerebral profunda, Núcleos subtalâmicos, Doença de Parkinson, Longo prazo

Abstract

Background: Deep brain stimulation of the subthalamic nucleus (STN-DBS) is effective in advanced Parkinson's disease (PD). There are few studies on mortality and long-term outcomes in PD treated with STN-DBS.

Objectives: To study the survival, preoperative predictors of mortality and the effects of STN-DBS on the long-term PD patients treated at our Center.

Methods: A retrospective analysis of PD patients who consecutively underwent bilateral STN-DBS was carried out. Kaplan-Meier and Cox regression were used to estimate post-surgery survival and to explore preoperative predictors of mortality. The generalized estimating equations were applied to explore the long-term clinical outcomes (up to 15 years) - Unified Parkinson's Disease Rating Scale (UPDRS)-I to IV, axial score, Schwab and England (S&E), Hoehn and Yahr (H&Y) and levodopa equivalent daily dose (LEDD).

Results: 101 patients were included (34.7% women). At the time of surgery, they were 60 (52.5-64.5) years old, have 11 (9-14) years of disease duration and 1560 (1290-1875) mg of LEDD. In the follow-up, 21 patients died (20.8%). Survival rates at 5, 8 and 10 years were 96.6%, 90.5% and 85.1%, respectively. The estimated mean survival time was 166.1 months (95% CI: 154.9, 177.4). Older age; higher scores on UPDRS-III OFF and ON and on axial score in ON; and lower scores on the Dementia Rating Scale-2 were predictors of shorter survival. Compared to the preoperative OFF, a statistically significant reduction of the UPDRS-III in ON-stimulation/OFF-medication and S&E in OFF scores was determined, showing a sustained benefit of the surgery over the entire follow-up, also objectified with the reduction of LEDD and UPDRS-IV. The benefit of the surgery, compared to the preoperative OFF, tends to decline over time for the UPDRS-II in OFF, the axial score and the H&Y, in ON-stimulation/OFF-medication. Comparisons with the ON scores at baseline revealed a deterioration in all the parameters evaluated.

Conclusions: The observed mortality rate (regardless of cause) is relatively low and comparable to other cohorts. These results are useful in the selection of patients for STN-DBS, and there may be greater benefit in younger patients, with less severe motor symptoms, responsive to levodopa and with less cognitive disfunction. STN-DBS has a positive impact, at long-term, on OFF in the preop, motor symptoms, activities of daily living and independence, allowing the reduction of both motor complications and medication. However, some symptoms, especially when compared to the ON in preoperative, suffer a deterioration as the disease continues to progress.

Keywords: Mortality, Deep brain stimulation, Subthalamic nucleus, Parkinson's disease, Long-term

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Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder following Alzheimer's disease, with higher rates among older individuals and men [1, 2]. According to The Global Burden of Disease Study 1990-2019, over 8.5 million people worldwide are affected by PD [3].

The diagnosis of PD is clinically defined by the presence of cardinal motor symptoms – bradykinesia and rigidity or rest tremor – along with additional supporting and exclusionary criteria, which vary depending on the specific diagnostic guidelines employed, such as those from the Movement Disorder Society (MDS) and the United Kingdom Parkinson's Disease Society Brain Bank [4, 5]. PD patients manifest non-motor symptoms, which may predate the onset of classic motor symptoms, that include sleep disorders, cognitive impairment (involving frontal executive dysfunction, memory retrieval deficits, and dementia), neuropsychiatric disorders (e.g., depression, anxiety, apathy, and hallucinations), autonomic dysfunction (mostly orthostatic hypotension, urogenital dysfunction, and constipation), sensory abnormalities (specially hyposmia), pain and fatigue [6-8].

Over the years, the progression of PD is characterized by increasing disability due to the growing prevalence and severity of non-motor symptoms and treatment-resistant motor symptoms, such as freezing of gait, postural instability, falling, choking, and cognitive impairment, and the development of levodopa-induced motor complications, including motor fluctuations (the "ON" phenomenon with good therapeutic response and the "OFF" phenomenon with poorly controlled symptoms) and dyskinesias [9-12]. These complications are thought to be linked both to disease duration with dopamine depletion as well as to the dose of levodopa treatment [13, 14].

Even though symptomatic pharmacological treatment remains the main therapeutic strategy for PD, over the last two decades, deep brain stimulation of the subthalamic nucleus (STN-DBS) has become a steadily used therapeutic option for PD patients whose levodopa responsive motor symptoms cannot be adequately managed with medication, as well as for controlling levodopa-induced motor complications [15, 16]. Randomized controlled trials have demonstrated the superiority of STN-DBS over the best medical treatment in controlling motor complications and improving quality of life [17-20]. Long term studies [21-33] have demonstrated that STN-DBS leads to a sustained reduction in levodopa equivalent daily dose (LEDD) and continued control of motor symptoms. This effect appears to persist for up to 15 years of follow-up [31], with sustained benefit in dyskinesia and motor fluctuations, although the magnitude of the benefit tends to diminish over time. The patients' overall condition may deteriorate with time due to disease progression, with

evolution of axial symptoms and deterioration of non-motor symptoms, such as cognitive impairment [34, 35].

It is known that patients with PD have an increased risk of mortality compared to the general population [36]. Therefore, evaluating the effect of STN-DBS on the long-term survival of these patients has become a topic of interest. Previous studies have investigated the mortality of patients who underwent STN-DBS [25, 32, 37-47] and some compared the mortality with a control group [48-52], obtaining conflicting findings. Further research is needed to assess the long-term impact of this surgical treatment on the mortality of PD patients.

The aims of this study are to evaluate the overall survival and preoperative predictors of mortality and to describe the effects of STN-DBS on the long-term in PD patients treated at our Center.

Methods

Study design and participants

We carried out a retrospective longitudinal observational study of PD patients who consecutively underwent bilateral STN-DBS from January 2007 to March 2024 at *Centro Hospitalar Universitário de Santo António* (CHUdSA). A total of 104 patients with PD were selected for surgical treatment and were submitted to STN-DBS. The selection criteria for surgery included: diagnosis of PD according to the United Kingdom Parkinson's Disease Society Brain Bank Criteria [5]; at least 5 years of disease duration; a favorable response to levodopa, with an improvement of 30% or more; fluctuations or dyskinesias causing disability; levodopa resistant tremor causing disability; no contraindications in the neuropsychological assessment; absence of decompensated psychiatric disorder; no significant changes in magnetic resonance imaging; no medical conditions interfering with the procedure; a good understanding of the procedure and motivation for this treatment.

Three patients were excluded from the survival analyses due to missing or inaccessible data. Only patients with at least one postop evaluation were included in the exploration of the long-term clinical outcomes of STN-DBS. Thus, for these analyses, seven patients were excluded due to the inexistence of postoperative (postop) data.

The local ethical committee approved the study protocol.

Surgical procedure

The surgical procedure consists of the bilateral implantation of quadripolar electrodes (DBS 3389, Medtronic) in the subthalamic nucleus, under local anesthesia, using a Leksell® stereotactic system. The subthalamic nucleus is located using theoretical stereotactic coordinates in parallel with direct visualization of the subthalamic nucleus in magnetic resonance imaging, with minor

individual adjustments. Target and trajectory planning is done using dedicated software and both are co-registered with computed tomography imaging on the day of the surgery. Using Ben-Gun® equipment, the intraoperative microelectrode recording is done, with 3 to 5 simultaneous trajectories, 2 mm apart from each other. The intraoperative stimulation is performed with simultaneous neurological examination to select the best location for definitive implantation. In the same operating session, a programmable Internal Pulse Generator (Kinetra®, Medtronic; Activa PC®, Medtronic; Activa RC, Medtronic; and Gevia or Genus, Boston Scientific) is also implanted, under general anesthesia. Stimulation settings and medication are progressively adjusted, mainly until the third month after surgery, with only minor changes afterwards.

Data collection

Clinical records were reviewed up to October 2024 and the following data was collected: sex, education, age at surgery, age of onset (onset of first motor symptoms), disease duration at surgery, preoperative (preop) and postop clinical evaluations, pharmacological treatment, follow-up time and date of death (month and year), if applicable.

Patients underwent a preop evaluation and postop annual follow-up clinical assessments, in which the following measures were applied: the Unified Parkinson's Disease Rating Scale (UPDRS) parts I, II, III and IV, the Hoehn and Yahr stages (H&Y), and Schwab and England activities of daily living scale (S&E). Axial scores were derived from the UPDRS-III, by calculating the sum of UPDRS-III items 18 (speech), 27 (arising from a chair), 28 (posture), 29 (postural instability), and 30 (gait). UPDRS-III, axial scores and H&Y were evaluated in ON and OFF-medication states preoperatively and in ON-stimulation/OFF-medication postoperatively. UPDRS-II and S&E were applied with reference to the ON and OFF-medication states. At the preop, the ON-medication state was evaluated with an acute levodopa test and patients were at least 12 hours without antiparkinsonian medication.

The Dementia Rating Scale-2 (DRS-2) was applied in ON-medication state as part of the preop assessment [53].

Levodopa-equivalent daily dose (LEDD)[54] was determined preoperatively and at every visit of postop period.

Statistical analysis

Descriptive statistics were used for demographic and clinical characterization of the cohort.

The Kaplan-Meier curve was used to estimate survival time until death. The hazard ratios (HR) for death associated with demographic and clinical variables at baseline were estimated with Cox regression for each variable. The following variables were analyzed: sex, education, family history of PD and/or essential tremor, age at surgery, age of onset, disease duration at surgery,

isolated tremor as first symptom, tremor as one of the first symptoms, UPDRS-I score, UPDRS-II score (OFF-medication and ON-medication), UPDRS-III score (OFF-medication and ON-medication), axial score (OFF-medication and ON-medication), UPDRS-IV score, H&Y and S&E scores (OFF-medication and ON-medication), LEDD, and DRS-2 scores (Total and subscales Attention, Initiation/Perseveration, Construction, Conceptualization, and Memory). The significant variables obtained from the univariable analyses were combined in a multivariable Cox regression model to assess whether each variable remains an independent predictor of mortality after adjusting for other variables.

We used generalized estimating equations (GEE) to explore changes over time on UPDRS (including axial subscores), H&Y, S&E, and LEDD, from preop to subsequent follow-up measures. This model permits establishing a correlation between repeated measures from the same subjects while estimating population-averaged effects. Time (preop and available postop annual measures) was included as a predictor and the model applied used an identity link function with a normal distribution for the dependent variable. The working correlation matrix structure was specified as independent, assuming no correlation between measures within subjects.

The statistical analyses were performed using IBM SPSS Statistics version 29 and *p* values below 0.05 were considered statistically significant.

