

MESTRADO INTEGRADO EM MEDICINA

Establishing the profile of cognitive complaints associated with neurodegenerative dementia

Mafalda Sofia Maia da Silva

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2025



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ÁREA: NEUROLOGIA

TIPO: DISSERTAÇÃO

TRABALHO EFETUADO SOB A ORIENTAÇÃO DE: DR. RUI MANUEL MOREIRA ARAÚJO
E SOB A COORIENTAÇÃO DE: DRA. MARIA CAROLINA GEMELGO CORREIA

TRABALHO ORGANIZADO DE ACORDO COM AS NORMAS DA REVISTA: JOURNAL OF
NEUROLOGY



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TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

Establishing the profile of cognitive complaints associated with neurodegenerative dementia

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ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTES TRABALHOS APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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Eu, Mafalda Sofia Maia da Silva, abaixo assinado, nº mecanográfico 201905388, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro que:

- ☒ Não procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* para nenhuma das tarefas no contexto do meu trabalho de Dissertação ou Monografia
- ☐ Procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia, encontrando-se todas as interações (*prompts* e respostas) transcritas em anexo bem como a indicação das aplicações utilizadas.

Neste sentido, confirmo que a eventual utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia foi exclusivamente descrita na sequência de *prompts* e respostas transcritos em anexo e nas aplicações indicadas.

Faculdade de Medicina da Universidade do Porto, 17/03/2025

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Dedicatória

Gostaria de expressar a minha gratidão a todos aqueles que contribuíram para a realização deste trabalho.

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“Establishing the profile of cognitive complaints associated with neurodegenerative dementia”

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Abstract

Differentiating neurodegenerative and non-neurodegenerative disorders is important for several reasons, e.g., approval of disease-specific modifying treatments. Identifying patients in the early stages of a neurodegenerative disorder is a notoriously difficult task in primary care and in general outpatient clinics. This study aimed to identify the characteristics of people with cognitive complaints presenting to a Neurology appointment who later develop a neurodegenerative condition.

We conducted a retrospective, single-center study of patients referred by primary care to the neurology outpatient clinic for cognitive complaints. Sociodemographic and clinical data were collected. The diagnoses of a “neurodegenerative disorder” or “non-degenerative disorder” were established per the judgement of the attending physician.

Among 283 patients, 169 (59.7%) had a non-degenerative condition, 108 (38.2%) a neurodegenerative disease and 6 (2.1%) lost follow-up. The main characteristics associated with neurodegenerative disorder were: older age (OR 1.05), major cognitive complaints (i.e history of cognitive impairment likely to cause harm or requiring assistance from spouse / caretaker) (OR 2.27), a total score of Mini-Mental State Examination below the appropriate cut-off (OR 7.88), difficulties in memory recall bedside testing (OR 66.00), evidence of focal or asymmetrical atrophy in CT or MRI reports (OR 2.40). The multivariate analysis shows 93.4% accuracy, 87.4% sensitivity and 88% specificity in differentiating degenerative from non-degenerative cognitive disorders.

This study identified traits that differentiate neurodegenerative from non-neurodegenerative cognitive complaints. Prospective application of this model should ideally be further explored in primary care, hopefully leading to more efficient triage of people presenting with cognitive complaints to primary care.

Key Words: Dementia, Cognitive Complaints, Neurodegenerative Disease, Alzheimer, Mild cognitive impairment, Non-neuro degenerative cognitive complaints

Introduction

On a global scale, dementia affects between 6 and 50 million people and is one of the main causes of referral to neurology appointments [1]. It is expected that the number of people at risk for cognitive impairment will rise significantly in the forthcoming years [2].

The therapeutic landscape in dementia, particularly in Alzheimer's Disease, is undergoing significant transformation, driven by the recent approval of anti-amyloid treatments for early-stage Alzheimer's disease in many countries across the world, (i.e. United States of America, Japan, China, South Korea, Great Britain, Mexico, Israel, etc). In Europe, in November 2024, the treatment received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommending approval. Despite the discussion regarding the efficacy, safety and costs of these innovative drugs, this approval is likely to lead to major changes in the organization of health care systems, specifically the establishment of adequate triage and referencing protocols in order to diagnose and treat the largest number of patients who are likely to benefit from these new treatments [2]. Also, establishing an early diagnosis of Alzheimer's disease may also be important even in the absence of disease-modifying treatments, as it enables patients to plan for their future, consider symptomatic treatment, and take steps to preserve their quality of life and autonomy for as long as possible [3].

The initial stages of a neurodegenerative disorder, and specifically Alzheimer's disease, may be characterized by ordinary, seemingly irrelevant cognitive complaints, such as banal "senior moments", a self-perception of diminished intellectual performance, in the absence of repercussions in a person's daily life. It may be very similar to attention deficits and concentration difficulties, associated with mood issues, poor sleep, and long and stressful work schedules, which are nearly ubiquitous in the adult population in modern Western societies. The contribution of these multiple factors, e.g. poor sleep, depressive and anxious disorders, and medication side effects, leads people to frequently seek medical care, often motivated by the legitimate fear that they may be in an early stage of Alzheimer's Disease [4, 5].

The emergence of disease-modifying drugs indicated for pre-dementia stages makes the situation even more problematic, both due to the foreseeable increase in demand for specialized care and access to Neurology appointments, as well as because of the technological and human resource costs required to establish this type of diagnosis. While it is expected that blood biomarkers will emerge in the foreseeable future to measure proteins associated with the classic biomarkers of Alzheimer's Disease, it is still uncertain how these tests will influence the patient's clinical pathway [6] either as supportive criteria or screening tools [3].

The methods currently available for the initial assessment or screening of a patient with cognitive complaints, such as the Mini Mental State Examination (MMSE), are not used systematically and are not always scored correctly. The criteria for referral to neurological evaluation are also highly variable, and it is difficult to predict, based on clinical records, whether the patient has a high or low probability of having a progressive neurodegenerative condition and what its nature might be [7]. Thus, it is important to have appropriate clinical criteria that optimize the distinction between early-stage and incipient cases of degenerative forms of dementia (with a focus on Alzheimer's Disease) which are likely to benefit from quick referral for a neurological evaluation and follow-up, and cognitive complaints associated with non-degenerative conditions (psychiatric conditions, functional cognitive disorder, attention deficits or poor concentration, meta-memory problems, etc.). Remarkably, in these two situations, cognitive bedside testing lacks specificity [8-10].

We aimed to study which clinical and demographic characteristics correlated with a diagnosis of neurodegenerative disorder and a non-neurodegenerative condition, in order to better triage patients presenting with cognitive complaints from primary care.

Material and methods

Study design and setting

We conducted an observational, retrospective cohort, hospital-based, single-center study, analyzing the demographic and clinical data of adult patients who were referred to a Neurology outpatient clinic at the São João Local Health Unit (ULS São João) due to cognitive complaints. The data collected were obtained from the hospital's computerized medical records from January 2019 to July 2024. Patients' clinical files referred from primary care for cognitive complaints were extensively retrospectively reviewed.

Inclusion and exclusion criteria

The inclusion criteria comprised patients referred for cognitive complaints to a Neurology outpatient clinic at ULS São João who were 18 years of age or older. Patients referred to the Neurology clinic due to cognitive complaints who had a diagnosis of dementia established at the first appointment or had been previously diagnosed with dementia were excluded.

Diagnosis of neurodegenerative and non-degenerative disorder

Participants were considered to have a neurodegenerative disease if the attending neurologist established a diagnosis of dementia, mild cognitive impairment, or considered the patient to have features suggestive of a neurodegenerative disorder even if the patient did not meet strict clinical criteria for dementia or mild cognitive impairment, and merited follow-up and ancillary examinations (usually brain imaging, neuropsychological evaluation, and CSF or PET studies). If, after follow-up, a neurodegenerative disorder was ruled out, the patient was reclassified as "non-neurodegenerative disorder".

Participants were classified as having cognitive complaints in a non-degenerative context if they were considered to occur due to attention deficit, functional neurological disorder, psychopathology and/or concentration difficulties, or associated with medication side effects and/or other medical conditions.

Study variables

Patients' data were collected from computerized medical records. All clinical and paraclinical data were collected by the same researcher and, in case of

uncertainty, other researchers were consulted. Data were collected from the records of two different doctors (DF, RA).

We collected sociodemographic data including age, gender, education level, occupation, employment status, marital status and household composition. Clinical data included the duration of cognitive symptoms, personal medical history, including psychiatry conditions and chronic pain, and other medical conditions such as cardiovascular risk factors (hypertension, dyslipidemia, diabetes, smoking, excessive alcohol consumption, heart conditions, chronic obstructive pulmonary disease), hearing loss, sleep disorders, nutritional deficits. Additionally, family history of dementia, exposure to responsibility-demanding tasks (which included driving, working, managing money and medication, being a caregiver for others), and major cognitive complaints (leaving the stove on, selling or buying things in an inappropriate way, getting lost in a familiar place or any action that endangers oneself or others) were assessed. Other specific cognitive complaints were also collected, including memory complaints such as difficulty retaining information and repetitive speech; temporal or spatial disorientation; mood and behavior changes such as disinhibition, aggressiveness, anxiety or depressive symptoms, and apathy; executive dysfunction, including difficulty planning. Furthermore, we recorded the existence of a recognizable precipitating event prior to the beginning of the complaints and whether cognitive complaints were self-reported or reported by a family member. Objective clinical examination findings assessed included the presence of primitive reflexes, focal neurological signs, and parkinsonism. Performance in the MMSE was evaluated, with cognitive decline defined as scores falling below the established cut-off values for the Portuguese population: 22 for individuals with 0–2 years of education, 24 for those with 3–6 years, and 27 for those with 7 or more years of education. We also evaluated the cognitive domains preferentially affected, if the patients justified a correct answer, and the delayed recall. Additional clinical signs analyzed included the head-turning sign (patients who turn their head towards their accompanying family member to seek assistance with the questions and tasks proposed by the examiner) and the attended alone sign (patients who appear alone to the appointment). Imaging findings from computed tomography (CT) or magnetic resonance imaging (MRI), when

available, were reviewed, to identify specific characteristics, mainly focal or asymmetric atrophy, global atrophy and existence of cerebrovascular disease. Initially, sociodemographic and clinical data of patients with cognitive complaints who met the inclusion criteria were collected and classified as having a probable neurodegenerative or non-neurodegenerative disease based on the clinician's first impression. Subsequently, the patients' clinical trajectory was monitored, using medical records from the ULS São João and family physician records to determine whether there was a diagnostic change from a non-degenerative disease to a neurodegenerative disease. Finally, we re-analysed the data of all patients who had either a first diagnosis as a probable neurodegenerative disease or who switched to this diagnosis over time.

Statistical analysis

Data were analyzed using SPSS software (version 30.0). Descriptive statistics are presented as frequencies (n) and percentages (%) for categorical variables, and medians (Med) and quartiles (Q1 – Q3) for continuous variables. Logistic regression models were implemented to assess the association between multiple covariates with cognitive complaints in a degenerative context, as well as the subsequent transition from a non-degenerative diagnosis to a degenerative diagnosis. For multivariate adjustment, we selected variables related to symptoms, objective examination findings and complementary diagnostic tests that had $p < 0.10$. These variables were carefully selected, considering the sample size and the number of events. ROC curves were computed to assess the predictive capacity of multivariate logistic models and the Youden index was used to determine the optimal cut-off point.

Ethics committee approval

This study was approved by the Ethics Committee of ULS São João/Faculty of Medicine of the University of Porto on October 31st, 2024.

Results

Study population

- Sociodemographic data

The study sample comprised 283 patients, of whom 165 (58.3%) were female, with a median age of 73.0 years (interquartile range (IQR) 65.0-79.0).

In terms of educational attainment, 61.1% of participants completed up to 4 years of schooling, 26.1% had completed 5 to 12 years of school, and 5.7% had obtained a higher education degree. Additionally, 7.1% of the sample had an unknown level of education.

Regarding professional status, 15.9% were employed, 7.4% were unemployed, and 75.6% were retired. A small percentage (1.1%) had an unknown employment status.

In terms of marital status, data showed that 2.1% of the sample was single, 61.1% was married, 6.0% was divorced, 11.0% was widowed, and 19.8% had an unknown marital status. Regarding living arrangements, 75.6% lived with others, 13.4% lived alone, and 11.0% had an unknown living situation.

- Personal medical background

Personal medical history data revealed that 29.2% of participants had a history of psychiatric condition or chronic pain. Cardiovascular risk factors were present in 79.2% of the participants. Other relevant health conditions included hearing loss (18.0%), nutritional deficits (7.4%) and sleep disorders (11.7%).

- Family medical background

A family history of dementia was identified in 18.4% of patients.

- Symptoms

Symptoms reported by patients or their family members included spatial disorientation (12.0%), temporal disorientation (14.8%), difficulty in retaining information/repetitive speech and difficulty planning (10.2%). Anxiety and

depressed mood were reported in 17.0% and 17.7% of the patients, respectively, while aggressiveness was found in 9.9%, apathy in 6.0%, and disinhibition in 2.1% of cases. Exposure to responsibility-demanding tasks were present in 53.4% of patients, and 14.5% had major cognitive complaints, defined as history of cognitive impairment likely to cause harm to self or others, and/or requiring assistance from spouse / caretaker. The mean duration of cognitive symptoms was 1.1 years. Symptoms were attributed to a precipitating event in 15.5% of patients, and 25.8% reported non-cognitive complaints. Symptoms were self-reported by the patient in 62.9% of cases, while family members reported them in 52.7%.

- Objective examination

On neurological examination, primitive reflexes were present in 8.5%, parkinsonism (defined by a combination of bradykinesia, rigidity, and gait changes, with or without overt tremor) in 5.3%, and focal neurological signs in 11.0% of participants. The median MMSE score was 27.0 (IQR: 23.0–29.0). Based on education-specific cut-off values for the Portuguese population, 71.7% of patients were classified as having no cognitive decline. Regarding MMSE sub-scores, 49.5% failed the recall task, 43.1% failed the temporal orientation task, 36.4% failed the spatial orientation task, 34.6% failed the attention and calculation task, 30.0% failed the copying task, 25.1% failed the language task and 4.6% failed the registration task. In the delayed recall task, 12.4% recalled all three words, 9.5% recalled two words, 2.5% recalled only one word, and 4.2% were unable to recall any words. No information on this task was available for 71.4% of the sample. Among those who recall at least one word, semantic and multiple-choice cues were provided. Following these cues, 12.4% of patients retrieved at least one word, while 3.9% still could not recall any words.

- Complementary means of diagnosis

Imaging findings from brain CT or MRI revealed that 32.2% of patients had focal or asymmetric atrophy, while 7.8% had global atrophy. Cerebrovascular disease was present in 41.7% of cases. Notably, the majority of these findings came from

neuroradiology reports, and the images were not available to either the primary care physician and to the attending neurologist.

- **Diagnosis**

A diagnosis of a neurodegenerative condition was made in 38.2% of patients, while 59.7% were diagnosed with a non-degenerative condition. A subsequent change in diagnosis to a degenerative condition occurred in 9.5% of the sample, with a median time to diagnosis change of 16.0 months (IQR: 7.0–23.0 months).

(Table 1)

Sample characteristics and association with a probable neurodegenerative disease diagnosis

- **Sociodemographic data**

Regarding gender, 39.1% of individuals in the non-degenerative group and 46.3% in the degenerative group were male, while 60.9% of the non-degenerative group and 53.7% of the degenerative group were female. There was no statistically significant difference between females and males (OR=0.74, $p=0.234$). The median age was 71.0 years (IQR: 61.0–77.0) in the non-degenerative group and 76.0 years (IQR: 71.0–80.0) in the degenerative group, with older age being significantly associated with a degenerative diagnosis (OR=1.05, $p<0.001$).