Results

Participants characteristics

The baseline clinical and demographic features of the PD patients who underwent surgery are displayed in **Table I**. From the 101 patients with PD who underwent STN-DBS included in this study, 35 (34.7%) were women and 66 (65.3%) were men. The median age at disease onset was 47 (41-53) years, the median age at surgery was 60 (52.5-64.5) years, and the median disease duration at surgery was 11 (9-14) years. At the time of surgery, the median LEDD was 1560 (1290-1875) mg. The median preop UPDRS-III motor scores ON-medication and OFF-medication were 14 (11-19) and 40 (33-45.5), respectively. The average follow-up time post-surgery was 104 (63.5-150.5) months. The number of patients assessed at 5, 8, and 10 years of follow-up was, respectively, 72, 41 and 28 patients.

Survival analysis and mortality predictors

During the follow-up, 21/101 patients (20.8%) died, 6 were women (28.6%) and 15 were men (71.4%). Their median age at PD onset was 50 (43-54) years and the median age at surgery was 62 (60-66) years. Their median disease duration until surgery was 12 (10.5-19) years. These deaths occurred 31-162 months after surgery (median = 129 months). The survival rates at 5, 8 and

10 years were 96.6%, 90.5% and 85.1%, respectively. The estimated mean survival time was 166.1 months (95% CI: 154.9, 177.4).

As shown in **Table II**, the time-dependent Cox regression analyses revealed that older age at surgery (HR = 1.124, 95% CI = 1.044–1.210, p =0.002), higher preop UPDRS-III score in OFF-medication state (HR = 1.044, 95% CI = 1.010–1.080, p = 0.012), higher preop UPDRS-III score in ON-medication state (HR = 1.116, 95% CI = 1.045–1.192, p = 0.001), higher preop axial score in ON-medication state (HR = 1.291, 95% CI = 1.045–1.596, p = 0.018), lower preop DRS-2 Total score (HR = 0.943, 95% CI = 0.896–0.992, p = 0.022), and the lower preop DRS-2 Attention Subscale score (HR = 0.829, 95% CI = 0.713–0.965, p = 0.016) were associated with poorer survival.

Survival was not significantly correlated with sex, education, family history of PD and/or essential tremor, age at PD onset, disease duration at surgery, isolated tremor as first symptom, tremor as one of the first symptoms, UPDRS-I score, UPDRS-II score (OFF-medication and ON-medication), axial score in OFF-medication state, UPDRS-IV score, H&Y and S&E scores (OFF-medication and ON-medication), LEDD, and DRS-2 Subscales Initiation/Perseveration, Construction, Conceptualization, and Memory.

For the multivariable Cox regressions, the results are shown in **Table III**. Age at surgery, as well as the UPDRS-III score in ON-medication were consistent and independent predictors of mortality. UPDRS-III score in OFF-medication remained statistically significant when the total DRS-2 score was removed.

Long-term outcomes

Through GEE analysis the estimated marginal means (EMM), and the parameter estimates for UPDRS scores (including axial subscore), H&Y, and S&E at each time point (baseline to 15 years of postop) were calculated (**Tables IV-X** and **Graphics 1-12**).

The UPDRS-I score decreased significantly (p = 0.011) on the first year postop, from an EMM of 1.60 (95% CI: 1.35-1.85) to 1.18 (95% CI: 0.89-1.48). This gain was no longer present on the second-year postop forward. The UPDRS-I score started to be significantly higher than preop in the eighth year after surgery.

Regarding the UPDRS-II score, when comparing the postop ON-stimulation/OFF-medication state with the preop OFF-medication state, the results demonstrated statistically significant (p < 0.05) gains over thirteen years of follow-up. However, the UPDRS-II score postop ON-stimulation/ON-medication state was significantly higher (p < 0.01) than the preop ON-medication state throughout the entire follow-up period.

For the UPDRS-III score, the comparison of the postop ON-stimulation/OFF-medication state score with the preop UPDRS-III OFF-medication state score showed a consistent and

significant reduction throughout the follow-up, up to 15 years ($p < 0.001$). The mean preoperative UPDRS-III in the OFF-medication state decreased by 62.4%, 52.5% and 42.1% at 1, 5 and 10 years, respectively. In comparison to the preop ON-medication state, the postop ON-stimulation/OFF-medication UPDRS-III score was significantly higher on the third year onward. The UPDRS-III score ON-stimulation/OFF-medication in the first year of postop was similar to the preop ON-medication state ($p = 0.973$).

For the axial score, when comparing the postop ON-stimulation/OFF-medication state with the preop axial OFF-medication state, the results demonstrated a statistically significant ($p < 0.001$) reduction over the first six years of follow-up. In parallel, the postop axial ON-stimulation/OFF-medication state was significantly higher ($p < 0.05$) than the preop ON-medication score throughout the entire follow-up period.

Regarding UPDRS-IV score, the postop score comparation with the preop score showed a sustained reduction over time ($p < 0.001$), suggesting a lasting effect of surgery on UPDRS-IV score.

For the S&E scale, when comparing the postop ON-stimulation/OFF-medication state with the preop OFF-medication state, the results demonstrated a statistically significant increase over time, suggesting a sustained effect of surgery on the independence of the patients relative to the OFF-medication state. However, in comparison to the preop ON-medication state, the postop ON-stimulation/ON-medication S&E score started to deteriorate significantly ($p < 0.05$) in the fourth year of postop.

For the H&Y stages, the comparison of the postop ON-stimulation/OFF-medication state with the preop OFF-medication state showed a statistically significant ($p < 0.05$) reduction over eleven years of follow-up. The postop ON-stimulation/OFF-medication state H&Y score was significantly higher (for most follow-up timepoints $p < 0.01$) in comparison to the preop ON-medication state. However, the H&Y score ON-stimulation/OFF-medication in the first year of postop was similar to the preop ON-medication state ($p = 0.939$).

LEDD changes

Table XI and **Graphic 13** present the results of the GEE analysis for LEDD changes. A sustained benefit of the surgery on LEDD reduction was determined over the entire follow-up period, with statistical significance ($p < 0.001$). The mean preoperative LEDD decreased by 67.3%, 60.3% and 62.0% at 1, 5 and 10 years, respectively.

Discussion

Twenty-one patients (20.8%) of a total of 101 patients submitted to STN-DBS died over a median follow-up period of 104 (63.5-150.5) months. Mortality rates reported in other studies with

a mean follow-up of at least seven years range from 16.0 to 43.0% [25, 32, 41, 43, 44, 46, 47, 50], which is comparable to our findings. The survival rate obtained for 5 years (96.6%) is somewhat similar to other studies (Rocha *et al.* [44] with 92.8%; Park *et al.* [32] with 95.0%; Kim *et al.* [46] with 81.1%). The survival rate at 10 years (85.1%) in our cohort is slightly higher than in other studies (79.0% and 59.7% for Park *et al.* [32] and Kim *et al.* [46], respectively). The population characteristics of these studies [32, 44, 46], including age of PD onset, age at surgery and disease duration at surgery were comparable to our cohort. It is important to compare cohorts with similar demographic characteristics due to the important contribution of age to mortality.

We identified older age at surgery, higher preop UPDRS-III score in both ON and OFF-medication states, higher preop axial score in the ON-medication state, and a lower preop DRS-2 Total score (especially lower preop Attention score) as predictors of mortality. From the multivariable analysis, the results suggest that older age at surgery is a consistent and independent predictor of mortality, along with higher preop UPDRS-III score in ON-medication state. Several other studies have also concluded that older age at surgery is associated with poorer survival [39-41, 43, 46, 47, 49]. Similar to other reports, more severe motor symptoms (i.e., higher UPDRS-III score) in OFF-medication state [39, 47], more severe axial symptoms in ON-medication state, [43, 45] and poorer cognitive function [37] at preop were associated with shorter survival post STN-DBS. Inconsistent with other studies, male gender [41, 42, 44, 46], older age at PD onset [45, 46], longer disease duration [44], and higher preop total LEDD [45] were not significant predictors of mortality in our cohort.

The relationship between older age at surgery and higher mortality observed in our study can be understood in the context of the patient's natural history, given that older individuals are more likely to die than younger ones [40]. Nevertheless, some studies concluded that older age at surgery was significantly associated with higher axial symptom severity after surgery [43], and the development of both falls and freezing of gait [47], which can be interpreted as contributing factors to the morbimortality of patients with late-stage PD [10].

Our results show that higher scores of UPDRS-III in both ON and OFF-medication states are associated with higher mortality. Preop UPDRS-III in ON-medication state as a predictor of mortality in PD patients treated with STN-DBS is a novel finding. The axial score in ON-medication, which is derived from the UPDRS-III, in the present study, was related to higher mortality. The association between the axial score in OFF-medication and survival did not reach statistical significance. Another study also reported an association between higher preop axial score in ON and greater postop axial symptoms and more falls in the long-term [55]. These set of findings suggest that levodopa-resistant axial symptoms are predictive of poorer prognosis. It is reasonable to speculate that more severe axial symptoms in ON-medication state, which correspond to the nonresponsive

symptoms to levodopa, reflect a more extensive PD pathology, involving structures other than the substantia nigra [56].

Similar to a previous report [37], poorer preop cognitive performance on the DRS-2, particularly in measures of attention, was a significant predictor of mortality in PD patients treated with STN-DBS. The literature has provided strong evidence that dementia is predictive of increased mortality in PD patients in general, regardless of the treatment [11, 57]. There are also reports that poor preop neuropsychological evaluation may increase the likelihood of greater cognitive decline after surgery, which is a known predictor of mortality [58].Previous studies also found that lower DRS scores are associated with lower postop benefits in quality of life[59] and that frontal dysfunction is associated with axial worsening in the long-term [55] in PD patients submitted to STN-DBS.

The present study analyzed all-cause mortality and cause of death was not available. Progression of PD and pneumonia are among the most prevalent and frequently mentioned causes of death in patients who have undergone STN-DBS [25, 32, 37, 40-46, 50, 51]. Studies focusing on mortality in PD patients have shown that patients are at higher risk of death from pneumonia, possibly due to the progression to end-stage parkinsonism, which leads to severe motor impairment and dementia, leaving them bedridden and more susceptible to fatal infections and aspiration [11, 60, 61]. Suicide is another cause of death commonly reported as being associated with patients who have been submitted to STN-DBS [32, 37-45, 51, 62].

Regarding the long-term results of the surgery, the findings of the present study are consistent with the literature.

The UPDRS-I scale explores memory and neuropsychiatric symptoms, such as hallucinations, depression, and apathy. In our cohort, surgery does not have a consistent impact on the variation of the UPDRS-I score. This negative result suggests that STN-DBS does not significantly affect these nonmotor symptoms or may even protect from worsening.

The UPDRS-II score in OFF-medication state improved after surgery up to 13 years. The benefit of STN-DBS on this score has been consistently demonstrated in previous studies [21-23, 25-27, 33], up to 5 years post-surgery. However, for more than 5 years, the results are variable, with one study reporting a sustained benefit after 10 years [25]. An increase in UPDRS-II score in later follow-up years may reflect PD progression and the development of motor and non-motor symptoms nonresponsive to levodopa [9-11]. In any case, our study results show that postop stimulation of the subthalamic nucleus has long-term benefit in the activities of daily living, when the patients are in OFF-medication state.

In congruency with the literature, UPDRS-III score in the ON-stimulation/OFF-medication state was better than the preop OFF-medication state throughout the follow-up timepoints. There

are multiple reports of sustained gains for 5 years [21-23, 33], and even more than 8 years [24-26, 28-30]. Even though postop gains tend to diminish over time, in our study, the UPDRS-III score OFF-medication state at 10 years of postop declined 42.1% from the preop level, reflecting a post-surgical long-term reduction in OFF-medication motor symptom severity. The diminished score gains over time can be partially explained by the deterioration of axial symptoms in long-term studies [21-26, 28-30, 33]. In the present study, after 6 years of follow-up, the efficacy of the surgery on the axial score was no longer noticeable, as scores tended to return to preop levels. These findings support the fact that, besides the positive impact of the surgery on the motor score in OFF-medication state, the progression of the disease does not stop.

The sustained effect of subthalamic stimulation in reducing motor complications – and consequently the UPDRS-IV score – throughout the long follow-up period is consistent with literature [21-33]. The indication for surgery reflects this intended effect, by including the presence of levodopa-induced motor complications causing disability as a requirement [63]. The postop reduction of LEDD probably contributes to the significant and sustained benefit observed in the UPDRS-IV score throughout the entire follow-up period. LEDD decreased 67.3% in the 1st year and 60.3% in the fifth year postop. Other studies have reported an average decrease of 52% at first year (range 39–83%) and 45% at fifth year (range −11% to 63%) [34]. The reduction of LEDD over the entire follow-up is evidence of the sustained motor benefit enabled by the STN-DBS.

Surgery had a sustained positive impact on the independence of the patients over the entire follow-up time, as demonstrated by the sustained increase on the S&E in OFF-medication state. Two other long-term studies have also shown an improvement up to 5 years post-surgery in the OFF-medication state. [21, 23].

In our study, a reduction of the H&Y stages was determined over 11 years of follow-up in the OFF-medication state, when for other study, a decline was detected from 1 to 5 years [23]. Our results are in line with the benefit in the OFF-medication state that we found for the patient's independence in S&E and UPDRS-II in the same state. The deterioration of the H&Y over the years, compared to ON-medication state at preop, is expected due to disease progression, with worsening of axial symptoms and the installation of the debilitating state of advanced Parkinson's disease.

The postop ON-medication state assessment scores were consistently poorer than the preop ON-medication state in all the parameters evaluated. The gradual deterioration was evident starting in the first year postop for UPDRS-II and axial scores, after the second year for the UPDRS-III and H&Y, and after the third year for the S&E. The study findings provide support to the notion that surgery is a symptomatic treatment of the OFF periods and does not improve symptoms during the ON period [34]. This deterioration probably reflects the progressive character of PD.

This is a single center study, which may limit the generalization of the findings. To strengthen the external validity of the findings and support them, a multicenter study would be required. In the survival analysis, the imprecision of the date of death, with a margin of error of one month, may have an impact on the accuracy of the results. The cause of death was also not available.

The inexistence of a non-surgical control group prevents conclusions from being made about the long-term impact of surgery on the survival of PD patients. Studies comparing the mortality of patients submitted to STN-DBS with those receiving only medical management have produced conflicting findings. Some reported no differences between the groups [48, 52], others describe a longer survival for DBS patients [50, 51], and some reporting a trend toward higher risk of death in patients who underwent DBS [49]. However, case-control studies on this topic are limited by demographic and clinical differences between surgical candidates and those who do not meet the criteria for STN-DBS.

The patients were evaluated in the postop on the ON-stimulation/OFF-medication condition for UPDRS-III, axial and H&Y. This condition may represent poorer symptom control than the patient usually has under the effect of medication. However, most patients don't have motor fluctuations, as seen in UPDRS-II in OFF compared to ON, in the UPDRS-IV and in the S&E in OFF and ON. The marked reduction in LEDD also makes this aspect less important.

Another limitation of this study is the variable follow-up period and the presence of missing data. Generalized estimating equations were applied to address this limitation, as this statistical approach is considered well-suited for analyzing data with repeated measures and for handling missing data effectively.

Some advantages of this study include the minimal loss to follow-up and the fact that the patients were evaluated by neurologists specialized in movement disorders, which enhances the consistency of the assessments.

Conclusions

The observed mortality rate, regardless of cause, was relatively low and comparable to other cohorts. As expected, older age at surgery is associated with shorter survival. More severe motor symptoms in OFF and ON (especially axial symptoms in ON) and worse performance on a cognitive screening measure are also predictive of earlier death. These results are useful in the selection of patients for STN-DBS with less severe motor symptoms, with motor symptoms that respond to levodopa and with less cognitive disfunction.

STN-DBS has a clear positive impact, at very long-term, on OFF-medication state in the preop, motor symptoms, activities of daily living and independence. STN-DBS allows the reduction

of both motor complications (ON/OFF fluctuations and dyskinesias) and LEDD, also in the long-term. However, some symptoms, especially when compared to ON-medication state in preop, suffer a deterioration as the disease continues to progress.

Tables

Table I. Demographic and clinical characteristics of the total sample at baseline

Variable	
Sex (*n = 101*)	
Women	35 (34.7%)
Men	66 (65.3%)
Family history of PD (*n = 95*)	
Yes	25 (26.3%)
No	70 (73.7%)
Family history of Essential Tremor (*n = 96*)	
Yes	6 (6.3%)
No	90 (93.8%)
Tremor in first symptoms (*n = 100*)	
Yes	50 (50%)
No	50 (50%)
Isolated tremor as first symptom (*n = 100*)	
Yes	27 (27%)
No	73 (73%)
Age of onset, y (*n = 101*)	47 (41-53)
Age at surgery, y (*n = 101*)	60 (52.5-64.5)
Disease duration, y (*n = 101*)	11 (9-14)
LEDD preop, mg/D (*n = 101*)	1560 (1290-1875)
UPDRS-I preop (*n = 99*)	1 (1-2)
UPDRS-II OFF preop (*n = 97*)	21 (17-25)
UPDRS-II ON preop (*n = 97*)	4 (2-7)
UPDRS-III OFF preop (*n = 101*)	40 (33-45.5)
UPDRS-III ON preop (*n = 101*)	14 (11-19)
UPDRS-IV preop (*n = 99*)	9 (7-10)
Axial OFF preop (*n = 100*)	7 (6-8)
Axial ON preop (*n = 100*)	3 (2-4)
H&Y OFF preop (*n = 101*)	3 (3-4)
H&Y ON preop (*n = 101*)	2 (2-2.5)
S&E OFF preop (*n = 100*)	60 (50-70)
S&E ON preop (*n = 100*)	90 (90-90)
DRS-2 Total preop (*n = 96*)	130 (124-135)
Abbreviations: DRS-2 = Dementia Rating Scale-2; H&Y = Hoehn and Yahr stages; LEDD = levodopa equivalent daily dose; PD = Parkinson's disease; S&E = Schwab and England activities of daily living scale; UPDRS = Unified Parkinson's Disease Rating Scale. Data are reported as frequencies (%) and as median (25th–75th percentiles)	

Table II. Unadjusted hazard ratio for death of the total sample

Variable	HR	95% CI	*p* value
Sex (*n = 101*)	1.237	0.479, 3.192	0.660
Education (*n = 100*)	0.972	0.867, 1.089	0.621
Family history of PD (*n = 95*)	0.521	0.153, 1.772	0.297
Family history of Essential Tremor (*n = 96*)	1.498	0.348, 6.448	0.588
Tremor in first symptoms (*n = 100*)	1.622	0.669, 3.932	0.285
Isolated tremor as first symptom (*n = 100*)	1.391	0.585, 3.307	0.456
Age at surgery (*n = 101*)	1.124	1.044, 1.210	0.002
Age of onset (*n = 101*)	1.058	0.999, 1.120	0.055
Disease duration (*n = 101*)	1.054	0.981, 1.133	0.154
LEDD preop (*n = 101*)	1.000	0.999, 1.001	0.855
UPDRS-I preop (*n = 99*)	0.855	0.593, 1.233	0.401
UPDRS-II OFF preop (*n = 97*)	1.078	0.982, 1.182	0.113
UPDRS-II ON preop (*n = 97*)	1.011	0.918, 1.114	0.822
UPDRS-III OFF preop (*n = 101*)	1.044	1.010, 1.080	0.012
UPDRS-III ON preop (*n = 101*)	1.116	1.045, 1.192	0.001
UPDRS-IV preop (*n = 99*)	0.893	0.743, 1.074	0.231
Axial OFF preop (*n = 100*)	1.118	0.978, 1.278	0.102
Axial ON preop (*n = 100*)	1.291	1.045, 1.596	0.018
H&Y OFF preop (*n = 101*)	1.885	0.894, 3.976	0.096
H&Y ON preop (*n = 101*)	2.724	0.753, 9.859	0.127
S&E OFF preop (*n = 100*)	0.984	0.943, 1.027	0.455
S&E ON preop (*n = 100*)	1.024	0.948, 1.106	0.551
DRS-2 Total preop (*n = 96*)	0.943	0.896, 0.992	0.022
DRS-2 Attention preop (*n = 96*)	0.829	0.713, 0.965	0.016
DRS-2 Initiation/Perserveration preop (*n = 96*)	0.935	0.840, 1.040	0.218
DRS-2 Construction preop (*n = 96*)	0.900	0.593, 1.365	0.619
DRS-2 Conceptualization preop (*n = 96*)	0.893	0.793, 1.006	0.062
DRS-2 Memory preop (*n = 96*)	0.934	0.771, 1.131	0.483

Abbreviations: CI = confidence interval; DRS-2 = Dementia Rating Scale-2; HR = Hazard Ratio; H&Y = Hoehn & Yahr; LEDD = levodopa equivalent daily dose; PD = Parkinson's disease; S&E = Schwab and England activities of daily living scale; UPDRS = Unified Parkinson's Disease Rating Scale.