In terms of education levels, there were significant differences observed in the group who completed up to 5-12y of school, having lower chances of a neurodegenerative disorder. Regarding professional status, retired individuals had significantly higher odds of receiving a degenerative diagnosis compared to employed individuals (OR=3.42, $p=0.002$). No significant association was found between living alone and a degenerative diagnosis (OR=1.40, $p=0.346$).

- **Personal medical background**

With respect to personal medical history, psychiatric conditions and chronic pain was less common in the degenerative group (29.6%) compared to the non-degenerative group (43.8%), with a statistical significance (OR=0.54, $p=0.019$).

- **Family medical background**

A family history of dementia was not significantly associated with a degenerative diagnosis.

- **Symptoms**

Engagement in responsibility-demanding tasks was less common in the degenerative group (45.4%) compared to the non-degenerative group (58.6%), with a significant association (OR=0.50, $p=0.015$). Major cognitive complaints were more frequently reported in the degenerative group (21.3%) compared to the non-degenerative group (10.7%), with a significant association (OR=2.27, $p=0.017$). Difficulty in retaining information and repetitive speech was also more frequently observed in the degenerative group (39.8%) compared to the non-degenerative group (27.8%), with a significant association (OR=1.71, $p<0.045$). Anxiety was less common in the degenerative group (9.3%) compared to the non-degenerative group (22.5%), with a significant association (OR=0.34, $p=0.005$). Apathy was more prevalent in the degenerative group (3.7%) than in the non-degenerative group (0.6%), without a significant association (OR = 6.30, $p = 0.102$).

Patient self-awareness of symptoms was less common in the degenerative group (48.1%) compared to the non-degenerative group (71.0%), with a significant association (OR=0.47, $p=0.021$).

- **Objective examination**

Neurological examination findings revealed that primitive reflexes were more frequently observed in the degenerative group (11.1%) compared to the non-degenerative group (7.1%), but without significance (OR=1.64, $p=0.251$). The median MMSE score was significantly lower in the degenerative group (23.5, IQR: 21.0–26.0) compared to the non-degenerative group (28.0, IQR: 26.0–29.0), with a significant association (OR=0.80, $p<0.001$). Being classified as having cognitive decline according to the MMSE score was significantly more common in the degenerative group (52.8%) compared to the non-degenerative group (12.4%), with a significant association (OR=7.88, $p<0.001$).

The MMSE sub-scores demonstrated significant differences between the two groups, with poorer performance in the degenerative group across various cognitive domains. For temporal orientation, 31.4% of the non-degenerative group scored incorrectly, compared to 63.0% in the degenerative group, with a significant association (OR=3.81, $p=0.001$). For spatial orientation, 26.6% of the non-degenerative group scored incorrectly, compared to 52.8% in the degenerative group, with a significant association (OR=3.07, $p<0.001$). For recall, 38.5% of the non-degenerative group scored incorrectly, compared to 68.5% in the degenerative group, with a significant association (OR=3.66, $p<0.001$). For language, 16.6% of the non-degenerative group scored incorrectly, compared to 38.9% in the degenerative group, with a significant association (OR=2.90, $p<0.001$). For copying, 17.8% of the non-degenerative group scored incorrectly, compared to 50.0% in the degenerative group, with a significant association (OR=4.83, $p<0.001$). Additionally, the head-turning sign was significantly more frequent in the degenerative group (OR 2.89, $p=0.031$), while the attended alone sign was significantly more common in the non-degenerative group (OR 0.15, $p<0.001$).

- Complementary diagnostic tests

Complementary diagnostic tests revealed that focal or asymmetric atrophy was more common in the degenerative group (44.4%) compared to the non-degenerative group (24.9%), with a significant association (OR=2.40, $p=0.001$). In contrast, global atrophy and cerebrovascular disease did not show significant associations with diagnosis.

Table 2 and **Fig. 1** presents odds ratios (OR) and p-values to assess associations with a diagnosis of a neurodegenerative condition.

Sample characteristics and association with change of diagnosis to neurodegenerative disease

- Sociodemographic data

Regarding gender distribution, 39.4% of individuals in the group with no change in diagnosis and 33.3% of those whose diagnosis progressed to a neurodegenerative disease were male, whereas 60.6% and 66.7%, respectively, were female. Female patients had slightly higher odds of transitioning to a neurodegenerative diagnosis compared to males, but this was not statistically significant (OR=1.30, $p=0.547$). The median age was 71.0 years (IQR: 61.0–78.0) in the no-change group and 75.0 years (IQR: 69.0–79.0) in the group with a change in diagnosis, with age significantly associated with a change to a neurodegenerative diagnosis (OR=1.04, $p=0.042$). Education levels were similar between groups, with no significant differences observed. Regarding professional status, retired individuals had higher odds of changing to a neurodegenerative diagnosis compared to those who were employed, though this was not statistically significant (OR=2.34, $p=0.188$). Living alone was not significantly associated with a change in diagnosis (OR=0.63, $p=0.557$).

- Personal medical background

No significant associations were identified between a personal history of psychiatry conditions or chronic pain and a change in the diagnosis (OR 0.65, $p=0.321$).

Similarly, the presence of cardiovascular risk factors were not significantly associated with a change in diagnosis. Hearing impairment exhibited a trend toward significance, with higher odds in those who changed to a neurodegenerative diagnosis (OR=2.23, $p=0.088$).

- Family medical background

A family history of dementia did not show significant associations with a change in diagnosis.

- Symptoms

Apathy showed a similar trend toward significance, with higher odds in the group where a change to a neurodegenerative diagnosis occurred (OR=4.40, $p=0.053$). The presence of precipitating events before the onset of cognitive complaints was less common in this group, with a trend toward significance (OR=0.17, $p=0.088$).

- Objective examination

Neurological examination findings revealed that parkinsonism was significantly more common in those whose diagnosis changed to neurodegenerative (14.8%) compared to the no-change group (4.1%), with a significant association (OR=4.05, $p=0.035$). The median MMSE score was significantly lower in the group where the diagnosis changed to degenerative disease (24.0, IQR: 23.0–25.5) compared to those with no change in diagnosis (28.0, IQR: 26.0–29.0), with a significant association (OR=0.86, $p=0.001$). Cognitive impairment, based on MMSE classification, was significantly more common in the group where the diagnosis changed to neurodegenerative disease (37.0%) compared to those with no change in diagnosis (12.4%), with a statistically significant association (OR=4.17, $p=0.002$).

Analysis of specific MMSE sub-scores showed significant differences between groups. For temporal orientation, 52.4% of individuals with no change in diagnosis answered correctly, compared to 40.7% of those whose diagnosis changed, with a trend toward significance (OR=2.29, $p=0.056$). For spatial orientation, 57.1% of the no-change group answered correctly, compared to 33.3% in the group with diagnosis change, with a significant association (OR=4.07, $p=0.002$). In the recall task, 43.5% of the no-change group scored correctly, compared to 29.6% in those with diagnosis change, with a significant association (OR=2.70, $p=0.029$). In the language domain, 64.7% of the no-change group performed correctly, compared to 48.1% in the change to degenerative group, with a significant association (OR=4.23, $p=0.001$). In the copying task, 64.7% of the no-change group scored correctly, compared to 40.7% of those whose diagnosis changed, with a significant association (OR=5.00, $p<0.001$).

- Complementary means of diagnosis

Complementary diagnostic tests indicated that focal or asymmetric atrophy showed a trend toward significance, with higher odds in the group whose diagnosis has changed (OR=2.22, $p=0.076$). However, neither global atrophy nor cerebrovascular disease exhibited significant associations with diagnostic change.

Table 3 presents crude odds ratios (OR) and p-values to assess associations with change to a neurodegenerative diagnosis.

Multivariate analysis

After conducting univariate analysis, we carefully selected a set of potentially explanatory variables for a diagnosis of a neurodegenerative disease and for the change of first diagnosis to a neurodegenerative diagnosis over time. Given the small sample size, we ended up choosing the variables that we consider most important taking into account what we see in clinical practice. The set of explanatory variables for a neurodegenerative diagnosis included: age, presence of major cognitive complaints, MMSE score classification with cognitive decline, MMSE temporal orientation task, MMSE recall task, MMSE delayed recall task and presence of focal or asymmetric atrophy (**Table 4**).

Regarding age, the adjusted odds ratio (aOR) was 1.08 ($p = 0.135$). For major cognitive complaints, the aOR was 1.62 ($p = 0.898$), while MMSE-classified cognitive decline had an aOR of 1.45 ($p = 0.675$). Failure in the MMSE temporal orientation task showed an aOR of 2.93 ($p = 0.210$), whereas failure in the MMSE recall task had an aOR of 0.91 ($p = 0.909$).

In the MMSE delayed recall task, not achieving any of the words was significantly associated with a higher likelihood of a neurodegenerative diagnosis, with aOR values of 39.66. The presence of focal or asymmetric atrophy was significantly associated with the diagnosis, with an aOR of 10.21 ($p = 0.014$).

The set of explanatory variables for change to neurodegenerative diagnosis over time included: age, MMSE score classification, MMSE recall task, presence of

focal or asymmetric atrophy on imaging and presence of signs of parkinsonism. **(Table 5)**

Age had an aOR of 1.01 ($p=0.554$), while MMSE-classified cognitive decline had an aOR of 2.49 ($p=0.111$). Failure in the MMSE recall task had an aOR of 1.49 ($p=0.444$), and focal/asymmetric atrophy had an aOR of 2.05 ($p=0.149$). The presence of parkinsonism was significantly associated with diagnostic change, with an aOR of 1.27 ($p=0.007$).

Finally, we evaluated the diagnostic performance of the two multivariate models for predicting a neurodegenerative diagnosis and the likelihood of a change to a neurodegenerative diagnosis over time. A score was computed based on the non-exponentiated coefficients of each multivariate model and applied to the included patients. **(Table 6)**

ROC curves were constructed to assess the predictive quality of the models. The predictive capacity for a neurodegenerative diagnosis was 93.4%.

The Youden index was used to determine the optimal sensitivity and specificity balance. Hence, for identifying clinical characteristics indicative of a neurodegenerative disease as a final diagnosis, a score ≥ 7.56 yielded a sensitivity of 87.0% and a specificity of 88.4%. **(Fig. 2)**

Discussion

Sample Characteristics Associated with Neurodegenerative Disease

It is expected that the number of people at risk for cognitive impairment and dementia will rise significantly in the coming years, either due to the aging of the population, or the increase in chronic diseases [4, 11]. Identifying at-risk states and detecting early neurodegenerative disease are essential for effective targeted dementia prevention [12]. Therefore, it is essential to understand which sociodemographic and clinical characteristics may help identify these patients, in order to refer them to the neurology outpatient clinic more efficiently and at an earlier stage.

In our cohort, **female and younger patients** had lower odds of having a degenerative diagnosis, which is noteworthy since age is one of the most well-established risk factor for developing dementia [4]. Regarding professional status, **retirement** was significantly associated with a degenerative diagnosis, which may be explained not only by the fact that this group comprises older individuals, but also by the reduced cognitive stimulation experienced at this stage of life. Research suggests that a lack of mentally challenging activities might exacerbate the loss of cognitive function. Based on this premise, retirement has been proposed as a factor that may elevate the risk of cognitive decline, and a significant reduction in the risk of developing dementia among individuals who retire at an older age has also been observed [13]. On the other hand, a deterioration in cognitive function can adversely impact the ability to manage work-related tasks and, consequently, may influence the decision to retire in this group of patients [14].

Concerning personal medical history, we observed a reduced frequency of a **psychiatry conditions** diagnosis in the degenerative group. The results in the literature are ambiguous regarding the impact of depression on cognitive complaints. While the association between a major depressive episode and diminished cognitive performance is well documented, it remains uncertain whether cognitive impairment persist following the resolution of the depressive episode [15]. Interestingly, some studies have shown a positive relationship between depression and a higher risk of dementia. However, it remains uncertain whether neurodegeneration or a risk factor for dementia, represents an early

manifestation of neurodegeneration, or arises as a response to initial cognitive deficits [16]. **Cardiovascular disease** and cognitive decline share several risk factors, and hypertension is considered the most significant modifiable vascular risk factor for the onset and progression of cognitive decline, but no significant association was found on our study [17].

On the other hand, although we would expect to observe an association between the existence of a **family history of dementia** and a degenerative diagnosis, as family history of dementia is a known risk factor for dementia independently of known genetic risk factors for AD, we speculate that this association was not found in our cohort due to the low representation of patients with a family history of dementia [18]. In addition, it is expected that a family history of dementia is associated with increased concern and vigilance for cognitive symptoms in other family members, which may lead to hypervigilance and overvaluation of minor symptoms that do not indicate degenerative causes of dementia, potentially blurring the differences found between both groups [6, 19]. The overvaluation of minor cognitive symptoms in this group is also in consistent with our findings, which show an association between major cognitive complaints with degenerative causes of dementia.

The capacity of **performing responsibility-demanding tasks**, such as driving, working, managing money and medication or being a caregiver for others was significantly less common in the degenerative group. In the non-degenerative group, individuals usually maintain the ability to perform all their daily tasks adequately, while in the degenerative, either because others around them notice some difficulties and take away these tasks of responsibility, or because they themselves stop performing them due to incapacity.

Complaints of **difficulty in retaining information and repetitive speech**, most commonly in the form of repetitive questions and statements or stories, as well as repetitive behavior were also more frequent in the degenerative group, and may provide useful clues for identifying patients belonging to this group [20].

Similarly, **apathy** showed significance in relation to a diagnosis of a neurodegenerative disease, as apathy is one of the most prevalent and enduring symptoms of dementia [21]. AD was identified as the condition most frequently associated with apathy and this clinical manifestation is also more prevalent in patients with higher vascular load [22].

As expected, patient self-awareness of symptoms was less common in the degenerative group, in contrast to the family's concern, which was more prevalent in this group. In non-degenerative conditions, as previously mentioned, symptoms often result from hypervigilance of minor issues, leading to greater awareness of complaints. Patients with degenerative dementia, on the other hand, often do not recognize their cognitive decline, and it is typically family members who report the symptoms and express concern [10].

The **head turning sign**, although not sensitive, is highly specific for cognitive impairment, with a high positive predictive value, and was significantly more common in the degenerative group. Conversely, **the attended alone sign** was much less common in the degenerative group, serving as a robust marker of both the absence of dementia and of cognitively healthy individuals with cognitive complaints [23, 24].

As expected, being classified as having **cognitive decline according to the MMSE** score was significantly more common in the degenerative group, with this tool correctly classifying only 58% of degenerative cases. In fact, the presence of false negatives constitutes a limitation of the MMSE, as it may be insufficiently sensitive for subtle cognition changes in MCI patients, and for dementias without an important decline in the memory domain [7, 25]. Regarding the MMSE sub-scores, significant differences were found between the non-degenerative and degenerative groups, in **temporal and spatial orientation, language, and copying and drawing** with poorer performance in the degenerative group, particularly in temporal orientation.

This highlights that, even if the final MMSE score is within the normal range, patients who struggle with these specific tasks, might warrant more attention regarding the possibility of an underlying degenerative process.

In the **delayed recall task**, we found that people who were unable to recall any of the words appear to have a higher risk of a neurodegenerative disease. Three-word recall task is commonly employed as brief assessments of verbal memory function. Although performance on the three-word recall task declines with age, most individuals experiencing normal aging can typically recall 2 or 3 words. This contrasts sharply with individuals with dementia, who are often able to recall 0 or 1 word, which is line with our results. [26]

Complementary diagnostic tests revealed that **focal or asymmetrical atrophy** was more common in the degenerative group, with a significant association. This was an anticipated finding, as both clinical manifestations and focal atrophy correlate to the pattern of dysfunctional protein accumulation involved in the pathophysiology of dementias. In AD, for example, the initial changes occur in the medial temporal lobe structures, including the entorhinal and perirhinal cortex, as well as the hippocampus, and then spread throughout the brain, affecting other regions in more advanced stages of the disease [27, 28].

Sample Characteristics Associated with Change to a Neurodegenerative Diagnosis

Once again, **age and retirement status** were significantly associated with a transition to a degenerative condition. **Hearing impairment** also exhibited a trend toward significance in relation to a change in diagnosis, which may be attributed to reduced cognitive stimulation in affected patients. Hearing impairment potentially contributes to cognitive decline by impairing language perception and communication, leading to decreased engagement in social interaction and participation in communication-dependent activities. Moreover, age-related hearing loss has been associated with functional decline and has been causally linked to frailty syndrome, which is a known risk factor for dementia [29, 30].

Similarly, **apathy**, defined as lack of interest and reduced emotional expression, showed a trend toward significance in relation to changes in diagnosis. As previously mentioned, apathy is one of the most prevalent symptoms of dementia. However, distinguishing it from mood disorders, such as depression, is not straightforward, and an initial misdiagnosis of cognitive complaints related to mood disorders may explain this trend towards an association between apathy and a subsequent change to a degenerative diagnosis.

Neurological examination findings revealed that **parkinsonism** was significantly more common in the group where a change in diagnosis occurred. Parkinsonism typically emerges in association with cognitive complaints in diseases such as Parkinson's disease-associated dementia, dementia with Lewy bodies, and normal pressure hydrocephalus, which are challenging diagnosis in the early stages but may become clearer as the disease progresses [31-33]. This finding highlights the importance of thorough neurological examination including the

extrapyramidal system, as the presence of even subtle parkinsonian features should prompt clinicians to consider neurodegenerative etiologies and maintain closer follow-up, even when initial cognitive assessments suggest non-degenerative causes.

Once again, it was observed that **cognitive decline, according to MMSE classification**, was significantly more common in the group where the diagnosis changed to degenerative disease and focal or asymmetric atrophy showed a trend toward significance, with higher odds in the group whose diagnosis changed.

The predictive capacity of the multivariate models as diagnostic tools for a degenerative diagnosis was 93.4%. Thus, our proposed diagnostic model, proves to be a valuable predictor of degenerative disease with a sensitivity of 87.4% and a specificity of 88.0%. Regarding diagnostic change, we observed lower sensitivity and specificity values, reflecting the lower number of events and reduced diagnostic accuracy.

Based on these findings, we recommend that clinicians remain particularly alert to the variables included in our model when evaluating patients with cognitive complaints, as these seem to be the strongest associations with a neurodegenerative disease diagnosis.

Limitations:

As a retrospective, single-center study, based on clinical records from only two physicians, with a relatively small sample size, the design introduces an inherent selection and self-confirmation biases. Thus, the patient sample may not accurately represent the broader population with cognitive complaints. Furthermore, the external validity of our findings is potentially compromised, as the results could reflect specific clinical practices of these particular physicians. In addition, the retrospective data collection methodology resulted in some missing values, which may have led to additional selection and information biases.

Another important limitation is that our study examined only cases initially classified as non-degenerative that were later reclassified as degenerative, without investigating the reverse scenario. Although less frequent, the exclusion

of this scenario means our study may fail to fully capture the extent of diagnostic errors and may not address all the clinical challenges and uncertainties clinicians face when evaluating cognitive complaints. Also, the diagnosis of a neurodegenerative disorder and non-degenerative was mainly based on clinical judgement, rather than having a biomarker confirmed diagnosis. This notwithstanding, the follow-up period allows a reasonable amount of time to account for misdiagnosis, assuming that a patient with a neurodegenerative disorder misdiagnosed as non-degenerative, would have later returned to the clinic. Also, the other way around is also possible, i.e people with non-degenerative being labelled as neurodegenerative – these are notoriously more challenging cases, and this lack of objective / paraclinical criteria may limit the conclusions.

Additionally, AD constitutes the predominant cause of dementia among patients in our cohort. Consequently, the characteristics identified as associated with neurodegenerative pathology primarily reflect the clinical profile of AD, rather than representing the full spectrum of neurodegenerative conditions that also warrant referral to Neurology specialized appointments.

Given the above-listed limitations, we suggest further validation through prospective, multicenter studies to confirm the reliability and generalizability of our proposed diagnostic model.

Despite these constraints, our study demonstrates several notable strengths. We were able to assemble a significant substantial sample size and analyzed a comprehensive set of clinical and sociodemographic variables. In addition, the application of a multivariate analysis enhances the statistical rigor of our findings by taking into account potential confounding factors and interactions between variables.

For future research directions, we propose implementing our model in diverse clinical settings with appropriate longitudinal follow-up.

Conclusion

In conclusion, our study has identified several key sociodemographic and clinical characteristics that should alert clinicians to a potential neurodegenerative pathology. Specifically, we propose that patients with the following specific profile should be prioritized in the triage process of memory clinics primarily concerned with diagnosing patients with early Alzheimer's disease who may be eligible for disease modifying treatments, if and when these are available. **(Table 7)**

With the emergence of novel therapeutic approaches and the increasing prevalence of cognitive complaints in primary health care settings, it is essential to equip primary care physicians with effective tools to identify patients who should be referred to neurology outpatient clinic. Characteristics such as advanced age, retirement status, cognitive decline as measured by the MMSE score, the head turning sign, and poorer performance in specific MMSE domains, particularly time and spatial orientation, language and copy and in delayed recall, as well as neuroimaging evidence of focal or asymmetric atrophy, strongly indicate in our study the possibility of a neurodegenerative pathology. This may change in the future, with the appearance of smartphone apps and remote testing concerning cognitive impairment, and also blood-based biomarkers testing, both of which may very well revolutionize current clinical practice in dementia and pre-dementia diagnosis. However, until then, clinical evaluation remains the gold standard of dementia and mild cognitive impairment diagnosis, and we hope our paper will empower clinicians in primary care as well as triaging in specialized healthcare settings.

We believe these are valuable clinical markers that can be readily assessed in primary care settings, potentially improving the efficiency of the referral process and ensuring that patients with neurodegenerative conditions receive timely specialist evaluation and appropriate interventions.

References

1. Nicolás Pérez Palmer M, a, Barbara Trejo Ortega, MD Pallavi Josh. Cognitive Impairment in Older Adults
Epidemiology, Diagnosis, and Treatment. *Psychiatr Clin North Am.* 2022;45(4):639–61.
2. The Lancet N. Dementia diagnosis in the anti-amyloid era. *Lancet Neurol.* 2024;23(3):219.
3. Porsteinsson AP, Isaacson RS, Knox S, Sabbagh MN, Rubino I. Diagnosis of Early Alzheimer's Disease: Clinical Practice in 2021. *J Prev Alzheimers Dis.* 2021;8(3):371-86.
4. Atri A. The Alzheimer's Disease Clinical Spectrum: Diagnosis and Management. *Med Clin North Am.* 2019;103(2):263-93.
5. Ball HA, McWhirter L, Ballard C, Bhome R, Blackburn DJ, Edwards MJ, et al. Functional cognitive disorder: dementia's blind spot. *Brain.* 2020;143(10):2895-903.
6. Schindler SE, Li Y, Li M, Despotis A, Park E, Vittert L, et al. Using Alzheimer's disease blood tests to accelerate clinical trial enrollment. *Alzheimers Dement.* 2023;19(4):1175-83.
7. Arevalo-Rodriguez I, Smailagic N, Roque-Figuls M, Ciapponi A, Sanchez-Perez E, Giannakou A, et al. Mini-Mental State Examination (MMSE) for the early detection of dementia in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev.* 2021;7(7):CD010783.
8. Bennett K, Diamond C, Hoeritzauer I, Gardiner P, McWhirter L, Carson A, et al. A practical review of functional neurological disorder (FND) for the general physician. *Clin Med (Lond).* 2021;21(1):28-36.
9. Cabreira V, McWhirter L, Carson A. Functional Cognitive Disorder: Diagnosis, Treatment, and Differentiation from Secondary Causes of Cognitive Difficulties. *Neurol Clin.* 2023;41(4):619-33.
10. Hallett M, Aybek S, Dworetzky BA, McWhirter L, Staab JP, Stone J. Functional neurological disorder: new subtypes and shared mechanisms. *Lancet Neurol.* 2022;21(6):537-50.
11. Larson EB, Yaffe K, Langa KM. New insights into the dementia epidemic. *N Engl J Med.* 2013;369(24):2275-7.
12. Jessen F, Amariglio RE, van Boxtel M, Breteler M, Ceccaldi M, Chételat G, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers Dement.* 2014;10(6):844-52.
13. Dufouil C, Pereira E, Chêne G, Glymour MM, Alépovitch A, Saubusse E, et al. Older age at retirement is associated with decreased risk of dementia. *Eur J Epidemiol.* 2014;29(5):353-61.
14. Xue B, Cadar D, Fleischmann M, Stansfeld S, Carr E, Kivimäki M, et al. Effect of retirement on cognitive function: the Whitehall II cohort study. *Eur J Epidemiol.* 2018;33(10):989-1001.
15. Semkovska M, Quinlivan L, O'Grady T, Johnson R, Collins A, O'Connor J, et al. Cognitive function following a major depressive episode: a systematic review and meta-analysis. *Lancet Psychiatry.* 2019;6(10):851-61.
16. Sáiz-Vázquez O, Gracia-García P, Ubillos-Landa S, Puente-Martínez A, Casado-Yusta S, Olaya B, et al. Depression as a Risk Factor for Alzheimer's

- Disease: A Systematic Review of Longitudinal Meta-Analyses. *J Clin Med*. 2021;10(9).
17. Qiu C, Fratiglioni L. A major role for cardiovascular burden in age-related cognitive decline. *Nat Rev Cardiol*. 2015;12(5):267-77.
 18. Wolters FJ, van der Lee SJ, Koudstaal PJ, van Duijn CM, Hofman A, Ikram MK, et al. Parental family history of dementia in relation to subclinical brain disease and dementia risk. *Neurology*. 2017;88(17):1642-9.
 19. Vrijse J, Abu-Hanna A, de Rooij SE, Smidt N. Association between dementia parental family history and mid-life modifiable risk factors for dementia: a cross-sectional study using propensity score matching within the Lifelines cohort. *BMJ Open*. 2021;11(12):e049918.
 20. Cullen B, Coen RF, Lynch CA, Cunningham CJ, Coakley D, Robertson IH, et al. Repetitive behaviour in Alzheimer's disease: description, correlates and functions. *Int J Geriatr Psychiatry*. 2005;20(7):686-93.
 21. Gilmore-Bykovskyi A, Block L, Johnson R, Goris ED. Symptoms of apathy and passivity in dementia: A simultaneous concept analysis. *J Clin Nurs*. 2019;28(3-4):410-9.
 22. Tiel C, Sudo FK, Calmon AB. Neuropsychiatric symptoms and executive function impairments in Alzheimer's disease and vascular dementia: The role of subcortical circuits. *Dement Neuropsychol*. 2019;13(3):293-8.
 23. Soysal P, Usarel C, Ispirli G, Isik AT. Attended With and Head-Turning Sign can be clinical markers of cognitive impairment in older adults. *Int Psychogeriatr*. 2017;29(11):1763-9.
 24. Larner AJ. Screening Utility of the "Attended Alone" Sign for Subjective Memory Impairment. *Alzheimer Disease & Associated Disorders*. 2014;28(4):364-5.
 25. Guerreiro* M. Testes de rastreio de defeito cognitivo e demência: uma perspectiva prática. *Revista Portuguesa de Clínica Geral* 2010;26(1).
 26. Chandler MJ, Lacritz LH, Cicerello AR, Chapman SB, Honig LS, Weiner MF, et al. Three-word recall in normal aging. *J Clin Exp Neuropsychol*. 2004;26(8):1128-33.
 27. Jack CR, Jr., Dickson DW, Parisi JE, Xu YC, Cha RH, O'Brien PC, et al. Antemortem MRI findings correlate with hippocampal neuropathology in typical aging and dementia. *Neurology*. 2002;58(5):750-7.
 28. van Oostveen WM, de Lange ECM. Imaging Techniques in Alzheimer's Disease: A Review of Applications in Early Diagnosis and Longitudinal Monitoring. *Int J Mol Sci*. 2021;22(4).
 29. Lin FR, Ferrucci L, An Y, Goh JO, Doshi J, Metter EJ, et al. Association of hearing impairment with brain volume changes in older adults. *Neuroimage*. 2014;90:84-92.
 30. Lin FR, Metter EJ, O'Brien RJ, Resnick SM, Zonderman AB, Ferrucci L. Hearing loss and incident dementia. *Arch Neurol*. 2011;68(2):214-20.
 31. Koros C, Stefanis L, Scarmeas N. Parkinsonism and dementia. *J Neurol Sci*. 2022;433:120015.
 32. Aloisio S, Satolli S, Bellini G, Lopriore P. Parkinsonism in complex neurogenetic disorders: lessons from hereditary dementias, adult-onset ataxias and spastic paraplegias. *Neurol Sci*. 2023;44(10):3379-88.
 33. Mostile G, Fasano A, Zappia M. Parkinsonism in idiopathic normal pressure hydrocephalus: is it time for defining a clinical tetrad? *Neurol Sci*. 2022;43(9):5201-5.

Tables and Figures

Table 1. Sample characteristics

	Statistic
Sociodemographic data	
Gender	
Female	165 (58.3%)
Age	73.0 (65.0 - 79.0)
Education	
0-4y	173(61.1%)
5-12y	74 (26.1%)
>12y	16 (5.7%)
Professional status	
Employed	45 (15.9%)
Unemployed	21 (7.4%)
Retired	214 (75.6%)
Unknown	3 (1.1%)
Marital status	
Single	6 (2.1%)
Married	173 (61.1%)
Divorced	17 (6.0%)
Widower	31 (11.0%)
Unknown	56 (19.8%)
Live alone	38 (13.4%)
Unknown	31 (11.0%)
Personal medical background	
Psychiatric conditions and chronic pain	108 (38.2%)
Cardiovascular risk factors	224 (79.2%)
Hearing impairment	51 (18.0%)
Sleep disorders	33 (11.7%)
Nutritional deficits	21 (7.4%)
Family medical background	
Family history of dementia	58 (18.4%)
Symptoms	
Time of evolution (years)	1.1 (0.8 - 4.0)
Responsibility tasks	151 (53.4%)
Unknown	54 (19.1%)
Major cognitive complaints	41 (14.5%)
Spatial disorientation	34 (12.0%)
Unknown	17 (6.0%)
Temporal disorientation	42 (14.8%)
Unknown	16 (5.7%)
Difficulty in retaining information, repetitive speech	87 (30.7%)
Unknown	16 (5.7%)
Unknown	16 (5.7%)
Disinhibition	6 (2.1%)
Unknown	16 (5.7%)
Aggressiveness	28 (9.9%)
Unknown	16 (5.7%)
Anxiety	48 (17.0%)
Unknown	16 (5.7%)
Depression	50 (17.7%)
Unknown	16 (5.7%)
Apathy	17 (6.0%)
Unknown	16 (5.7%)
Difficulty planning	29 (10.2%)
Unknown	17 (6.0%)
Precipitating Event	44 (15.5%)
Unknown	4 (1.4%)