Table III. Adjusted hazard ratio for death of the total sample

Variable	HR	95% CI	*p* value
Age at surgery (*n = 101*) **UPDRS-III OFF preop (*n = 101*)** **Total DRS-2 preop (*n = 96*)**	1.125 1.036 0.986	1.038, 1.219 0.992, 1.083 0.919, 1.059	0.004 0.112 0.986
Age at surgery (*n = 101*) **UPDRS-III ON preop (*n = 101*)** **Total DRS-2 preop (*n = 96*)**	1.119 1.099 1.003	1.033, 1.212 1.005, 1.203 0.932, 1.080	0.006 0.039 0.934
Age at surgery (*n = 101*) **Axial ON preop (*n = 100*)** **Total DRS-2 preop (*n = 96*)**	1.109 1.078 0.962	1.024, 1.201 0.842, 1.381 0.909, 1.019	0.011 0.551 0.192
Age at surgery (*n = 101*) **UPDRS-III OFF preop (*n = 101*)**	1.125 1.044	1.042, 1.215 1.008, 1.082	0.003 0.017
Age at surgery (*n = 101*) **UPDRS-III ON preop (*n = 101*)**	1.113 1.099	1.031, 1.201 1.026, 1.177	0.006 0.007
Age at surgery (*n = 101*) **Axial ON preop (*n = 100*)**	1.108 1.123	1.026, 1.198 0.886, 1.422	0.009 0.338
Abbreviations: CI = confidence interval; DRS-2 = Dementia Rating Scale; HR = Hazard Ratio; UPDRS = Unified Parkinson's Disease Rating Scale.			

Table IV. Generalized estimating equations analysis for UPDRS-I

UPDRS-I				
Time points	**β**	**SE**	***p* value**	**EMM (95% CI)**
Preop				1.60 (1.35-1.85)
Postop 1y	-0.418	0.165	0.011	1.18 (0.89-1.48)
Postop 2y	-0.089	0.186	0.632	1.51 (1.19-1.84)
Postop 3y	0.148	0.238	0.534	1.75 (1.32-2.18)
Postop 4y	0.185	0.264	0.484	1.79 (1.26-2.31)
Postop 5y	0.283	0.275	0.303	1.89 (1.35-2.42)
Postop 6y	0.106	0.251	0.672	1.71 (1.24-2.17)
Postop 7y	0.552	0.316	0.081	2.15 (1.59-2.72)
Postop 8y	0.773	0.346	0.026	2.38 (1.75-3.00)
Postop 9y	0.678	0.349	0.052	2.28 (1.66-2.90)
Postop 10y	1.311	0.504	0.009	2.91 (1.97-3.85)
Postop 11y	1.443	0.496	0.004	3.05 (2.11-3.98)
Postop 12y	2.216	0.669	0.001	3.82 (2.56-5.07)
Postop 13y	1.826	0.849	0.032	3.43 (1.76-5.09)
Postop 14y	1.398	1.014	0.168	3.00 (1.02-4.98)
Postop 15y	0.148	0.984	0.881	1.75 (-0.13-3.63)

Table V. Generalized estimating equations analysis for UPDRS-II

	UPDRS-II OFF				UPDRS-II ON			
Time points	**β**	**SE**	***p* value**	**EMM (95% CI)**	**β**	**SE**	***p* value**	**EMM (95% CI)**
Preop				21.54 (20.51-22.56)				5.27 (4.40-6.15)
Postop 1y	-13.644	0.655	<0.001	7.89 (6.88-8.91)	1.515	0.603	0.012	6.79 (5.85-7.73)
Postop 2y	-12.628	0.626	<0.001	8.91 (7.97-9.85)	2.456	0.515	<0.001	7.73 (6.91-8.55)
Postop 3y	-11.583	0.676	<0.001	9.96 (8.87-11.04)	2.916	0.614	<0.001	8.19 (7.17-9.21)
Postop 4y	-10.637	0.720	<0.001	10.90 (9.77-12.03)	4.299	0.691	<0.001	9.57 (8.45-10.70)
Postop 5y	-10.342	0.666	<0.001	11.20 (10.14-12.26)	4.725	0.699	<0.001	10.00 (8.81-11.19)
Postop 6y	-10.038	0.785	<0.001	11.50 (10.06-12.94)	4.642	0.764	<0.001	9.92 (8.61-11.23)
Postop 7y	-8.744	0.893	<0.001	12.79 (11.24-14.35)	6.879	0.905	<0.001	12.15 (10.55-13.76)
Postop 8y	-7.320	1.067	<0.001	14.22 (12.32-16.12)	7.850	1.094	<0.001	13.13 (11.15-15.10)
Postop 9y	-7.178	1.109	<0.001	14.36 (12.19-16.53)	7.845	1.048	<0.001	13.12 (11.22-15.02)
Postop 10y	-6.365	1.028	<0.001	15.17 (13.30-17.04)	9.638	1.023	<0.001	14.91 (12.99-16.83)
Postop 11y	-7.357	1.744	<0.001	14.18 (12.12-16.24)	8.453	1.167	<0.001	13.73 (11.58-15.87)
Postop 12y	-6.629	1.662	<0.001	14.91 (11.49-18.33)	9.453	1.807	<0.001	14.73 (11.16-18.29)
Postop 13y	-3.396	2.187	0.041	18.14 (14.84-21.44)	12.225	1.786	<0.001	17.50 (13.98-21.02)
Postop 14y	-3.253	1.545	0.137	18.29 (14.08-22.49)	13.011	2.181	<0.001	18.29 (14.08-22.49)
Postop 15y	-1.288	0.524	0.404	20.25 (17.36-23.14)	14.725	1.746	<0.001	20.00 (16.75-23.25)

Table VI. Generalized estimating equations analysis for UPDRS-III

	UPDRS-III OFF				UPDRS-III ON			
Time points	**β**	**SE**	***p* value**	**EMM (95% CI)**	**β**	**SE**	***p* value**	**EMM (95% CI)**
Preop				40.69 (38.71-42.68)				15.38 (14.21-16.56)
Postop 1y	-25.334	1.016	<0.001	15.36 (14.04-16.68)	-0.023	0.668	0.973	15.36 (14.04-16.68)
Postop 2y	-24.460	1.013	<0.001	16.23 (14.85-17.62)	0.852	0.650	0.190	16.23 (14.85-17.62)
Postop 3y	-23.075	1.143	<0.001	17.62 (15.97-19.26)	2.237	0.819	0.006	17.62 (15.97-19.26)
Postop 4y	-22.441	1.235	<0.001	18.25 (16.52-19.98)	2.871	0.851	0.001	18.25 (16.52-19.98)
Postop 5y	-21.564	1.192	<0.001	19.13 (17.58-20.68)	3.748	0.858	<0.001	19.13 (17.58-20.68)
Postop 6y	-21.503	1.198	<0.001	19.19 (17.36-21.03)	3.809	0.978	<0.001	19.19 (17.36-21.03)
Postop 7y	-20.168	1.447	<0.001	20.53 (18.30-22.75)	5.143	1.231	<0.001	20.53 (18.30-22.75)
Postop 8y	-19.320	1.371	<0.001	21.38 (18.90-23.85)	5.992	1.313	<0.001	21.38 (18.90-23.85)
Postop 9y	-19.815	1.666	<0.001	20.88 (17.77-23.99)	5.497	1.611	0.001	20.88 (19.45-26.20)
Postop 10y	-17.869	1.847	<0.001	22.83 (19.45-26.20)	7.443	1.724	<0.001	22.83 (19.45-26.20)
Postop 11y	-19.331	2.063	<0.001	21.36 (17.63-25.10)	5.981	1.899	0.002	21.36 (17.63-25.10)
Postop 12y	-18.786	2.738	<0.001	21.91 (16.77-27.05)	6.526	2.633	0.013	21.91 (16.77-27.05)
Postop 13y	-13.480	3.434	<0.001	27.21 (20.58-33.84)	11.831	3.422	0.001	27.21 (20.58-33.84)
Postop 14y	-13.980	2.047	<0.001	26.71 (23.16-30.27)	11.331	1.871	<0.001	26.71 (23.16-30.27)
Postop 15y	-10.695	1.547	<0.001	30.00 (27.70-23.30)	14.617	1.282	<0.001	30.00 (27.70-32.30)

Table VII. Generalized estimating equations analysis for axial score

	AXIAL OFF				AXIAL ON			
Time points	**β**	**SE**	***p* value**	**EMM (95% CI)**	**β**	**SE**	***p* value**	**EMM (95% CI)**
Preop				7.46 (6.89-8.03)				3.15 (2.84-3.46)
Postop 1y	-3.754	0.324	<0.001	3.70 (3.20-4.20)	0.553	0.232	0.017	3.70 (3.20-4.20)
Postop 2y	-3.220	0.324	<0.001	4.24 (3.70-4.78)	1.087	0.245	<0.001	4.24 (3.70-4.78)
Postop 3y	-2.543	0.349	<0.001	4.91 (4.35-5.48)	1.764	0.272	<0.001	4.91 (4.35-5.48)
Postop 4y	-2.054	0.414	<0.001	5.40 (4.73-6.08)	2.253	0.333	<0.001	5.40 (4.73-6.08)
Postop 5y	-2.113	0.362	<0.001	5.34 (4.78-5.91)	2.194	0.286	<0.001	5.34 (4.78-5.91)
Postop 6y	-1.819	0.348	<0.001	5.64 (5.02-6.26)	2.488	0.316	<0.001	5.64 (5.02-6.26)
Postop 7y	-0.919	0.532	0.084	6.54 (5.59-7.48)	3.388	0.483	<0.001	6.54 (5.59-7.48)
Postop 8y	-0.801	0.502	0.110	6.66 (5.69-7.63)	3.506	0.485	<0.001	6.66 (5.69-7.63)
Postop 9y	-1.097	0.583	0.060	6.36 (5.20-7.52)	3.209	0.588	<0.001	6.36 (5.20-7.52)
Postop 10y	-0.457	0.695	0.510	7.00 (5.62-8.38)	3.849	0.660	<0.001	7.00 (5.62-8.38)
Postop 11y	-0.048	0.808	0.952	7.41 (5.80-9.02)	4.259	0.779	<0.001	7.41 (5.80-9.02)
Postop 12y	-0.639	1.137	0.574	6.82 (4.55-9.08)	3.668	1.128	0.001	6.82 (4.55-9.08)
Postop 13y	1.543	0.993	0.120	9.00 (7.00-11.00)	5.849	1.027	<0.001	9.00 (7.00-11.00)
Postop 14y	0.876	1.334	0.511	8.33 (5.73-10.93)	5.183	1.295	<0.001	8.33 (5.73-10.93)
Postop 15y	0.793	1.752	0.651	8.25 (4.83-11.67)	5.099	1.715	0.003	8.25 (4.83-11.67)

Table VIII. Generalized estimating equations analysis for UPDRS-IV

UPDRS-IV				
Time points	**β**	**SE**	***p* value**	**EMM (95% CI)**
Preop				8.73 (8.24-9.22)
Postop 1y	-6.968	0.316	<0.001	1.76 (1.37-2.15)
Postop 2y	-6.911	0.323	<0.001	1.82 (1.37-2.28)
Postop 3y	-6.393	0.356	<0.001	2.34 (1.81-2.87)
Postop 4y	-6.715	0.348	<0.001	2.02 (1.50-2.54)
Postop 5y	-6.830	0.291	<0.001	1.90 (1.44-2.37)
Postop 6y	-6.815	0.336	<0.001	1.92 (1.37-2.46)
Postop 7y	-7.270	0.327	<0.001	1.46 (0.99-1.94)
Postop 8y	-6.669	0.429	<0.001	2.06 (1.30-2.82)
Postop 9y	-6.811	0.427	<0.001	1.92 (1.11-2.73)
Postop 10y	-7.079	0.454	<0.001	1.65 (0.86-2.45)
Postop 11y	-7.413	0.330	<0.001	1.32 (0.79-1.84)
Postop 12y	-7.913	0.370	<0.001	0.82 (0.27-1.37)
Postop 13y	-6.945	0.498	<0.001	1.79 (0.81-2.76)
Postop 14y	-7.017	0.773	<0.001	1.71 (0.20-3.23)
Postop 15y	-5.981	1.302	<0.001	2.75 (0.22-5.28)

Table IX. Generalized estimating equations analysis for S&E

	S&E OFF				S&E ON			
Time points	**β**	**SE**	***p* value**	**EMM (95% CI)**	**β**	**SE**	***p* value**	**EMM (95% CI)**
Preop				58.94 (56.66-61.21)				90.43 (89.14-91.71)
Postop 1y	29.397	1.298	<0.001	88.33 (86.54-90.12)	0.087	0.896	0.922	90.51 (89.01-92.02)
Postop 2y	29.397	1.306	<0.001	88.33 (86.69-89.98)	-0.297	0.802	0.711	90.13 (88.92-91.33)
Postop 3y	26.946	1.510	<0.001	85.88 (83.76-88.01)	-1.749	1.078	0.105	88.68 (86.77-90.58)
Postop 4y	27.129	1.550	<0.001	86.07 (83.87-88.26)	-2.721	1.229	0.027	87.70 (85.51-89.90)
Postop 5y	27.621	1.379	<0.001	86.56 (84.75-88.37)	-2.721	1.136	0.017	87.70 (85.81-89.60)
Postop 6y	26.480	1.327	<0.001	85.42 (83.26-87.57)	-2.926	1.122	0.009	87.50 (85.46-89.54)
Postop 7y	25.679	1.670	<0.001	84.62 (81.97-87.26)	-4.272	1.441	0.003	86.15 (83.53-88.78)
Postop 8y	23.564	2.281	<0.001	82.50 (78.44-86.56)	-6.988	2.227	0.002	83.44 (79.41-87.46)
Postop 9y	23.864	2.043	<0.001	82.80 (79.04-86.56)	-5.626	1.832	0.002	84.80 (81.45-88.15)
Postop 10y	22.803	2.919	<0.001	81.74 (76.13-87.35)	-8.686	2.811	0.002	81.74 (76.13-87.35)
Postop 11y	22.427	2.984	<0.001	81.36 (75.55-87.18)	-8.607	2.998	0.004	81.82 (75.96-87.68)
Postop 12y	20.155	4.497	<0.001	79.09 (70.20-87.98)	-11.335	4.479	0.011	79.09 (70.20-87.98)
Postop 13y	14.635	4.601	0.001	73.57 (64.58-82.56)	-16.854	4.565	<0.001	73.57 (64.58-82.56)
Postop 14y	11.064	5.805	0.057	70.00 (58.80-81.20)	-20.426	5.752	<0.001	70.00 (58.80-81.20)
Postop 15y	13.564	6.424	0.035	72.50 (59.77-85.23)	-17.926	6.579	0.006	72.50 (59.77-85.23)

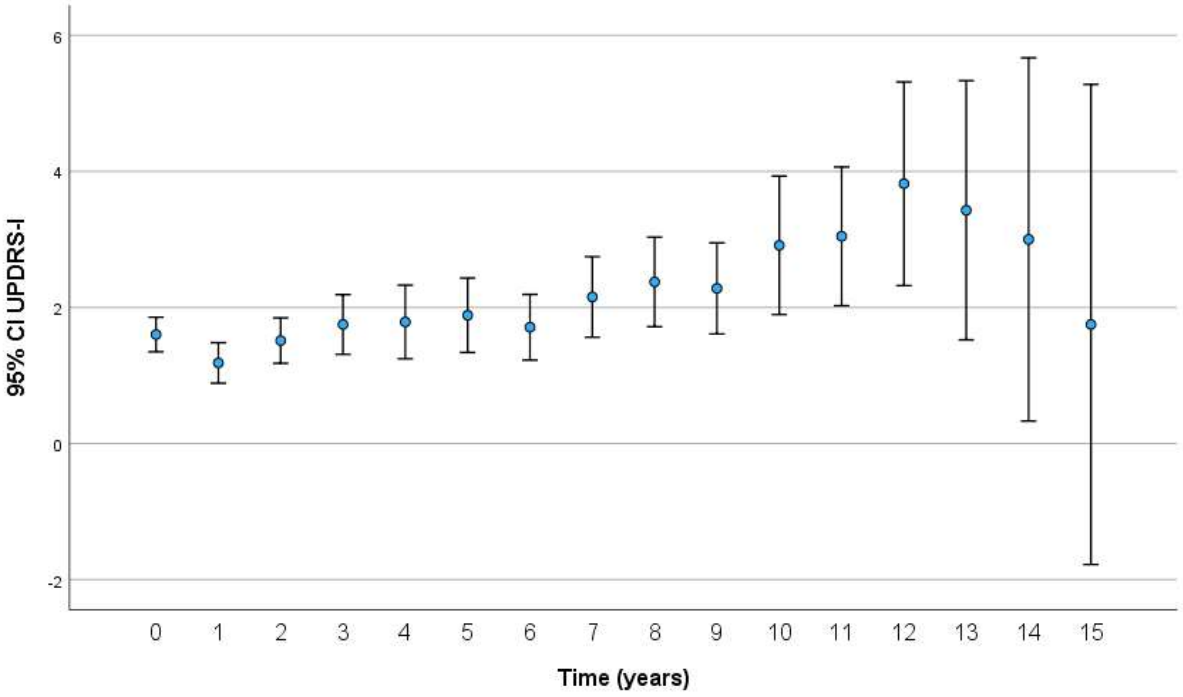
Table X. Generalized estimating equations analysis for H&Y

	H&Y OFF				H&Y ON			
Time points	**β**	**SE**	***p* value**	**EMM (95% CI)**	**β**	**SE**	***p* value**	**EMM (95% CI)**
Preop				3.232 (3.105-3.359)				2.271 (2.211-2.331)
Postop 1y	-0.955	0.086	<0.001	2.277 (2.136-2.417)	0.005	0.070	0.939	2.277 (2.136-2.417)
Postop 2y	-0.879	0.069	<0.001	2.353 (2.258-2.447)	0.081	0.045	0.074	2.353 (2.258-2.447)
Postop 3y	-0.768	0.077	<0.001	2.464 (2.359-2.569)	0.192	0.052	<0.001	2.464 (2.359-2.569)
Postop 4y	-0.732	0.083	<0.001	2.500 (2.390-2.610)	0.229	0.057	<0.001	2.500 (2.390-2.610)
Postop 5y	-0.658	0.081	<0.001	2.574 (2.465-2.682)	0.302	0.059	<0.001	2.574 (2.465-2.682)
Postop 6y	-0.679	0.076	<0.001	2.552 (2.451-2.653)	0.281	0.058	<0.001	2.552 (2.451-2.653)
Postop 7y	-0.552	0.085	<0.001	2.679 (2.554-2.805)	0.408	0.068	<0.001	2.679 (2.554-2.805)
Postop 8y	-0.466	0.098	<0.001	2.766 (2.604-2.928)	0.494	0.087	<0.001	2.766 (2.604-2.928)
Postop 9y	-0.612	0.088	<0.001	2.620 (2.470-2.770)	0.349	0.081	<0.001	2.620 (2.470-2.770)
Postop 10y	-0.405	0.136	0.003	2.826 (2.566-3.086)	0.555	0.133	<0.001	2.826 (2.566-3.086)
Postop 11y	-0.368	0.135	0.006	2.864 (2.595-3.132)	0.592	0.135	<0.001	2.864 (2.595-3.132)
Postop 12y	-0.459	0.261	0.079	2.773 (2.248-3.298)	0.501	0.265	0.059	2.773 (2.248-3.298)
Postop 13y	-0.124	0.193	0.520	3.107 (2.721-3.493)	0.836	0.193	<0.001	3.107 (2.721-3.493)
Postop 14y	-0.303	0.189	0.109	2.929 (2.562-3.295)	0.657	0.181	<0.001	2.929 (2.562-3.295)
Postop 15y	-0.107	0.273	0.696	3.125 (2.591-3.659)	0.854	0.266	0.001	3.125 (2.591-3.659)

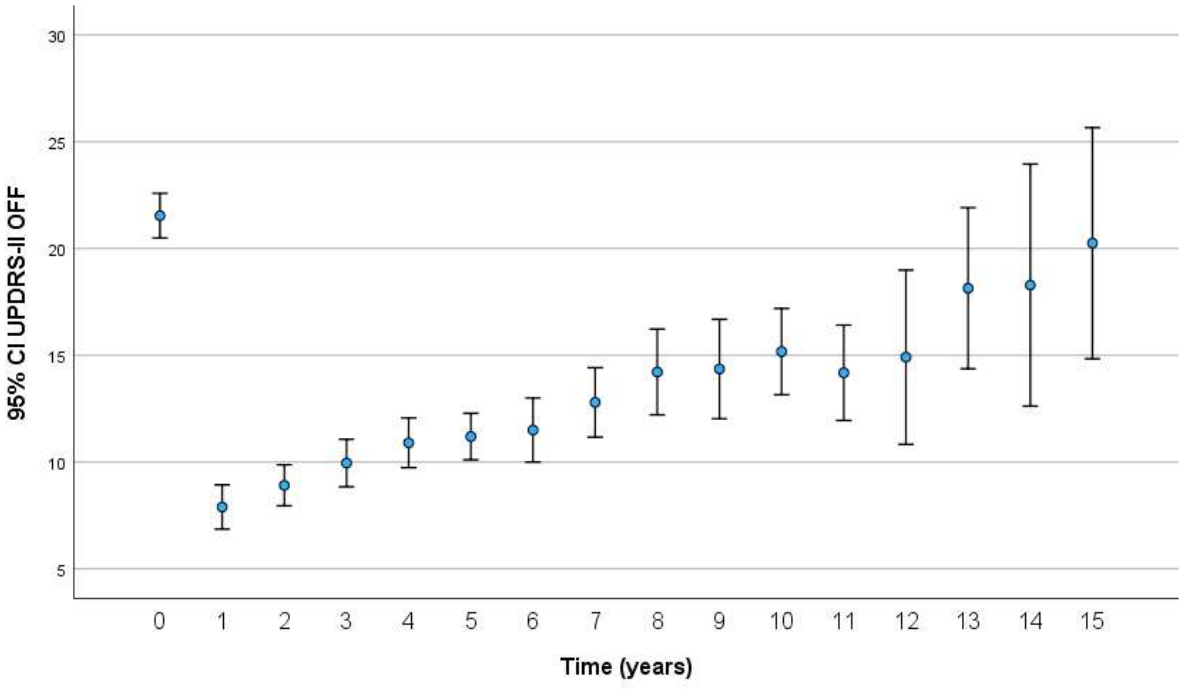
Table XI. Generalized estimating equations analysis for LEDD