	Statistic
Multiple Complaints	73 (25.8%)
Unknown	4 (1.4%)
Patient concern	178 (62.9%)
Unknown	55 (19.4%)
Family Concerns	149 (52.7%)
Unknown	120 (42.4%)
Objective examination	
Primitive reflexes	24 (8.5%)
Parkinsonism	15 (5.3%)
ocal signs	31 (11.0%)
Unknown	1 (0.4%)
MMSE score (0-30)	27.0 (23.0 - 29.0)
MMSE score classification with Cognitive decline	80 (28.3%)
MMSE Temporal Orientation- Fails	122 (43.1%)
Unknown	37 (13.1%)
MMSE Spatial Orientation-Fails	103 (36.4%)
Unknown	38 (13.4%)
MMSE Registration- Fails	13 (4.6%)
Unknown	44 (15.5%)
MMSE Attention and Calculation-Fails	98 (34.6%)
Unknown	41 (14.5%)
MMSE Recall-Fails	140 (49.5%)
Unknown	41 (14.5%)
MMSE Language-Fails	71 (25.1%)
Unknown	40 (14.1%)
MMSE Copying-Fails	85 (30.0%)
Unknown	42 (14.8%)
MMSE justification right answers	6 (2.1%)
MMSE delayed recall	
Hit 0	12 (4.2%)
Hit 1	7 (2.5%)
Hit 2	27 (9.5%)
Hit 3	35 (12.4%)
Unknown	202 (71.4%)
Head Turning Sign	19 (6.7%)
Attended alone Sign	47 (16.6%)
Complementary means of diagnosis	
Focal/asymmetric atrophy	91 (32.2%)
Unknown	28 (9.9%)
Global atrophy	22 (7.8%)
Unknown	28 (9.9%)
Cerebrovascular Disease	118 (41.7%)
Unknown	28 (9.9%)
Diagnosis	
Final diagnosis	
Non degenerative	169 (59.7%)
Degenerative	108 (38.2%)
Unknown	6 (2.1%)
Change of diagnosis to degenerative dementia	
No	170 (60.1%)
Yes	27 (9.5%)
Unknown	6 (2.1%)
Not applicable	80 (28.3%)
Time until change of diagnosis in months	16.0 (7.0 - 23.0)

Table 2. Crude odds ratios for associations with final diagnosis

	Final diagnosis: Non-degenerative (n=169)	Final diagnosis: Degenerative (n=108)	OR	p-value
Sociodemographic data				
Gender				
Male	66 (39.1%)	50 (46.3%)	REF	REF
Female	103 (60.9%)	58 (53.7%)	0.74	0.234
Age	71.0 (61.0-77.0)	76.0 (71.0-80.0)	1.05	<0.001***
Education				
0-4y	94 (61.0%)	75 (72.1%)	REF	REF
5-12y	51 (33.1%)	22 (21.2%)	0.54	0.039*
>12y	9 (5.8%)	7 (6.7%)	0.98	0.961
Unknown	15 (8.9%)	4 (3.7%)	Excluded	Excluded
Professional status				
Employed	36 (21.3%)	9 (8.3%)	REF	REF
Unemployed	18 (10.7%)	3 (2.8%)	0.67	0.577
Retired	112 (66.3%)	96 (88.9%)	3.42	0.002**
Unknown	3 (1.8%)	0 (0.0%)	Excluded	Excluded
Marital status				
Single	4 (2.4%)	2 (1.9%)	REF	REF
Married	104 (61.5%)	68 (63.0%)	1.31	0.76
Divorced	14 (8.3%)	3 (2.8%)	0.43	0.43
Widower	16 (9.5%)	13 (12.0%)	1.63	0.61
Unknown	31 (18.3%)	22 (20.4%)	Excluded	Excluded
Live alone	20 (11.8%)	17 (15.7%)	1.40	0.346
Unknown	17 (10.1%)	11 (10.2%)	Excluded	Excluded
Personal medical background				
Psychiatric conditions and chronic pain	74 (43.8%)	32 (29.6%)	0.54	0.019*
Cardiovascular risk factors	132 (78.1%)	87 (80.6%)	1.16	0.625
Hearing impairment	27 (16.0%)	24 (22.2%)	1.50	0.193
Sleep Disorders	22 (13.0%)	10 (9.3%)	0.68	0.342
Nutritional deficits	13 (7.7%)	8 (7.4%)	0.96	0.930
Family medical background				
Family history of dementia	32 (18.9%)	20 (18.5%)	0.97	0.931
Symptoms				
Time of evolution (years)	1.0 (0.58-3.00)	1.0 (0.83-2.0)	0.90	0.086‡
Responsibility tasks	99 (58.6%)	49 (45.4%)	0.50	0.015*
Unknown	32 (18.9%)	21 (19.4%)	Excluded	Excluded
Major cognitive complaints	18 (10.7%)	23 (21.3%)	2.27	0.017*
Spatial disorientation	18 (10.7%)	15 (13.9%)	1.34	0.434
Unknown	11 (6.5%)	6 (5.6%)	Excluded	Excluded
Temporal disorientation	20 (11.8%)	22 (20.4%)	1.87	0.064‡
Unknown	11 (6.5%)	5 (4.6%)	Excluded	Excluded
Difficulty in retaining information, repetitive speech	44 (27.8%)	41 (39.8%)	1.71	0.045*
Unknown	11 (6.5%)	5 (4.6%)	Excluded	Excluded
Disinhibition	5 (3.0%)	1 (0.9%)	0.30	0.275
Unknown	11 (6.5%)	5 (4.6%)	Excluded	Excluded
Aggressiveness	17 (10.1%)	11 (10.2%)	0.99	0.984
Unknown	11 (6.5%)	5 (4.6%)	Excluded	Excluded
Anxiety	38 (22.5%)	10 (9.3%)	0.34	0.005**
Unknown	11 (6.5%)	5 (4.6%)	Excluded	Excluded
Depression	35 (20.7%)	14 (13.0%)	0.58	0.086‡
Unknown	11 (6.5%)	5 (4.6%)	Excluded	Excluded
Apathy	5 (3.0%)	11 (10.2%)	3.36	0.019*
Unknown	11 (6.5%)	5 (4.6%)	Excluded	Excluded
Difficulty planning	19 (11.2%)	10 (9.3%)	0.78	0.550
Unknown	12 (7.1%)	5 (4.6%)	Excluded	Excluded
Precipitating Event	31 (18.3%)	12 (11.1%)	0.51	0.113
Unknown	2 (1.2%)	2 (1.9%)	Excluded	Excluded
Multiple Complaints	50 (29.6%)	22 (20.4%)	0.63	0.110
Unknown	1 (0.6%)	3 (2.8%)	Excluded	Excluded
Patient concern	120 (71.0%)	52 (48.1%)	0.47	0.021*
Unknown	23 (13.6%)	32 (29.6%)	Excluded	Excluded
Family Concerns	74 (43.8%)	72 (66.7%)	3.57	0.058‡
Unknown	84 (49.7%)	33 (30.6%)	Excluded	Excluded
Objective examination				
Primitive reflexes	12 (7.1%)	12 (11.1%)	1.64	0.251
Parkinsonism	7 (4.1%)	8 (7.4%)	1.85	0.248
Focal signs	18 (10.7%)	12 (11.1%)	1.06	0.883
Unknown	0 (0.0%)	1 (0.9%)	Excluded	Excluded
MMSE score (0-30)	28.0 (26.0-29.0)	23.5 (21.0-26.0)	0.80	<0.001***
MMSE score classification with Cognitive decline	21 (12.4%)	57 (52.8%)	7.88	<0.001***

	Final diagnosis: Non-degenerative (n=169)	Final diagnosis: Degenerative (n=108)	OR	p-value
MMSE Temporal Orientation-Fails	53 (31.4%)	68 (63.0%)	3.81	0.001***
Unknown	27 (16.0%)	10 (9.3%)	Excluded	Excluded
MMSE Spatial Orientation-Fails	45 (26.6%)	57 (52.8%)	3.07	<0.001***
Unknown	27 (16.0%)	11 (10.2%)	Excluded	Excluded
MMSE Registration-Fails	6 (3.6%)	7 (6.5%)	1.75	0.329
Unknown	31 (18.3%)	13 (12.0%)	Excluded	Excluded
MMSE Attention and Calculation-Fails	50 (29.6%)	46 (42.6%)	1.56	0.100
Unknown	31 (18.3%)	10 (9.3%)	Excluded	Excluded
MMSE Recall-Fails	65 (38.5%)	74 (68.5%)	3.66	<0.001***
Unknown	30 (17.8%)	11 (10.2%)	Excluded	Excluded
MMSE Language-Fails	28 (16.6%)	42 (38.9%)	2.90	<0.001***
Unknown	31 (18.3%)	9 (8.3%)	Excluded	Excluded
MMSE Copying-Fails	30 (17.8%)	54 (50.0%)	4.83	<0.001***
Unknown	29 (17.2%)	13 (12.0%)	Excluded	Excluded
MMSE justification right answers	4 (2.4%)	2 (1.9%)	0.78	0.775
MMSE delayed recall				
Hit 0	1 (0.6%)	11 (10.2%)	66.00	<0.001***
Hit 1	4 (2.4%)	3 (2.8%)	4.50	0.096‡
Hit 2	19 (11.2%)	6 (5.6%)	1.90	0.342
Hit 3	30 (17.8%)	5 (4.6%)	REF	REF
Unknown	115 (68.0%)	83 (76.9%)	Excluded	Excluded
Head Turning Sign	7 (4.1%)	12 (11.1%)	2.89	0.031*
Attended alone Sign	42 (24.9%)	5 (4.6%)	0.15	<0.001***
Complementary means of diagnosis				
Focal/asymmetric atrophy	42 (24.9%)	48 (44.4%)	2.40	0.001***
Unknown	18 (10.7%)	8 (7.4%)	Excluded	Excluded
Global atrophy	11 (6.5%)	10 (9.3%)	1.41	0.449
Unknown	18 (10.7%)	8 (7.4%)	Excluded	Excluded
Cerebrovascular Disease	70 (41.4%)	46 (42.6%)	0.99	0.956
Unknown	18 (10.7%)	8 (7.4%)	Excluded	Excluded

Results presented as n (%), OR and p-values; REF, reference category; unknown, not applicable or variables were at least one of the categories ≤ 1 for degenerative diagnosis were excluded; ‡p<0.10; *p<0.05; **p<0.01; ***p<0.001

Table 3. Crude odds ratios for associations with change of first diagnosis to degenerative

	Changed diagnosis: No (n=170)	Changed diagnosis: Degenerative (n=108)	OR	p-value
Sociodemographic data				
Gender				
Male	67 (39.4%)	9 (33.3%)	REF	REF
Female	103 (60.6%)	18 (66.7%)	1.30	0.547
Age	71.0 (61.0 - 78.0)	75.0 (69.0 - 79.0)	1.04	0.042*
Education				
0-4y	94 (61.0%)	15 (57.7%)	REF	REF
5-12y	51 (33.1%)	9 (34.6%)	1.11	0.825
>12y	9 (5.8%)	2 (7.7%)	1.39	0.690
Unknown	16 (9.4%)	1 (3.7%)	Excluded	Excluded
Professional status				
Employed	36 (21.2%)	3 (11.1%)	REF	REF
Unemployed	18 (10.6%)	2 (7.4%)	1.33	0.764
Retired	113 (66.5%)	22 (81.5%)	2.34	0.188
Unknown	3 (1.8%)	0 (0.0%)	Excluded	Excluded
Marital status				
Single	4 (2.4%)	0 (0.0%)	Excluded	Excluded
Married	105 (61.8%)	18 (66.7%)	Excluded	Excluded
Divorced	14 (8.2%)	2 (7.4%)	Excluded	Excluded
Widower	16 (9.4%)	0 (0.0%)	Excluded	Excluded
Unknown	31 (18.2%)	7 (25.9%)	Excluded	Excluded
Live alone	20 (11.8%)	2 (7.4%)	0.63	0.557
Unknown	17 (10.0%)	4 (14.8%)	Excluded	Excluded
Personal medical background				
Psychiatric conditions and chronic pain	74 (89.2%)	9 (33.3%)	0.65	0.321
Cardiovascular risk factors	133 (78.2%)	19 (70.4%)	0.66	0.368
Hearing impairment	27 (15.9%)	8 (29.6%)	2.23	0.088‡
Sleep Disorders	22 (12.9%)	4 (14.8%)	1.17	0.789
Nutritional deficits	13 (7.6%)	3 (11.1%)	1.51	0.543
Family medical background				
Family history of dementia	32 (18.8%)	5 (18.5%)	0.98	0.970
Symptoms				
Time of evolution (years)	2.0 (0.8 - 7.0)	1.0 (0.8 - 2.0)	0.86	0.213
Responsibility tasks	99 (58.2%)	13 (48.1%)	1.25	0.714
Unknown	33 (19.4%)	10 (37.0%)	Excluded	Excluded
Major cognitive complaints	18 (10.6%)	1 (3.7%)	0.32	0.284
Spacial disorientation	18 (10.6%)	5 (18.5%)	2.06	0.198
Unknown	11 (6.5%)	3 (11.1%)	Excluded	Excluded
Temporal disorientation	20 (11.8%)	5 (18.5%)	1.83	0.278
Unknown	11 (6.5%)	3 (11.1%)	Excluded	Excluded
Difficulty in retaining information, repetitive speech	44 (25.9%)	8 (29.6%)	1.31	0.567
Unknown	11 (6.5%)	3 (11.1%)	Excluded	Excluded
Disinhibition	5 (2.9%)	0 (0.0%)	0.00	0.999
Unknown	11 (6.5%)	3 (11.1%)	Excluded	Excluded
Aggressiveness	17 (10.0%)	2 (7.4%)	0.76	0.725
Unknown	11 (6.5%)	3 (11.1%)	Excluded	Excluded
Anxiety	38 (22.4%)	3 (11.1%)	0.45	0.222
Unknown	11 (6.5%)	3 (11.1%)	Excluded	Excluded
Depression	35 (20.6%)	4 (14.8%)	0.71	0.553
Unknown	11 (6.5%)	3 (11.1%)	Excluded	Excluded
Apathy	5 (2.9%)	3 (11.1%)	4.40	0.053‡
Unknown	11 (6.5%)	3 (11.1%)	Excluded	Excluded
Difficulty planning	20 (11.8%)	2 (7.4%)	0.63	0.548
Unknown	12 (7.1%)	3 (11.1%)	Excluded	Excluded
Precipitating Event	31 (18.2%)	1 (3.7%)	0.17	0.088‡
Unknown	2 (1.2%)	0 (0.0%)	Excluded	Excluded
Multiple Complaints	50 (29.4%)	7 (25.9%)	0.83	0.698
Unknown	1 (0.6%)	0 (0.0%)	Excluded	Excluded
Patient concern	120 (70.6%)	16 (59.3%)	1.16	0.828
Unknown	24 (14.1%)	8 (29.6%)	Excluded	Excluded
Family Concerns	74 (43.5%)	14 (51.9%)	2.08	0.499
Unknown	85 (50.0%)	12 (44.4%)	Excluded	Excluded
Objective examination				
Primitive reflexes	12 (7.1%)	1 (3.7%)	0.51	0.522
Parkinsonism	7 (4.1%)	4 (14.8%)	4.05	0.035*
Focal signs	18 (10.6%)	5 (18.5%)	1.92	0.240
MMSE score (0-30)	28.0 (26.0 - 29.0)	24.0 (23.0 - 25.5)	0.86	0.001**