LEDD				
Time points	**β**	**SE**	***p* value**	**EMM (95% CI)**
Preop				1571.01 (1485.30-1656.72)
Postop 1y	-1077.819	46.084	<0.001	493.19 (493.19-545.29)
Postop 2y	-1048.401	48.608	<0.001	522.61 (457.25-587.97)
Postop 3y	-1046.517	47.111	<0.001	524.49 (462.67-586.32)
Postop 4y	-975.940	48.748	<0.001	595.07 (519.71-670.43)
Postop 5y	-973.772	50.581	<0.001	597.24 (522.23-672.25)
Postop 6y	-975.046	49.870	<0.001	595.96 (515.97-675.96)
Postop 7y	-935.141	55.550	<0.001	635.87 (541.58-730.16)
Postop 8y	-923.774	60.311	<0.001	647.24 (539.08-755.39)
Postop 9y	-934.939	68.868	<0.001	636.07 (501.64-770.50)
Postop 10y	-1014.272	62.479	<0.001	556.74 (455.42-658.06)
Postop 11y	-995.556	64.655	<0.001	575.45 (457.89-693.02)
Postop 12y	-979.192	101.761	<0.001	591.82 (395.39-788.25)
Postop 13y	-943.868	91.119	<0.001	627.14 (455.49-798.79)
Postop 14y	-1091.011	89.501	<0.001	480.00 (311.26-648.74)
Postop 15y	-1206.011	72.184	<0.001	365.00 (251.24-478.76)

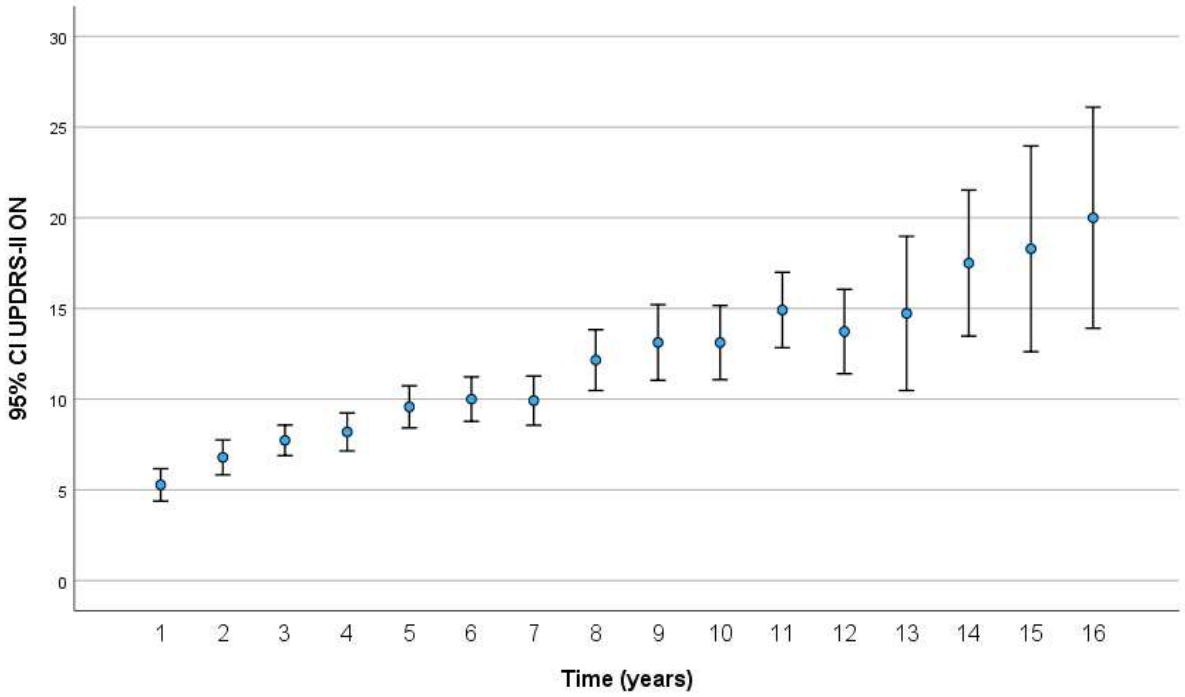
Graphics



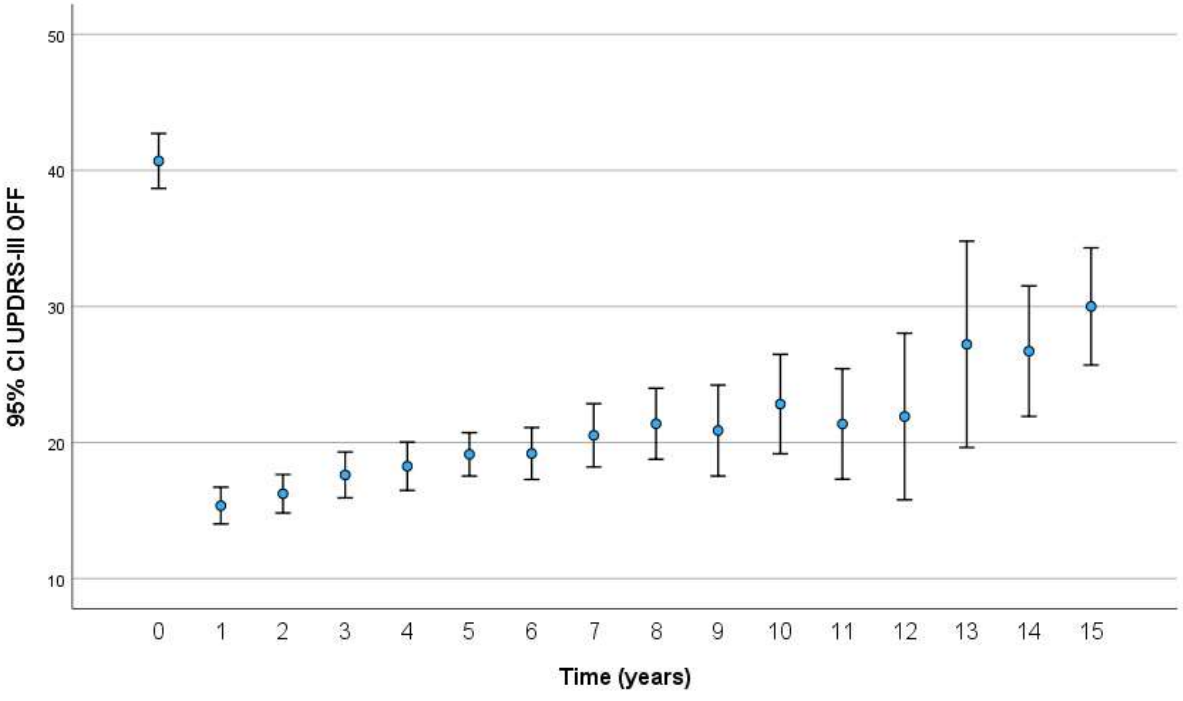
Graphic 1. Evolution of the UPDRS-I score



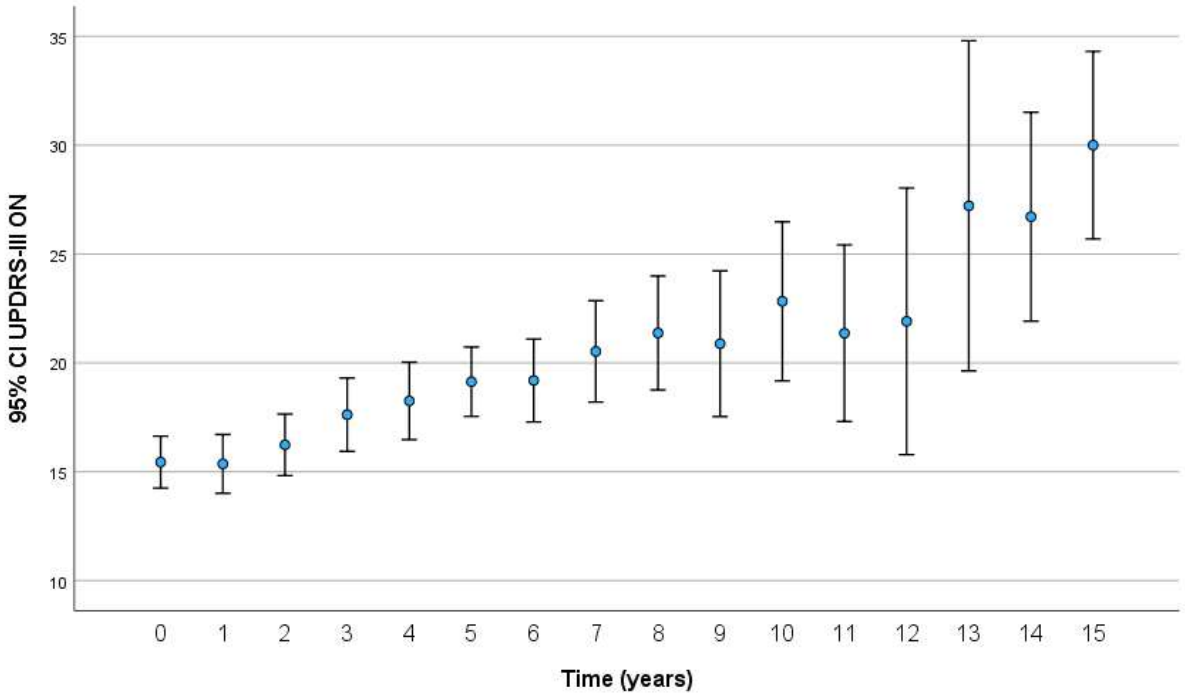
Graphic 2. Evolution of the UPDRS-II OFF score