	Changed diagnosis: No (n=170)	Changed diagnosis: Degenerative (n=108)	OR	p-value
MMSE score classification with Cognitive decline	21 (12.4%)	10 (37.0%)	4.17	0.002**
MMSE Temporal Orientation-Fails	53 (31.2%)	15 (55.6%)	2.29	0.056‡
Unknown	28 (16.5%)	1 (3.7%)	Excluded	Excluded
MMSE Spatial Orientation-Fails	45 (26.5%)	17 (63.0%)	4.07	0.002**
Unknown	28 (16.5%)	1 (3.7%)	Excluded	Excluded
MMSE Registration-Fails	6 (3.5%)	1 (3.7%)	0.88	0.908
Unknown	32 (18.8%)	1 (3.7%)	Excluded	Excluded
MMSE Attention and Calculation- Fails	50 (29.4%)	12 (44.4%)	1.41	0.422
Unknown	32 (18.8%)	0 (0.0%)	Excluded	Excluded
MMSE Recall-Fails	65 (38.2%)	19 (70.4%)	2.70	0.029*
Unknown	31 (18.2%)	0 (0.0%)	Excluded	Excluded
MMSE Language-Fails	28 (16.5%)	14 (51.9%)	4.23	0.001**
Unknown	32 (18.8%)	0 (0.0%)	Excluded	Excluded
MMSE Copying-Fails				<0.001**
Unknown	30 (17.6%)	15 (55.6%)	5.00	*
MMSE justification right answers	30 (17.6%)	1 (3.7%)	Excluded	Excluded
MMSE delayed recall	4 (2.4%)	2 (7.4%)	3.32	0.179
Hit 0	1 (0.6%)	1 (3.7%)	30.00	0.051
Hit 1	4 (2.4%)	0 (0.0%)	0.00	0.999
Hit 2	19 (11.2%)	2 (7.4%)	3.16	0.361
Hit 3	30 (17.6%)	1 (3.7%)	REF	REF
Unknown	116 (68.2%)	23 (85.2%)	Excluded	Excluded
Head Turning Sign	7 (4.1%)	2 (7.4%)	1.86	0.454
Attended alone Sign	42 (24.7%)	0 (0.0%)	0.00	0.997
Complementary means of diagnosis				
Focal/asymmetric atrophy	42 (24.7%)	11 (40.7%)	2.22	0.076‡
Unknown	18 (10.6%)	3 (11.1%)	Excluded	Excluded
Global atrophy	11 (6.5%)	3 (11.1%)	1.83	0.382
Unknown	18 (10.6%)	3 (11.1%)	Excluded	Excluded
Cerebrovascular Disease	71 (41.8%)	12 (44.4%)	1.14	0.764
Unknown	18 (10.6%)	3 (11.1%)	Excluded	Excluded

Results presented as n (%), OR and p-values; REF, reference category; unknown, not applicable or variables were at least one of the categories ≤ 1 for degenerative diagnosis were excluded; ‡p<0.10; *p<0.05; **p<0.01; ***p<0.001

Table 4. Multivariate analysis for final diagnosis

N=68, events= 19	aOR	p-value	95% CI
Age	1.08	0.135	0.98 – 1.19
Major cognitive complaints	1.62	0.898	0.12 – 11.44
MMSE score classification with cognitive decline	1.45	0.675	0.24 – 9.12
MMSE temporal orientation-Fails			
Fails	2.93	0.210	0.55– 15.76
MMSE recall-Fails			
Fails	0.91	0.909	0.19 – 4.41
MMSE delayed recall			
Hits 0	39.66	0.006	2.94-535.00
Hits 1	1.39	0.79	0.12-15.70
Hits 2	0.64	0.64	0.10 – 4.00
Hits 3	0.03	0.006**	0.02– 0.34
Focal/asymmetric atrophy	10.21	0.014*	1.59 – 65.56

Results presented as adjusted OR (aOR), p-values and 95% confidence intervals (95% CI); REF, reference;
‡p<0.10; *p<0.05; **p<0.01; ***p<0.001

Table 5. Multivariate analysis for change to degenerative diagnosis

N=151, events= 24	aOR	p-value	95% CI
Age	1.01	0.554	0.97 – 1.06
MMSE score classification with cognitive decline	2.49	0.111	0.81 – 7.65
MMSE recall-Fails	1.49	0.444	0.54 – 4.18
Focal/asymmetric atrophy	2.05	0.149	0.77 – 5.42
Parkinsonism	1.27	0.007**	1.89 – 55.94

Results presented as adjusted OR (aOR), p-values and 95% confidence intervals (95% CI); REF, reference;
‡p<0.10; *p<0.05; **p<0.01; ***p<0.001

Table 6. Coefficients of multivariate analysis for final and change to a degenerative diagnosis

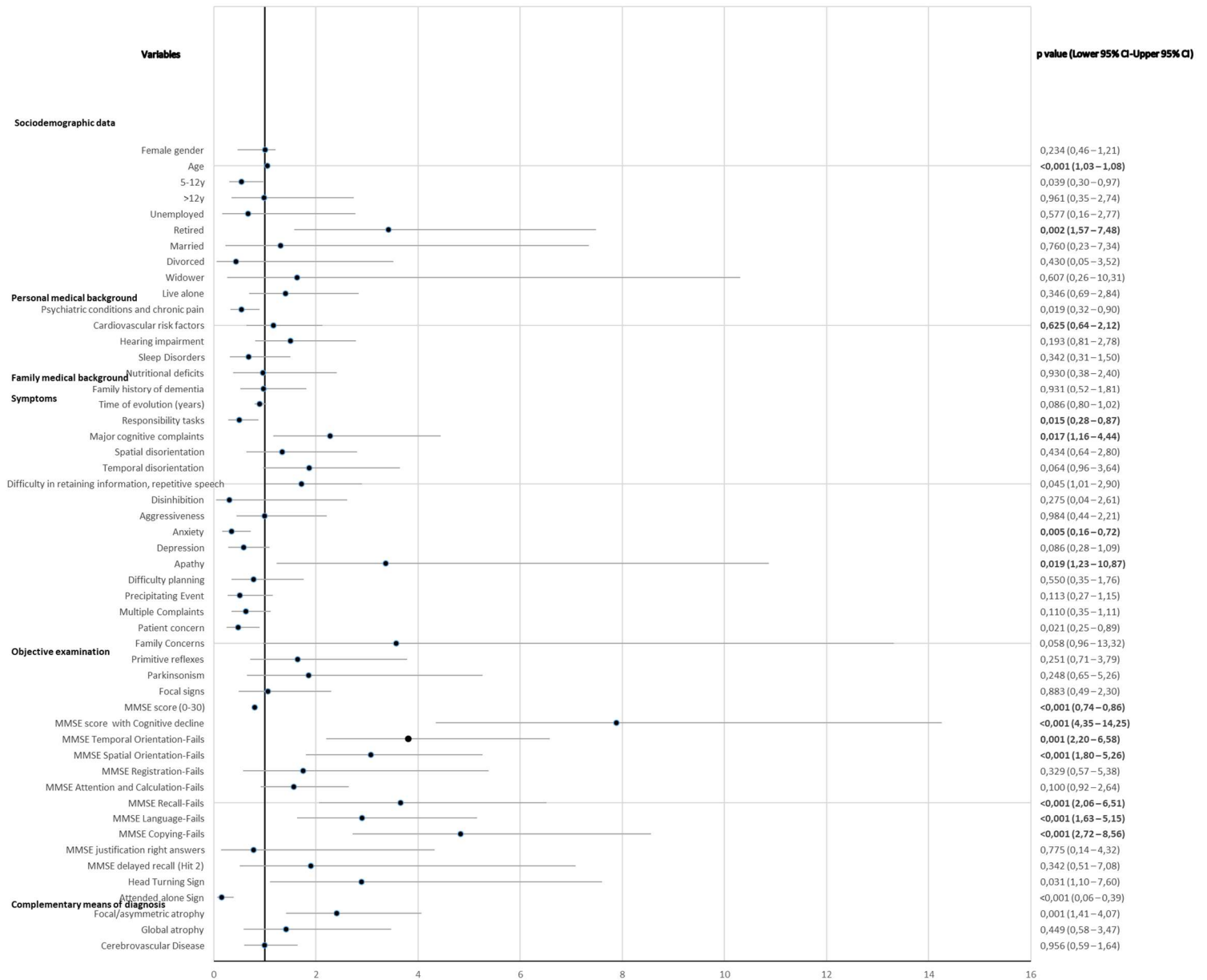
	First diagnosis		Change of diagnosis	
	B	S.E.	B	S.E.
Age	0.08	0.05	0.01	0.02
Major cognitive complaints	0.15	1.17		
MMSE score classification with cognitive decline	0.39	0.93	0.91	0.57
MMSE temporal orientation-Fails	1.08	0.86		
MMSE recall-Fails	-0.92	0.80	0.40	0.52
MMSE Delayed recall				
Hits 0	3.68	1.33		
Hits 1	0.33	1.24		
Hits 2	-0.44	0.93		
Focal/asymmetric atrophy	2.32	0.95	0.72	0.50
Parkinsonism			2.33	0.86
Mean score in data	6.98	0.29	1.88	0.06

B, unstandardized coefficient; S.E., standardized error

Table 7. Clinical characteristics in people presenting with cognitive complaints associated with a neurodegenerative diagnosis

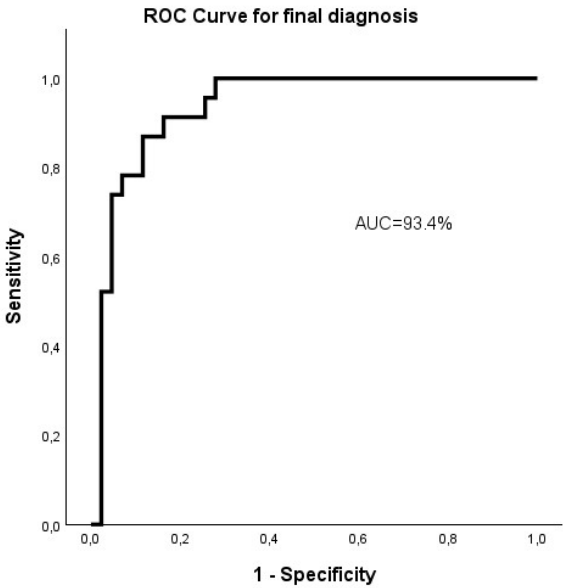
- Demographic:
 - Male gender
 - Older than 76 years
 - Retired
- History:
 - No previous psychiatric disorders
 - Difficulty performing highly-demanding tasks
 - Difficulty retaining information
 - Repetitive questioning and speech
 - Apathy
 - Impaired hearing
- Examination:
 - Head turning sign
 - Parkinsonism (bradykinesia, rigidity, gait problems)
 - MMSE below appropriate cut-offs (cut-off values for the Portuguese population: 22 for individuals with 0–2 years of education, 24 for those with 3–6 years, and 27 for those with 7 or more years of education)
 - MMSE errors in temporal orientation and/or copy (intersecting pentagons)
 - Errors in delayed recall testing
 - Focal or asymmetrical atrophy in head CT scan (as described in the report by the neuroradiologist)

Fig. 1 Schematic representation of the association between the various variables and the diagnosis of neurodegenerative disease



For the purpose of representativeness and improved readability of Figure 1, the values for the variables MMSE delayed recall (Hit 0) ($p < 0.001$ (CI 6.92-629.61)) and MMSE delayed recall (Hit 1) ($p = 0.096$ (CI 0.77-26.45)) were omitted from it.

Fig. 2 ROC curve for final diagnosis



Appendices:

- i. Reporting Guidelines (TRIPOD)
- ii. Submission guidelines of “Journal of Neurology”
- iii. Study Protocol
- iv. Ethics committee approval

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	Pg.1 "Establishing the profile of cognitive complaints associated with neurodegenerative dementia"
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	Pg 2 "Differentiating neurodegenerative and non-neurodegenerative disorders is important for several reasons, e.g., approval of disease-specific modifying treatments. Identifying patients in the early stages of a neurodegenerative disorder is a notoriously difficult task in primary care and in general outpatient clinics. This study aimed to identify the characteristics of people with cognitive complaints presenting to a Neurology appointment who later develop a neurodegenerative condition. We conducted a retrospective, single-center study of patients referred by primary care to the neurology outpatient clinic for cognitive complaints. Sociodemographic and clinical data were collected. The diagnoses of a "neurodegenerative disorder" or "non-degenerative disorder" were established per the judgement of the attending physician. Among 283 patients, 169 (59.7%) had a non-degenerative condition, 108 (38.2%) a neurodegenerative disease and 6 (2.1%) lost follow-up. The main characteristics associated with neurodegenerative disorder were: older age (OR 1.05), major cognitive complaints (i.e history of cognitive impairment likely to cause harm or requiring assistance from spouse / caretaker) (OR 2.27), a total score of Mini-Mental State Examination below the appropriate cut-off (OR 7.88), difficulties in memory recall bedside testing (OR 66.00), evidence of focal or asymmetrical atrophy in CT or MRI reports (OR 2.40). The multivariate analysis shows 93.4% accuracy, 87.4% sensitivity and 88% specificity in differentiating

			degenerative from non-degenerative cognitive disorders. This study identified traits that differentiate neurodegenerative from non-neurodegenerative cognitive complaints. Prospective application of this model should ideally be further explored in primary care, hopefully leading to more efficient triage of people presenting with cognitive complaints to primary care. “
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	Pg. 4 “The methods currently available for the initial assessment or screening of a patient with cognitive complaints, such as the Mini Mental State Examination (MMSE), are not used systematically and are not always scored correctly. The criteria for referral to neurological evaluation are also highly variable, and it is difficult to predict, based on clinical records, whether the patient has a high or low probability of having a progressive neurodegenerative condition and what its nature might be [7]. Thus, it is important to have appropriate clinical criteria that optimize the distinction between early-stage and incipient cases of degenerative forms of dementia (with a focus on Alzheimer's Disease) which are likely to benefit from quick referral for a neurological evaluation and follow-up, and cognitive complaints associated with non-degenerative conditions (psychiatric conditions, functional cognitive disorder, attention deficits or poor concentration, meta-memory problems, etc.). Remarkably, in these two situations, cognitive bedside testing lacks specificity [8-10].
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	Pg. 4 “We aimed to study which clinical and demographic characteristics correlated with a diagnosis of neurodegenerative disorder and a non-neurodegenerative condition, in order to better triage patients presenting with

			cognitive complaints from primary care.”
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	Pg.5 “We conducted an observational, retrospective cohort, hospital-based, single-center study”
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	Pg.5 “The data collected were obtained from the hospital’s computerized medical records from January 2019 to July 2024.”
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	Pg. 5 “analyzing the demographic and clinical data of adult patients who were referred to a Neurology outpatient clinic at the São João Local Health Unit (ULS São João) due to cognitive complaints.” “Patients clinical files referred from primary care for cognitive complaints were extensively retrospectively reviewed.”
	5b	Describe eligibility criteria for participants.	Pg. 5 “The inclusion criteria comprised patients referred for cognitive complaints to a Neurology outpatient clinic at ULS São João who were 18 years of age or older. Patients referred to the Neurology clinic due to cognitive complaints who had a diagnosis of dementia established at the first appointment or had been previously diagnosed with dementia were excluded.”
	5c	Give details of treatments received, if relevant.	Not applicable
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	Pg.5 “Participants were considered to have a neurodegenerative disease if the attending neurologist established a diagnosis of dementia, mild cognitive impairment, or considered the patient to have features suggestive of a neurodegenerative disorder even if the patient did not meet strict clinical criteria for dementia or mild cognitive impairment, and merited follow-up and ancillary examinations (usually brain imaging, neuropsychological evaluation, and CSF or PET studies). If, after follow-up, a neurodegenerative disorder was ruled out, the patient was reclassified as “non-neurodegenerative disorder”. Participants were classified as having cognitive complaints in a non-degenerative context if they were considered to occur due to attention deficit, functional neurological disorder,

			psychopathology and/or concentration difficulties, or associated with medication side effects and/or other medical conditions."
	6b	Report any actions to blind assessment of the outcome to be predicted.	Not applicable
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	Pg.6/7 "Patients' data were collected from computerized medical records. All clinical and paraclinical data were collected by the same researcher and, in case of uncertainty, other researchers were consulted. Data were collected from the records of two different doctors (DF, RA). We collected sociodemographic data including age, gender, education level, occupation, employment status, marital status and household composition. Clinical data included the duration of cognitive symptoms, personal medical history, including psychiatry conditions and chronic pain, and other medical conditions such as cardiovascular risk factors (hypertension, dyslipidemia, diabetes, smoking, excessive alcohol consumption, heart conditions, chronic obstructive pulmonary disease), hearing loss, sleep disorders, nutritional deficits. Additionally, family history of dementia, exposure to responsibility-demanding tasks (which included driving, working, managing money and medication, being a caregiver for others), and major cognitive complaints (leaving the stove on, selling or buying things in an inappropriate way, getting lost in a familiar place or any action that endangers oneself or others) were assessed. Other specific cognitive complaints were also collected, including memory complaints such difficulty retaining information and repetitive speech; temporal or spatial disorientation; mood and behavior changes such as disinhibition, aggressiveness, anxiety or depressive symptoms, and apathy; executive dysfunction, including difficulty planning. Furthermore, we recorded the

		existence of a recognizable precipitating event prior to the beginning of the complaints and whether cognitive complaints were self-reported or reported by a family member. Objective clinical examination findings assessed included the presence of primitive reflexes, focal neurological signs, and parkinsonism. Performance in the MMSE was evaluated, with cognitive decline defined as scores falling below the established cut-off values for the Portuguese population: 22 for individuals with 0–2 years of education, 24 for those with 3–6 years, and 27 for those with 7 or more years of education. We also evaluated the cognitive domains preferentially affected, if the patients justified a correct answer, and the delayed recall. Additional clinical signs analyzed included the head-turning sign (patients who turn their head towards their accompanying family member to seek assistance with the questions and tasks proposed by the examiner) and the attended alone sign (patients who appear alone to the appointment). Imaging findings from computed tomography (CT) or magnetic resonance imaging (MRI), when available, were reviewed, to identify specific characteristics, mainly focal or asymmetric atrophy, global atrophy and existence of cerebrovascular disease. Initially, sociodemographic and clinical data of patients with cognitive complaints who met the inclusion criteria were collected and classified as having a probable neurodegenerative or non-neurodegenerative disease based on the clinician's first impression. Subsequently, the patients' clinical trajectory was monitored, using medical records from the ULS São João and family physician records to determine whether there was a diagnostic change from
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			a non-degenerative disease to a neurodegenerative disease. Finally, we re-analysed the data of all patients who had either a first diagnosis as a probable neurodegenerative disease or who switched to this diagnosis over time."
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	Not applicable
Sample size	8	Explain how the study size was arrived at.	Pg.6 "Data were collected from the records of two different doctors (DF, RA)."
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	Complete-case analysis
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	Pg. 7 "Descriptive statistics are presented as frequencies (n) and percentages (%) for categorical variables, and medians (Med) and quartiles (Q1 – Q3) for continuous variables. Logistic regression models were implemented to assess the association between multiple covariates with cognitive complaints in a degenerative context, as well as the subsequent transition from a non-degenerative diagnosis to a degenerative diagnosis."
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	Pg.7 "For multivariate adjustment, we selected variables related to symptoms, objective examination findings and complementary diagnostic tests that had $p < 0.10$. These variables were carefully selected, considering the sample size and the number of events"
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	Pg.7 "ROC curve were computed to assess the predictive capacity of multivariate logistic models and the Youden index was used to determine the optimal cut-off point"
Risk groups	11	Provide details on how risk groups were created, if done.	Not applicable
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Pg.10 "A diagnosis of a neurodegenerative condition was made in 38.2% of patients, while 59.7% were diagnosed with a non-degenerative condition. A subsequent change in diagnosis to a degenerative condition occurred in 9.5% of the sample, with a median time to diagnosis change of 16.0 months (IQR: 7.0–23.0 months)."
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Pg.26/27 "Table 1. Sample characteristics"
Model development	14a	Specify the number of participants and outcome events in each analysis.	Pg.12 "Table 2 and Fig. 1 presents odds ratios (OR) and p-values to assess associations with a diagnosis of a neurodegenerative condition."

	14b	If done, report the unadjusted association between each candidate predictor and outcome.	Pg.12 "Table 2 and Fig. 1 presents odds ratios (OR) and p-values to assess associations with a diagnosis of a neurodegenerative condition."
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Pg.16 "Finally, we evaluated the diagnostic performance of the two multivariate models for predicting a neurodegenerative diagnosis and the likelihood of a change to a neurodegenerative diagnosis over time. A score was computed based on the non-exponentiated coefficients of each multivariate model and applied to the included patients"
	15b	Explain how to use the prediction model.	Pg.15 "The set of explanatory variables for a neurodegenerative diagnosis included: age, presence of major cognitive complaints, MMSE score classification with cognitive decline, MMSE temporal orientation task, MMSE recall task, MMSE delayed recall task and presence of focal or asymmetric atrophy"
Model performance	16	Report performance measures (with CIs) for the prediction model.	Pg. 16 "ROC curves were constructed to assess the predictive quality of the models. The predictive capacity for a neurodegenerative diagnosis was 93.4%."
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	Pg.21/22 "As a retrospective, single-center study, based on clinical records from only two physicians, with a relatively small sample size, the design introduces an inherent selection and self-confirmation biases. Thus, the patient sample may not accurately represent the broader population with cognitive complaints. Furthermore, the external validity of our findings is potentially compromised, as the results could reflect specific clinical practices of these particular physicians. In addition, the retrospective data collection methodology resulted in some missing values, which may have led to additional selection and information biases. Another important limitation is that our study examined only cases initially classified as non-degenerative that were later reclassified as degenerative, without investigating the reverse scenario."

			Although less frequent, the exclusion of this scenario means our study may fail to fully capture the extent of diagnostic errors and may not address all the clinical challenges and uncertainties clinicians face when evaluating cognitive complaints. Also, the diagnosis of a neurodegenerative disorder and non-degenerative was mainly based on clinical judgement, rather than having a biomarker confirmed diagnosis. This notwithstanding, the follow-up period allows a reasonable amount of time to account for misdiagnosis, assuming that a patient with a neurodegenerative disorder misdiagnosed as non-degenerative, would have later returned to the clinic. Also, the other way around is also possible, i.e people with non-degenerative being labelled as neurodegenerative – these are notoriously more challenging cases, and this lack of objective / paraclinical criteria may limit the conclusions. Additionally, AD constitutes the predominant cause of dementia among patients in our cohort. Consequently, the characteristics identified as associated with neurodegenerative pathology primarily reflect the clinical profile of AD, rather than representing the full spectrum of neurodegenerative conditions that also warrant referral to Neurology specialized appointments.”
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	Pg.17-21 “In our cohort, female and younger patients had lower odds of having a degenerative diagnosis, which is noteworthy since age is one of the most well-established risk factor for developing dementia(...)Based on these findings, we recommend that clinicians remain particularly alert to the variables included in our model when evaluating patients with cognitive complaints, as these seem to be the strongest associations with a neurodegenerative disease diagnosis.”

Implications	20	Discuss the potential clinical use of the model and implications for future research.	Pg.23 "We believe these are valuable clinical markers that can be readily assessed in primary care settings, potentially improving the efficiency of the referral process and ensuring that patients with neurodegenerative conditions receive timely specialist evaluation and appropriate interventions."
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Appendix iii.
Funding	22	Give the source of funding and the role of the funders for the present study.	Pg.1 "Conflicts of Interest and Source of Funding: None declared."

We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

Journal of Neurology

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- Book chapter

Brown B, Aaron M (2001) The politics of nature. In: Smith J (ed) The rise of modern genomics, 3rd edn. Wiley, New York, pp 230-257

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Cartwright J (2007) Big stars have weather too. IOP Publishing PhysicsWeb. <http://physicsweb.org/articles/news/11/6/16/1>. Accessed 26 June 2007

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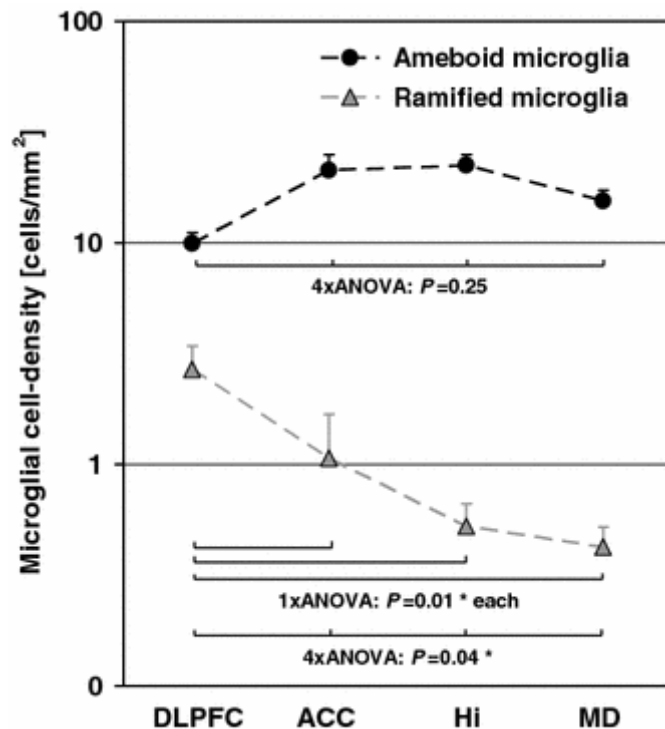
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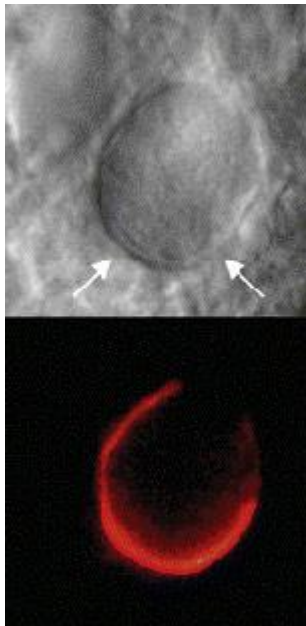
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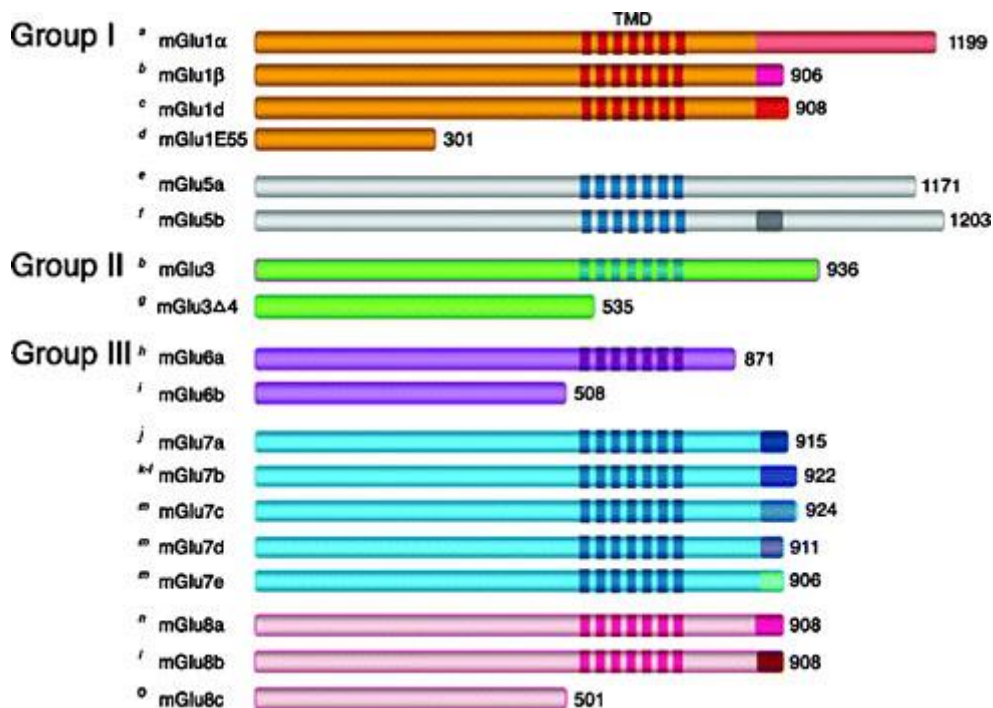
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- No funding was received for conducting this study.
- No funds, grants, or other support was received.

Examples of statements to be used when there are interests to declare:

- **Financial interests:** Author A has received research support from Company A. Author B has received a speaker honorarium from Company W and owns stock in Company X. Author C is consultant to company Y.

Non-financial interests: Author C is an unpaid member of committee Z.

- **Financial interests:** The authors declare they have no financial interests.

Non-financial interests: Author A is on the board of directors of Y and receives no compensation as member of the board of directors.

- **Financial interests:** Author A received a speaking fee from Y for Z. Author B receives a salary from association X. X where s/he is the Executive Director.

Non-financial interests: none.

- **Financial interests:** Author A and B declare they have no financial interests. Author C has received speaker and consultant honoraria from Company M and Company N. Dr. C has received speaker honorarium and research funding from Company M and Company O. Author D has received travel support from Company O.

Non-financial interests: Author D has served on advisory boards for Company M, Company N and Company O.

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- The authors have no relevant financial or non-financial interests to disclose.
- The authors have no competing interests to declare that are relevant to the content of this article.
- All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.
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Queixas cognitivas associadas a doença neurodegenerativa: definição de perfil de risco

Autores: Mafalda Silva¹, Carolina Correia², Rui Araújo^{2,3}

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Centro de Investigação: Serviço de Neurologia, ULS São João, Porto, Portugal

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PÁGINA DE ASSINATURA DOS INVESTIGADORES *(a ser assinada pelo Investigador Principal)*

Título do estudo: Queixas cognitivas associadas a doença neurodegenerativa: definição de perfil de risco

Data do Protocolo: Maio de 2024

Centro de Investigação: ULS São João, Porto

Investigadora Principal: Carolina Correia

A investigadora principal, abaixo assinado, é responsável pela condução do estudo no Centro Hospitalar e Universitário de São João e afirma que o estudo será realizado de acordo com o protocolo apresentado, quaisquer alterações a ele aprovadas e com todos os requerimentos aplicáveis das Autoridades de Saúde e Leis Nacionais.

O estudo não será desviado do protocolo sem consentimento prévio por escrito por parte dos restantes investigadores, exceto quando necessário de modo a evitar dano imediato do participante em estudo.

Assinatura: Maria Carolina Gemelgo Correia

Data: 09 de junho de 2024

1. RACIONAL

O panorama terapêutico nas demências, nomeadamente na Doença de Alzheimer, encontra-se em grande mudança. A aprovação recente de fármacos inovadores nos Estados Unidos da América e no Japão, nomeadamente anticorpos monoclonais dirigidos à proteína amiloide, indicados para fases precoces da Doença de Alzheimer, provavelmente conduzirão a grandes mudanças a nível da organização dos cuidados de saúde. Não obstante a controvérsia existente em relação à eficácia, segurança e custos associados ao diagnóstico e seleção adequada de doentes, à administração destes fármacos e à monitorização e vigilância de efeitos adversos, existe uma clara tendência para o diagnóstico precoce e suportado por biomarcadores de Doença de Alzheimer. (1)

O diagnóstico precoce de Doença de Alzheimer é especialmente desafiante. As fases iniciais da doença podem pautar-se por queixas aparentemente banais, como lapsos aparentemente benignos e sensação de rendimento intelectual inferior, sem repercussão significativa no quotidiano da pessoa e sem gerar alarme familiar ou social. A situação é muito semelhante aos défices atencionais e dificuldades de concentração, que são praticamente ubíquos na população adulta nas sociedades ocidentais modernas, que se associam a pesados horários de trabalho, com elevada exigência profissional e auto-crítica. A contribuição de fatores múltiplos, como o sono pouco conciliado, as perturbações depressivas e ansiosas e a iatrogenia associada a fármacos de variada natureza, leva a que as pessoas recorram com frequência aos cuidados médicos com o legítimo receio de poderem estar numa fase inicial da Doença de Alzheimer. (2)

O aparecimento de um fármaco modificador de doença com indicação para estes estádios iniciais torna a situação ainda mais problemática. Em primeiro lugar, pelo previsível aumento de procura de cuidados especializados e acesso a consultas de Neurologia e/ou consultas de Memória ou Demência. Em segundo lugar, pelos custos tecnológicos e de recursos humanos necessários para o estabelecimento deste tipo de diagnósticos. Ainda que, a médio prazo, se espera que surjam análises sanguíneas para doseamento de proteínas que se associam aos biomarcadores clássicos da Doença de Alzheimer, é ainda incerto como estas atuarão no percurso clínico do doente. (4) Contudo, em nenhum cenário se espera que estas venham a substituir a avaliação clínica por médico especialista, esperando-se sim que funcionem como critério de suporte ou rastreio. Os métodos atualmente disponíveis para avaliação inicial ou de rastreio de um doente com queixas cognitivas, como por exemplo o *Mini Mental State Examination*, não são usados de forma sistemática nem sempre pontuados corretamente. Os critérios de admissão à consulta são igualmente muito variáveis, sendo difícil prever, pelo registado previamente à consulta de Neurologia, se o doente tem elevada ou baixa probabilidade de um quadro demencial, e qual a sua natureza. (5)

Assim, importa ter critérios clínicos sólidos que permitam a mais precoce e fidedigna distinção possível entre quadros iniciais e incipientes de formas degenerativas de demência (com enfoque na Doença de Alzheimer) e queixas cognitivas associadas a quadros não degenerativos (quadros psiquiátricos, perturbação cognitiva funcional, défices atencionais ou concentração, problemas de meta-memória, etc). (6,7,8)

Para este fim, decidiu-se analisar as características clínicas de doentes referenciados por queixas de memória a consulta de Neurologia de um hospital terciário e verificar se existem diferenças substanciais entre os doentes posteriormente diagnosticados com quadros degenerativos e os doentes com situações não degenerativas.