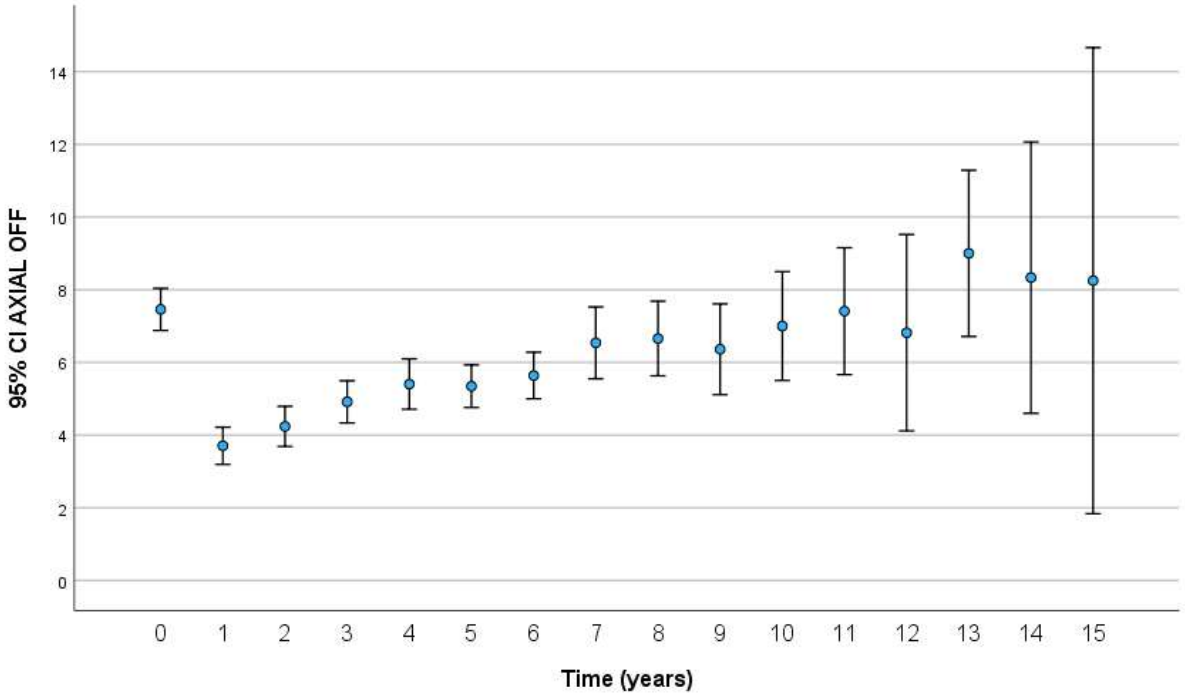
Graphic 3. Evolution of the UPDRS-II ON score



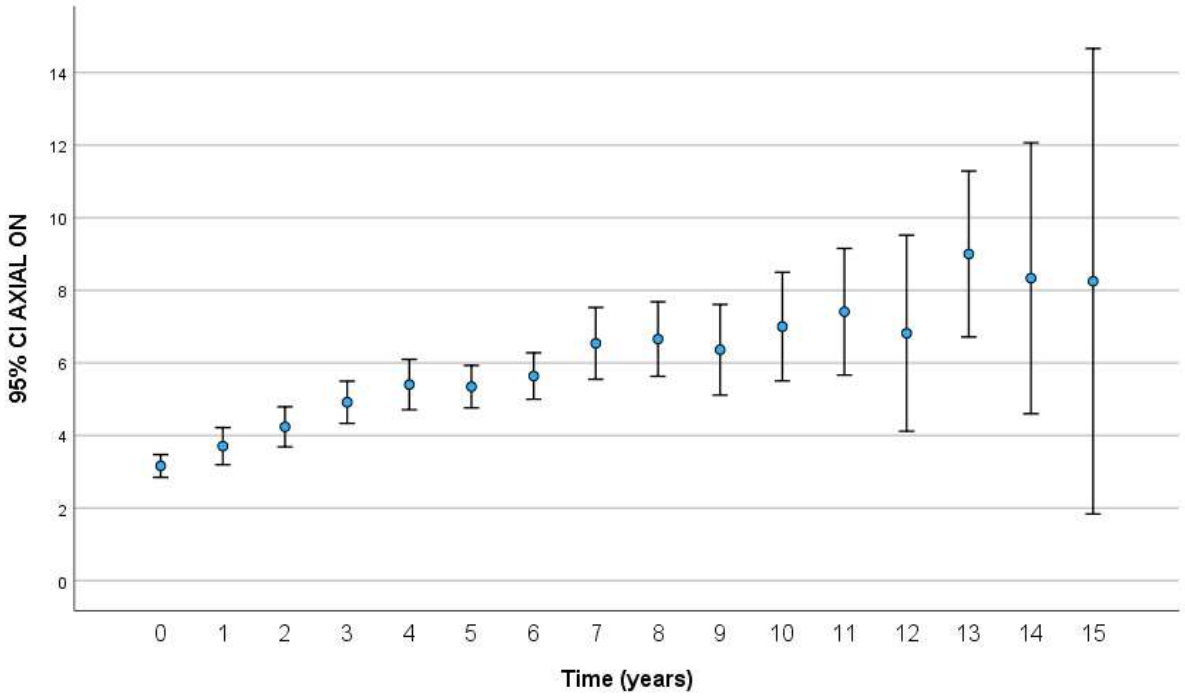
Graphic 4. Evolution of the UPDRS-III OFF score



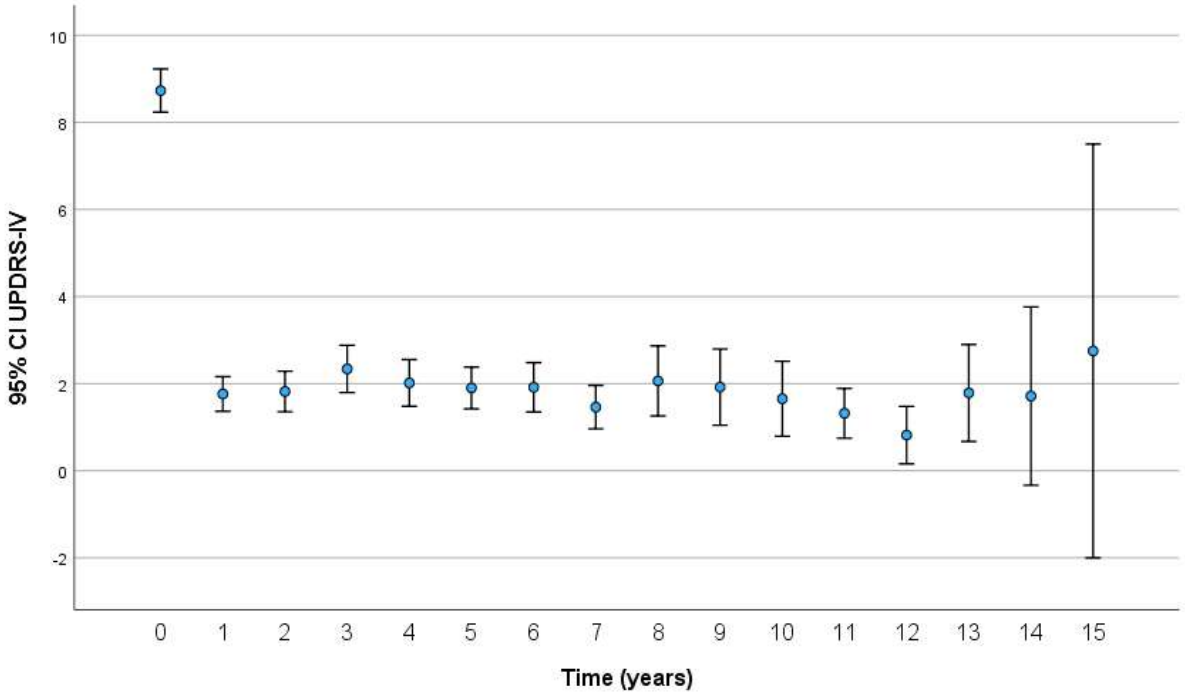
Graphic 5. Evolution of the UPDRS-III ON score



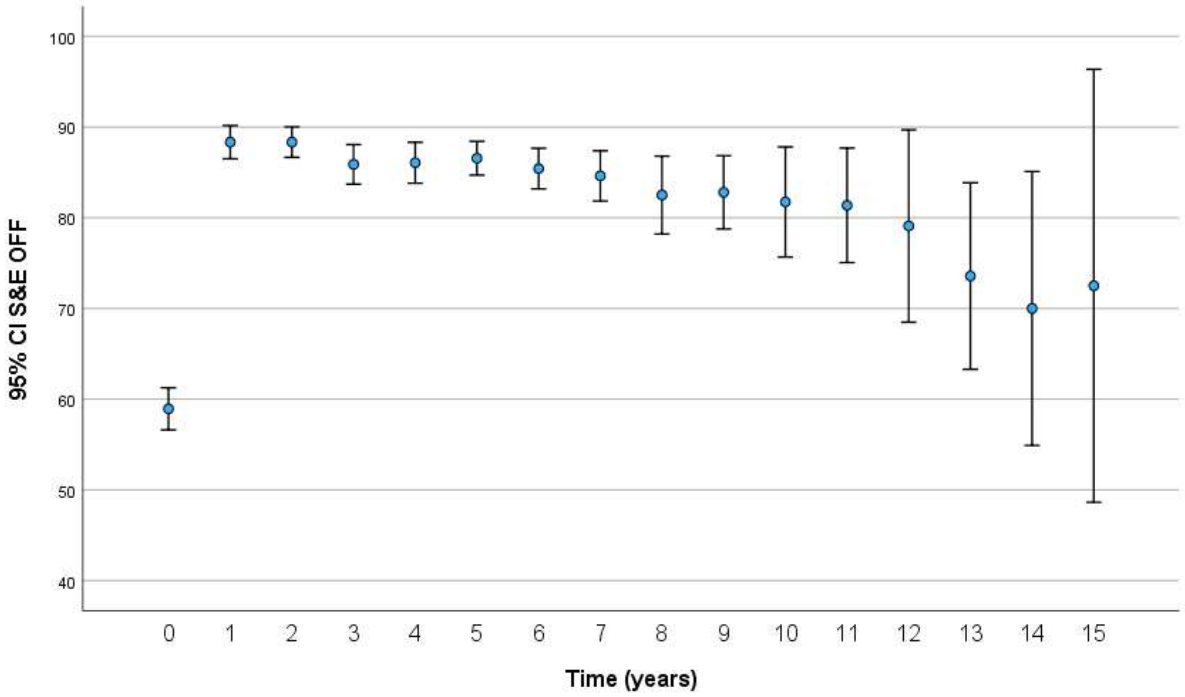
Graphic 6. Evolution of the Axial OFF score