2. OBJETIVO

Identificar características clínicas de doentes referenciados por queixas cognitivas a consulta de Neurologia da Unidade Local de Saúde São João que sejam específicas ou altamente sugestivas de quadros demenciais neurodegenerativos, em oposição a quadros não degenerativos.

3. PERGUNTA DE INVESTIGAÇÃO

Que características podem auxiliar na distinção entre doentes com queixas cognitivas subjetivas associadas a quadros demenciais neurodegenerativos de quadros não degenerativos?

4. METODOLOGIA DO ESTUDO

- Desenho do estudo: Estudo analítico, coorte retrospectivo, de base hospitalar, unicêntrico, nacional.
- Número de participantes previsto: 100
- Seleção dos participantes: Doentes referenciados à consulta externa de Neurologia da ULS São João por queixas cognitivas entre 2021 e 2023.
- Procedimentos/intervenções:
 - Submissão do protocolo do estudo para a Comissão de Ética (CE) da ULS São João.
 - Recolha de dados demográficos e clínicos dos participantes (que preencham os critérios de inclusão e não apresentem critérios de exclusão) de acordo com as variáveis do estudo (enumeradas no ponto 7), através do acesso aos registos clínicos eletrónicos (RCE) dos participantes.
 - Divisão dos participantes em dois grupos: “doença degenerativa” e “não degenerativa”.
 - Análise estatística para identificação de características presentes exclusivamente ou preferencialmente em cada um dos grupos.
 - Elaboração de *check-list* para utilização em consulta a nível dos cuidados de saúde primários ou em consulta de Neurologia Geral para identificar indivíduos com risco mais elevado de doença degenerativa.

5. CRITÉRIOS DE INCLUSÃO

- Doentes referenciados por queixas cognitivas à consulta externa de Neurologia da ULS São João (2021 – 2023).
- Doentes com idade igual ou superior a 18 anos.

6. CRITÉRIOS DE EXCLUSÃO

- Doentes referenciados à consulta externa de Neurologia por queixas cognitivas em que o diagnóstico de demência foi realizado na primeira consulta ou estava previamente estabelecido.

7. VARIÁVEIS DO ESTUDO

- Sociodemográficas: Idade, género, escolaridade, profissão, estado laboral, estado civil, agregado familiar
- Clínicas:
 - Tempo de follow-up;
 - Grau de autonomia;
 - Atividades quotidianas: rotinas do dia-a-dia, exposição a tarefas de responsabilidade;
 - Antecedentes pessoais: perturbação depressiva, ansiedade, outros diagnósticos de doenças psiquiátricas, outras doenças médicas (hipertensão arterial, tabagismo, hipoacusia, etc);
 - Antecedentes familiares: síndromes demenciais, patologia psiquiátrica;
 - Queixas cognitivas major a ponto de causar prejuízo e/ou risco elevado para si ou para terceiros;
 - Queixas mnésicas: esquecimento, desorientação temporal, dificuldade de retenção informação, existência de gradiente antigo-recente;
 - Alterações de humor/comportamento: desinibição, agressividade, ansiedade, depressão, apatia;
 - Alterações executivas: dificuldade em completar tarefas, seguir instruções, planeamento;
 - Alterações imagiológicas em tomografia computadorizada ou ressonância magnética.
 - Desempenho em provas cognitivas de cabeceira (MMSE com score total abaixo da idade ou escolaridade, dificuldade preferencial num domínio, justificação de resposta correta, etc)
 - Achados do exame objetivo (reflexos primitivos, sinais focais, etc)
- Definição operacional de doença neurodegenerativa

- Doente que médico neurologista estabelece diagnóstico de demência ou défice cognitivo ligeiro, por critérios clínicos
- Se o doente for submetido a biomarcadores (de LCR ou imagiológicos) e se estes forem positivos, considerar-se-á “D. Alzheimer definida por biomarcadores”
- Definição operacional de doença não degenerativa
 - Doente a quem foi estabelecido diagnóstico de queixas cognitivas no contexto de défice atencional/ psicopatologia/ défice atencional e/ou concentração, que foi mantido em seguimento para vigilância ou que tenha tido alta clínica.

8. MÉTODOS ESTATÍSTICOS

- Análise descritiva- as variáveis serão apresentadas através de estatística descritiva: frequência absoluta (n) e relativa (%) para variáveis qualitativas; média, mediana, desvio padrão, mínimo e máximo para variáveis quantitativas. Os dados omissos não serão substituídos. Avaliação analítica – será realizada usando o SPSS , com aplicação do teste de Chi-quadrado para comparação de duas variáveis categóricas; para comparação de uma variável contínua com distribuição normal, de acordo com uma variável categórica com dois grupos independentes será usado o teste t para amostras independentes e recorreremos ao teste one way ANOVA perante variáveis categóricas com vários grupos independentes. Em variáveis não normalmente distribuídas, serão utilizados os testes de Mann- Whitney U e o de Kruskal-Wallis. Será considerado como nível de significância estatística o valor de $p < 0,05$.

9. UTILIZAÇÃO E TRATAMENTO DE DADOS

Serão recolhidos dados através dos RCE dos doentes. Posteriormente, serão trabalhados estatisticamente. Os dados recolhidos serão confidenciais e pseudonimizados, sendo utilizados unicamente para o propósito do presente estudo.

10. PROPRIEDADE INTELECTUAL

Os dados clínicos dos doentes recolhidos através do acesso a RCE são da propriedade dos mesmos. A base de dados resultante desta recolha de dados é propriedade dos investigadores principais.

11. ÉTICA

O estudo será conduzido de acordo com os princípios éticos definidos pela Declaração de Helsínquia. A recolha de dados e o seu armazenamento cumprirão a legislação nacional aplicável, nomeadamente a Lei de Proteção de Dados Pessoais – Regulamento (UE) Nº.

2016/679, de 27 de abril de 2016. Uma cópia do protocolo do estudo será submetida à Comissão de Ética local com o objetivo de obter aprovação escrita para a realização do mesmo.

12. CALENDARIZAÇÃO DO PROTOCOLO

- Maio - Julho de 2024 – Redação e aprovação do protocolo
- Julho - Dezembro de 2024 - Colheita e análise de dados nos RCE

13. LIMITAÇÕES

Sendo um estudo retrospectivo, encontramos-nos dependentes da acuidade e do grau de detalhe dos registos clínicos, o que poderá interferir na colheita de variáveis clínicas e confundir os resultados.

O tempo de follow-up (1-3 anos) pode ser curto para sermos categóricos em relação ao carácter “não degenerativo” das queixas cognitivas.

14. CONSENTIMENTO INFORMADO

No caso de doentes que mantenham seguimento em consulta de Neurologia e/ou Demências da ULS São João, será solicitada autorização ao utente diretamente, de forma oportunista aquando da vinda do doente a consulta hospitalar de reavaliação, com explanação do estudo, partilha do protocolo deste, procedendo-se posteriormente à obtenção do consentimento informado.

No caso de doentes que já tenham tido alta hospitalar e não mantenham vínculo atual, procederemos a contacto telefónico solicitando autorização para avaliação dos registos clínicos no contexto do presente estudo, partilhando com o utente toda a informação tida por relevante.

Os dados recolhidos serão imediatamente anonimizados, pelo que o rastreamento da informação recolhida não será possível.

REFERÊNCIAS

1. The Lancet Neurology. Dementia diagnosis in the anti-amyloid era. Lancet Neurol. 2024 Mar;23(3):219. doi: 10.1016/S1474-4422(24)00041-3. PMID: 38365360.
2. Atri A. The Alzheimer's Disease Clinical Spectrum: Diagnosis and Management. Med Clin North Am. 2019 Mar;103(2):263-293. doi: 10.1016/j.mcna.2018.10.009. PMID: 30704681.
3. Ball HA, McWhirter L, Ballard C, et al. Functional cognitive disorder: dementia's blind spot. Brain 2020; 143: 2895–903.
4. Schindler SE, Li Y, Li M, Despotis A, Park E, Vittert L, et al. Using Alzheimer's disease blood tests to accelerate clinical trial enrollment. Alzheimer's & Dementia. 2022 Aug 7;

5. Arevalo-Rodriguez I, Smailagic N, Roqué-Figuls M, Ciapponi A, Sanchez-Perez E, Giannakou A, et al. Mini-Mental State Examination (MMSE) for the Early Detection of Dementia in People with Mild Cognitive Impairment (MCI). Cochrane Database of Systematic Reviews [Internet]. 2021 Jul 27;2021(7). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8406467/>
6. Bennett K, Diamond C, Hoeritzauer I, Gardiner P, McWhirter L, Carson A, et al. A practical review of functional neurological disorder (FND) for the general physician. Clinical Medicine [Internet]. 2021 Jan;21(1):28–36. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7850207/>
7. Cabreira V, McWhirter L, Carson A. Functional Cognitive Disorder. Neurologic Clinics. 2023 Mar;
8. Hallett M, Aybek S, Dworetzky BA, McWhirter L, Staab JP, Stone J. Functional neurological disorder: new subtypes and shared mechanisms. The Lancet Neurology. 2022 Apr;21

23 de Outubro de 2024

A Diretora do Centro de Epidemiologia Hospitalar

(Prof.ª Doutora Ana Azevedo)



SÃO JOÃO

n.º 213 / 2024

DIRECÇÃO CLÍNICA
2024-10-24

PEDIDO DE AUTORIZAÇÃO

Realização de Investigação

Deliberado concordar, nos
termos legais em vigor.Exmo(a). Senhor(a) Presidente do Conselho de Administração
do Centro Hospitalar Universitário de São João**Nome do Investigador Principal:**
Maria Carolina Gemelgo Correia**Título da Investigação:**Queixas cognitivas associadas a doença neurodegenerativa: definição de perfil
de riscoPretendo realizar no(s) Serviço(s) de:
Neurologiaa investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autoriza-
ção para a sua efetivação.Para o efeito, anexo toda a documentação referida no dossier da Comissão de Ética do Centro
Hospitalar Universitário de São João respeitante à investigação, à qual enderecei pedido de apre-
ciação e parecer.

Com os melhores cumprimentos.

O Investigador/Promotor

Porto, 09 de junho de 2024.

Maria Carolina Gemelgo Correia
assinatura

SÃO JOÃO

Encarregado
de Protecção de Dados
Data Protection Officer

Entrada

11/10/2024

• Centro Hospitalar São João •
Centro de Epidemiologia Hospitalar

11/10/2024

Parecer da Comissão de Ética do
Centro Hospitalar Universitário de São João
Unidade Local de Saúde de São João

Título do Projeto: Queixas cognitivas associadas a doença neurodegenerativa: definição de perfil de risco

Nome da Investigadora Principal: Dra. Maria Carolina Gemelgo Correia (interna de formação específica em Neurologia na ULS de São João). Serão co-investigadores Mafalda Sofia Maia da Silva (estudante da FMUP) e o Prof. Doutor Rui Manuel Moreira Araújo.

Onde decorre o Estudo: No Serviço de Neurologia da ULS de São João. Apresentou a declaração da Prof.^a Doutora Elsa Azevedo.

Objetivos do Estudo:

Identificar características clínicas de doentes referenciados por queixas cognitivas à consulta de Neurologia da Unidade Local de Saúde São João que sejam específicas ou altamente sugestivas de quadros demenciais neurodegenerativos, em oposição a quadros não degenerativos.

Conceção e Pertinência do estudo:

O estudo é pertinente e adequado, porquanto consta no protocolo submetido à CE: “importa ter critérios clínicos sólidos que permitam a mais precoce e fidedigna distinção possível entre quadros iniciais e incipientes de formas degenerativas de demência (com enfoque na Doença de Alzheimer) e queixas cognitivas associadas a quadros não degenerativos (quadros psiquiátricos, perturbação cognitiva funcional, défices atencionais ou concentração, problemas de meta-memória, etc). Para este fim, decidiu-se analisar as características clínicas de doentes referenciados por queixas de memória à consulta de Neurologia de um hospital terciário e verificar se existem diferenças substanciais entre os doentes posteriormente diagnosticados com quadros degenerativos e os doentes com situações não degenerativas”.

Serão recolhidos dados clínicos retrospectivos de doentes referenciados à consulta externa de Neurologia da ULS São João por queixas cognitivas entre 2021 e 2023, numa amostra estimada de 100 doentes.

A informação a recolher sobre os doentes englobará idade, género, escolaridade, profissão, estado laboral, estado civil, agregado familiar, tempo de follow-up, grau de autonomia, atividades quotidianas, rotinas do dia-a-dia, exposição a tarefas de responsabilidade, antecedentes pessoais, antecedentes familiares, queixas cognitivas major, queixas amnésicas, alterações de humor/ comportamento, alterações executivas, alterações imagiológicas, desempenho em provas cognitivas de cabeceira, achados do exame objetivo, definição operacional de doença neurodegenerativa, definição operacional de doença não degenerativa.

Benefício/risco: Não aplicável

Confidencialidade dos dados:

Os registos serão mantidos confidenciais. Após confirmação da ausência de registos duplicados, serão substituídos o número de utente por um número aleatório. Os dados serão mantidos em base de dados ao qual apenas os investigadores terão acesso. Os dados não serão utilizados para outros fins que não os do presente estudo.

Apresentou um pedido de reutilização de registos clínicos para Investigação e Desenvolvimento ao RAI, e uma 'avaliação sobre o impacto da proteção de dados' para o EPD.

Respeito pela liberdade e autonomia do sujeito de ensaio:

Dado o carácter retrospectivo do estudo, é admissível a dispensa de consentimento informado.

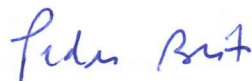
Curriculum da investigadora: Adequado à investigação.

Data previsível da conclusão do estudo: janeiro de 2025

Conclusão: Proponho um parecer favorável à realização do estudo.

Porto, 21 de junho de 2024

O Relator da CE, Doutor Pedro Brito





SÃO JOÃO

SUBMISSÃO DE PROJETO DE INVESTIGAÇÃO PARA PARECER E AUTORIZAÇÃO

Preenchimento em formato digital obrigatório

Caro/a Investigador/a

Este questionário vai ser objeto de apreciação pela Comissão de Ética (CE), que emitirá o competente parecer; pelo Responsável de Acesso à Informação (RAI), que emitirá um despacho de autorização ou indeferimento, relativamente à reutilização da informação a que pretende ter acesso; pelo Encarregado de Proteção de Dados (EPD), que emitirá um parecer, mediante a 'avaliação do impacto sobre a proteção de dados' (que deve anexar a este pedido); pelo Centro de Epidemiologia Hospitalar; sendo enviado, num último momento, para decisão institucional do Conselho de Administração do CHUSJ. Os respetivos despachos de parecer e autorização serão exarados no final deste documento, e enviados posteriormente, de modo a poder iniciar, nesse momento, a investigação a que se propõe.