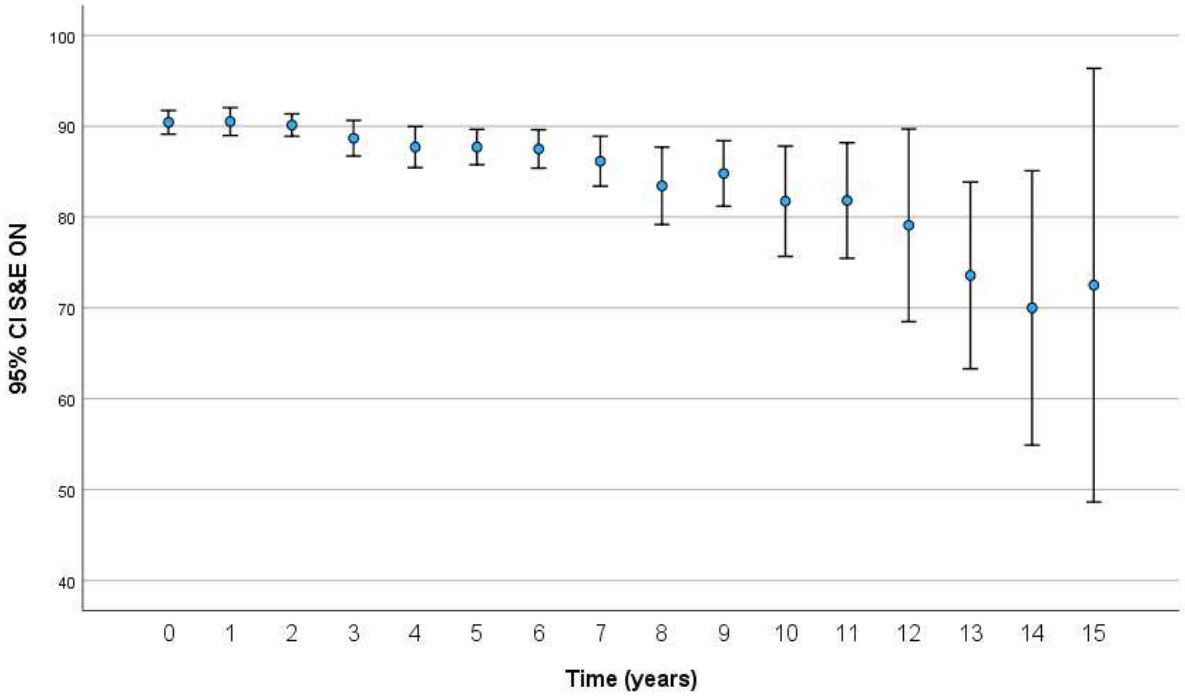
Graphic 7. Evolution of the Axial ON score



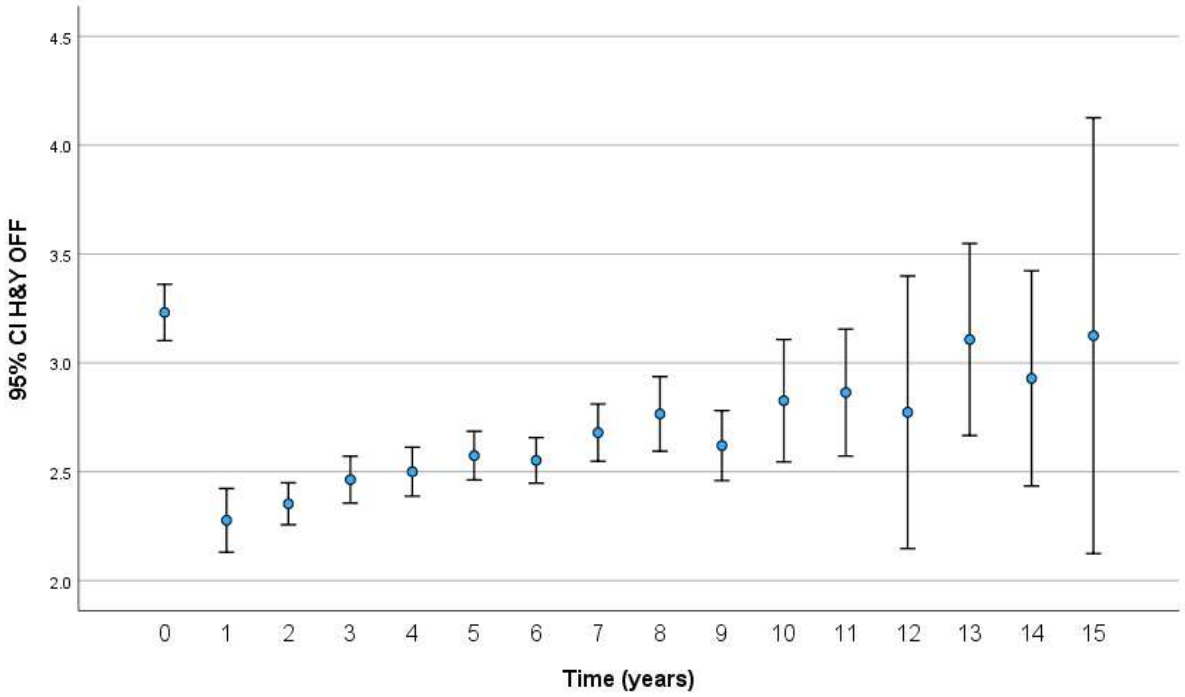
Graphic 8. Evolution of the UPDRS-IV score



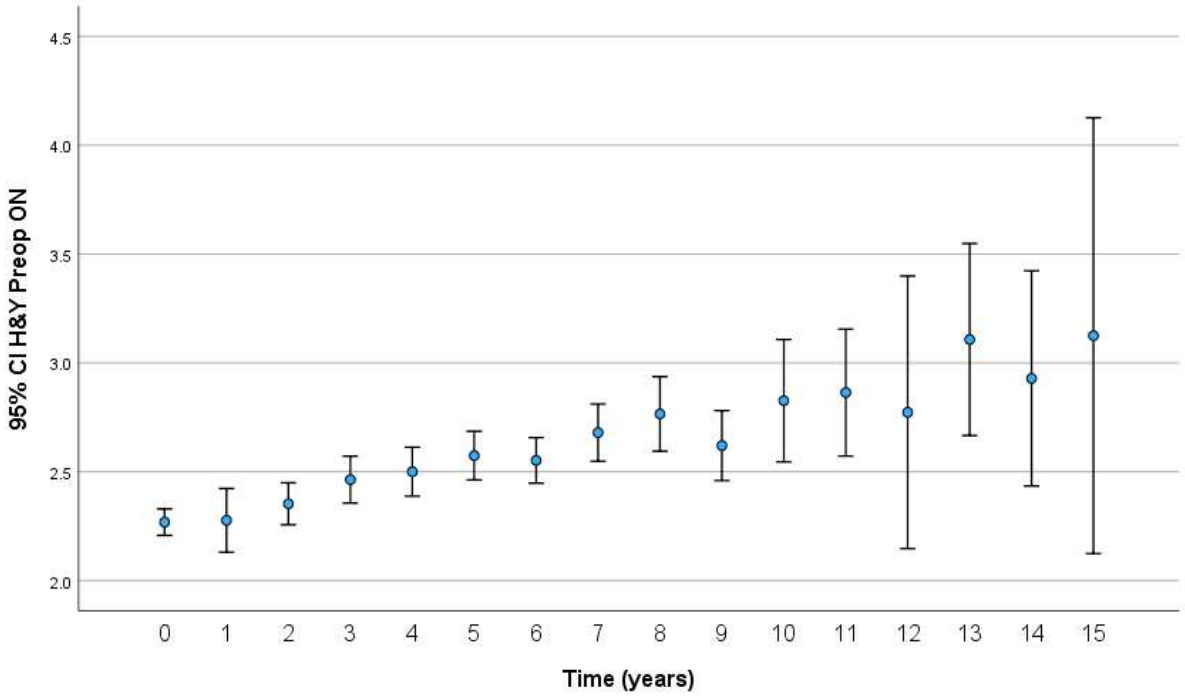
Graphic 9. Evolution of the S&E OFF score



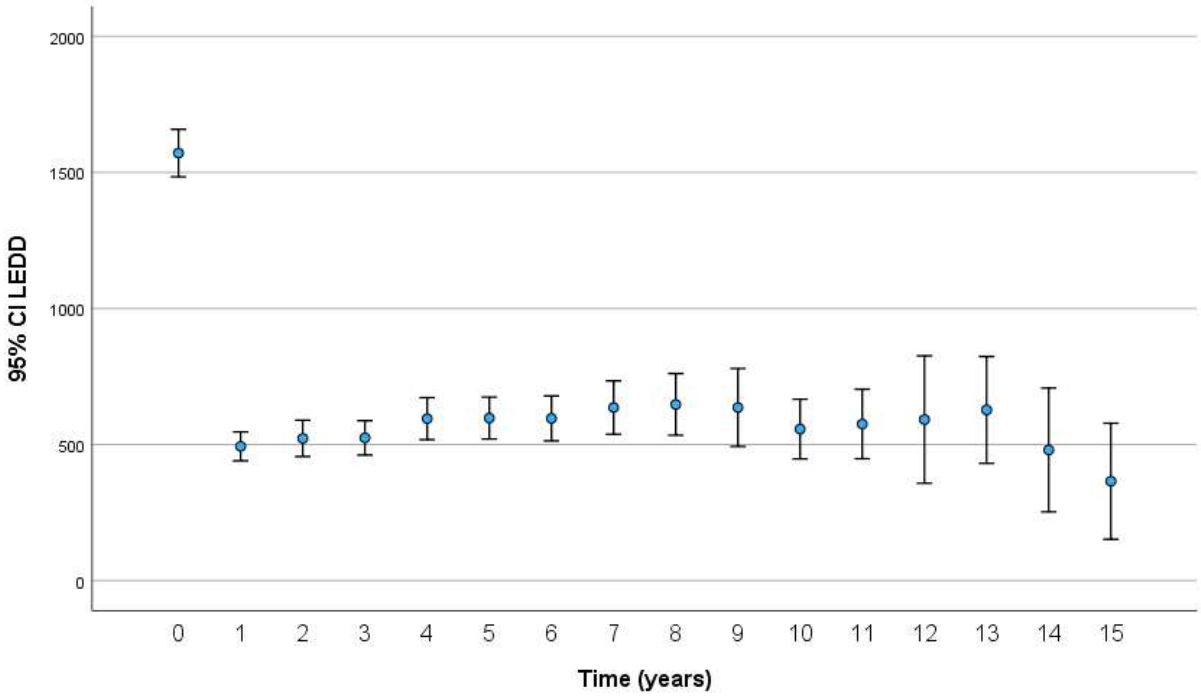
Graphic 10. Evolution of the S&E ON score



Graphic 11. Evolution of the H&Y OFF score



Graphic 12. Evolution of the H&Y ON score



Graphic 13. Evolution of LEDD

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