IDENTIFICAÇÃO DO ESTUDO

Título do projeto:

Queixas cognitivas associadas a doença neurodegenerativa: definição de perfil de risco

Data prevista para início: 01 / 07 / 202

Data prevista para o término: 31 / 01 / 202

EQUIPA DE INVESTIGAÇÃO

1. Investigador principal

Nome: Maria Carolina Gemelgo Correia

Afiliação institucional: ☒ CHUSJ ☒ FMUP Outro: _____

Serviço/ Departamento: Neurologia

Grupo profissional: Médico (IFE) Cédula Profissional n.º: 72030

Contacto telefónico: 917140276 Endereço eletrónico institucional: maria.carolina.correia@ulssjoao.min-saude.pt

Formação em Boas Práticas Clínicas (GCP): ☐ Não ☒ Sim

2. Co-investigadores

Nome: Mafalda Sofia Maia da Silva

Afiliação institucional: Faculdade de Medicina da Universidade do Porto

Grupo profissional: Estudante Cédula Profissional n.º: _____

Contacto telefónico: 964698587 Endereço eletrónico institucional: up201905388@edu.med.up.pt

Nome: Rui Manuel Moreira Araújo

Afiliação institucional: ULS SJoão, FMUP

Grupo profissional: Médico Cédula Profissional n.º: _____

Contacto telefónico: 917757675 Endereço eletrónico institucional: rui.araujo@ulssjoao.min-saude.pt

(acrescentar n.º de investigadores, se apropriado ao projeto de investigação)

3. Promotor (se aplicável): _____

CARACTERIZAÇÃO DA INVESTIGAÇÃO

1. Metodologia da investigação

☐ Qualitativa ☒ Mista (qualitativa+quantitativa) ☐ Outra. Qual? _____

Se quantitativa:

☐ Experimental ☒ Observacional ☐ Sem intervenção ☐ Com intervenção

Se experimental ou observacional com intervenção, qual o tipo de intervenção?

☐ Algoritmo de decisão diagnóstica/terapêutica ☐ Comunicação

☐ Outra. Qual? _____

2. Aleatorização dos braços de intervenção: ☒ Não ☐ Sim

3. Se observacional, qual o desenho?

☐ Coorte prospetivo ☒ Coorte retrospectivo ☐ Caso-controlo

☐ Transversal ☐ Ecológico ☐ Outro. Qual? _____

REALIZAÇÃO DA INVESTIGAÇÃO

Local onde se realiza a investigação: ☒ CHUSJ ☐ FMUP ☐ Outro

Serviço/ Departamento: Neurologia

Existem outros Centros onde se realizará a investigação? ☒ Não ☐ Sim. Quais? _____

ENTIDADE(S) QUE TUTELA(M) A INVESTIGAÇÃO

1. CHUSJ – Serviço: Neurologia

2. FMUP – Departamento: Departamento de Neurociências Clínicas e Saúde Mental

3. Outra instituição. Qual? _____

ORIENTADOR (se aplicável)

Nome: Rui Manuel Moreira Araújo

Afiliação: ULS SJoão, FMUP Endereço eletrónico institucional: ruia.araujo@ulssjoao.min-saude.pt

PROFISSIONAL DE LIGAÇÃO (se aplicável - ver anexo)

Nome: _____ Serviço: _____

ENQUADRAMENTO DA INVESTIGAÇÃO

Em trabalho académico? ☐ Não ☒ Sim Conferidor de grau? ☐ Não ☒ Sim

Síntese dos objetivos:

Identificar características clínicas de doentes referenciados por queixas cognitivas à consulta de Neurologia da Unidade Local de Saúde São João que sejam específicas ou altamente sugestivas de quadros demenciais neurodegenerativos, em oposição a quadros não degenerativos.

Fundamentação ética (incluir informação sumária sobre o estado da arte, ganhos em conhecimento/ inovação, ponderação geral sobre benefícios/risco):

PARTICIPANTES PREVISTOS PARA A INVESTIGAÇÃO

Estão definidos critérios de inclusão / de exclusão de doentes? ☐ Não ☒ Sim

Onde e como serão recrutados os participantes no estudo?

Doentes referenciados à consulta externa de Neurologia da ULS São João por queixas cognitivas entre 2021 e 2023.

Qual é o tamanho amostral? 100

Está prevista a recolha de material biológico específico para a investigação?

☒ Não ☐ Sim. Identifique e justifique:

BENEFÍCIO/RISCO DECORRENTE DA PARTICIPAÇÃO

Descreva os benefícios previsíveis:

Descreva os riscos/incómodos previsíveis:

Não se prevêem riscos/incómodos para os doentes

CONSENTIMENTO INFORMADO, ESCLARECIDO E LIVRE

Prevê a obtenção de consentimento informado? ☐ Sim ☒ Não

Se não, justifique: Estudo observacional retrospectivo

Prevê informação escrita para os participantes? ☐ Sim. Enviar modelo preenchido.

☒ Não. Justifique: Estudo observacional retrospectivo

O modelo para obtenção de consentimento é o modelo institucional do CHUSJ? ☐ Sim ☐ Não

PROTEÇÃO DE DADOS PESSOAIS

Necessita consultar registos clínicos? ☐ Não ☒ Sim

Está previsto o tratamento de dados pessoais? ☐ Não ☒ Sim

Se sim, de que forma é garantida a pseudonimização dos dados recolhidos? (codificação, uso de filtros, siglas...)

Os registos serão mantidos confidenciais. Após confirmação da ausência de registos duplicados, substituiremos o número de utente por um número aleatório. Os dados serão mantidos em base de dados ao qual apenas os investigadores terão acesso. Os dados não serão utilizados para outros fins que não os do presente estudo.

Descreva o património informacional a que pretende ter acesso (v.g.: nome, idade, data nascimento, idade, morada, diagnóstico, história clínica, tratamento...):

Idade, género, escolaridade, profissão, estado laboral, estado civil, agregado familiar, tempo de follow-up, grau de autonomia, atividades quotidianas, rotinas do dia-a-dia, exposição a tarefas de responsabilidade, antecedentes pessoais, antecedentes familiares, queixas cognitivas major, queixas mnésicas, alterações de humor/comportamento, alterações executivas, alterações imagiológicas, desempenho em provas cognitivas de cabeceira, achados do exame objetivo, definição operacional de doença neurodegenerativa, definição operacional de doença não degenerativa

Está prevista a criação de um Banco de Dados? ☐ Não ☒ Sim

Está previsto o registo de som ou de imagem dos participantes? ☒ Não ☐ Sim

O estudo envolve investigação genética? ☒ Não ☐ Sim

PROPRIEDADE INTELECTUAL

De quem será a propriedade intelectual da investigação e seus resultados?

☒ Investigador ☐ Promotor ☐ Serviço/CHUSJ ☐ Todos

DIVULGAÇÃO DOS RESULTADOS

Está prevista a divulgação dos resultados da investigação? ☐ Não ☒ Sim

Se sim, estão definidos critérios de publicação? ☒ Não ☐ Sim. Quais? _____

CONTRAPARTIDAS PARA OS PARTICIPANTES

Estão previstas contrapartidas para os participantes? ☒ Não ☐ Sim

Pela participação? ☒ Não ☐ Sim

Pelas deslocações? ☒ Não ☐ Sim

Pelas perdas salariais? ☒ Não ☐ Sim

Por outras perdas e/ou danos? ☒ Não ☐ Sim

EXAMES COMPLEMENTARES DE DIAGNÓSTICO

Estão previstos exames complementares de diagnóstico, para além dos inerentes à rotina assistencial?

☒ Não ☐ Sim. Quais? _____

Por quem serão suportados estes custos?

PROTOCOLO FINANCEIRO

Existe protocolo financeiro com o CHUSJ? ☒ Não ☐ Sim

SEGURO

Este estudo prevê intervenção clínica que implique a existência de um seguro para os participantes?

☒ Não ☐ Sim (se sim, junte cópia da respetiva Apólice)

Data previsível para fim do acesso aos dados: 31 / 12 / 2024

DOCUMENTOS ANEXOS *(em suporte digital)*

- ☒ Pedido de autorização ao Presidente do Conselho de Administração do CHUSJ
- ☒ Protocolo do estudo
- ☐ Caderno de recolha de dados (CRF)
- ☒ Declaração Diretor(es) Serviço(s)
- ☒ Informação Orientador
- ☐ Profissional de ligação
- ☒ Informação aos participantes
- ☒ Modelo de consentimento a utilizar
- ☐ Instrumentos de avaliação (*escalas, inquéritos*) _____
- ☒ Curriculum/a vitae (*investigador/es*)
- ☒ Questionário para Encarregado de Proteção de Dados (EPD)
- ☐ Termo de Responsabilidade do Centro Académico Clínico (*para investigadores da FMUP que não pertençam ao CHUSJ*)
- ☐ Protocolo financeiro
- ☐ Outros: _____

TERMO DE RESPONSABILIDADE

Aceitação dos termos e condições de reutilização

Cumulativamente com as obrigações decorrentes da *Lei n.º 26/2016, de 22 de agosto*, maxime dos *n.º 2 e 3 do artigo 21 e o n.º 1 e 2 do artigo 12*, ao submeter o presente pedido, concordo e fico ainda juridicamente vinculado aos seguintes termos e condições:

- Comprometo-me a manter confidencial toda a informação à qual vou ter acesso;
- Após explicação do RAI do CHUSJ, embora a *Lei 26/2016, de 22 de agosto*, imponha como requisito a anonimização sem possibilidades de reversão, tal desiderato, é não só uma impossibilidade matemática já comprovada, como ainda resulta num prejuízo para a investigação, face à quantidade e à qualidade da informação a retirar à fonte, razão pela qual, concordando com o RAI, assumimos como compromisso a pseudonimização, o que impõe uma avaliação e gestão do risco, num quadro ético-jurídico que aceitamos e nos comprometemos a colaborar e respeitar;
- Não vou elaborar registos, suscetíveis de identificar ou tornar identificável a identidade das pessoas a quem os mesmos dizem respeito;
- Comprometo-me a consultar os processos clínicos nos termos e locais que me forem indicados para o efeito;
- Tomei conhecimento, que a violação de qualquer dos compromissos aqui assumidos, poderá resultar no apuramento de responsabilidades disciplinares, civis e penais, e ainda, à impossibilidade futura de aceder a informação de saúde para fins de investigação.
- Independentemente de requerer a Certidão de Reutilização, DAta REuse Certificate for Research (DARE), comprometo-me a citar as fontes, sempre que publicitar, no todo ou em parte, resultados da presente investigação.

COMPROMISSO DE HONRA E DECLARAÇÃO DE INTERESSES

Eu, Maria Carolina Gemelgo Correia,

abaixo assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes na Declaração de Helsínquia (1960, e sucessivas emendas), da Organização Mundial de Saúde, da Convenção de Oviedo e das 'Boas Práticas Clínicas' (GCP/ICH) no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CE de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo, nos últimos três meses. Comprometo-me a entregar à CE o relatório final da investigação, assim que concluído.

Data: 09 / 06 / 2024

Maria Carolina Gemelgo Correia

assinatura

COMISSÃO DE ÉTICA CHUSJ/FMUP

Parecer da CE, emitido na reunião plenária de 21 / 06 / 2024

A Comissão de Ética para a Saúde
APROVA por unanimidade o parecer do
Relator, pelo que nada tem a opor à
realização deste projecto de investigação.

-Centro Hosp. Univ. São João
Comissão de Ética
Manuel Vaz Silva
Presidente

RAI

24013733

RAI - Responsável pelo Acesso à Informação no Centro Hospitalar Universitário de São João (Art. 9º, Lei 26/2016 de 22 de Agosto)



AUTORIZADO
RAI Responsável pelo Acesso
à Informação no Centro
Hospitalar de São João
(Art. 9º, Lei 26/2016, de 22/8)

16/07/2024

CENTRO DE EPIDEMIOLOGIA HOSPITALAR



CUIDADOS
DE SAÚDE PRIMÁRIOS

Título do Projeto

Queixas cognitivas associadas a doença neurodegenerativa: definição de perfil de risco

Responsável pelo tratamento Maria Carolina Gemelgo Correia

Instituição Unidade Local de Saúde de São João (ULS SÃO JOÃO)

Faculdade de Medicina da Universidade do Porto (FMUP)

Investigador ☒ Interno ☐ Externo

Contacto telefónico 917140276

Endereço Electrónico u018233@ulssjoao.min-saude.pt

Profissional de Ligação Não aplicável

Amostra 100

Análise de Risco ☐ Tolerável ☒ Baixo ☐ Elevado ☐ Muito Elevado

Parecer do EPD:

Data: 09/10/2024

Finalidade: identificar características clínicas de doentes referenciados por queixas cognitivas à consulta de Neurologia da Unidade Local de Saúde São João que sejam específicas ou altamente sugestivas de quadros demenciais neurodegenerativos, em oposição a quadros não degenerativos.

Licitude: fundamento previsto no artigo 9(2)(j), com as garantias do 89(1) do RGPD, e artigo 31(1) da LERGD.

Categorias de dados pessoais: variáveis identificadas com detalhe na AIPD, datada de 17/07/2024, ponto 13, tendo presente o princípio da minimização dos dados.

Conservação: os dados serão alvo de pseudonimização, armazenados em local seguro, em área restrita com acesso limitado ao Investigador Principal, com acesso a ficheiros protegido por palavra-passe, efetuando-se a conservação até a conclusão da investigação, durante o prazo máximo de seis (6) meses. Os dados recolhidos serão destruídos após a finalização do estudo.

Comunicação de Dados: não há partilha de dados pessoais.

Conclusão: Face ao exposto, e observadas as recomendações, entende-se que o presente projeto está em conformidade com o RGPD pelo que sou de parecer favorável quanto à sua realização.

Recomendações:

1. Reforçar as medidas de segurança previstas para a conservação dos documentos em formato de papel que impeçam o acesso à informação a pessoas não autorizadas, bem como o seu manuseamento indevido;
2. Garantir medidas de segurança adicionais no transporte dos dados com recurso a dispositivos electrónicos de armazenamento (Laptop), nomeadamente através de medidas de cifragem e autenticação;
3. Garantir medidas de segurança adicionais (ex. transformar os dados com recursos a técnicas de generalização, perturbação e/ou como último recurso, a supressão de dados) para os dados que, ainda que pseudonimizados, contém elementos informativos que no seu conjunto possibilitam a re-identificação dos participantes, tendo presente a amostra em estudo (Doentes referenciados à consulta externa de Neurologia por queixas cognitivas), em particular na fase de disseminação ou publicação dos resultados (incluindo repositórios científicos).
4. A chave de decodificação que permite a re-identificação dos titulares dos dados (doentes) deve ficar sempre na posse do Investigador Principal ULSSJOAO e protegida de acessos indevidos / terceiros;
5. Em caso de necessidade de extensão de prazo e/ou de qualquer alteração dos pressupostos atinentes ao presente parecer o Investigador Principal deverá solicitar a reapreciação do projeto de investigação junto do EPD.

Revisão AIPD:

☐ Data da próxima revisão:

☒ Não carece de revisão.

Anexos:

1. Processo CES n.º 213/2024
2. Parecer CES (21/06/2024)
3. AIPD (17/07/2024)
4. Protocolo de Investigação

Encarregado de Protecção de Dados
Assinado por: **PAULO ALEXANDRE MOTA DA SILVA**
Data: 2024.10.09 15:58:11+01'00'
Localização: ULS SÃO JOÃO



CARTÃO DE CIDADÃO
• • • • •

FACULDADE DE MEDICINA

