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Vascular Cognitive Impairment after Ischemic Stroke

Isabel Medeiros dos Santos Queirós

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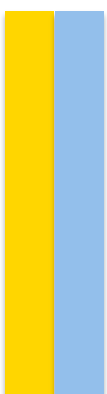

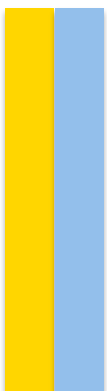

Vascular Cognitive Impairment after Ischemic Stroke

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Dissertação de Mestrado Integrado em Medicina

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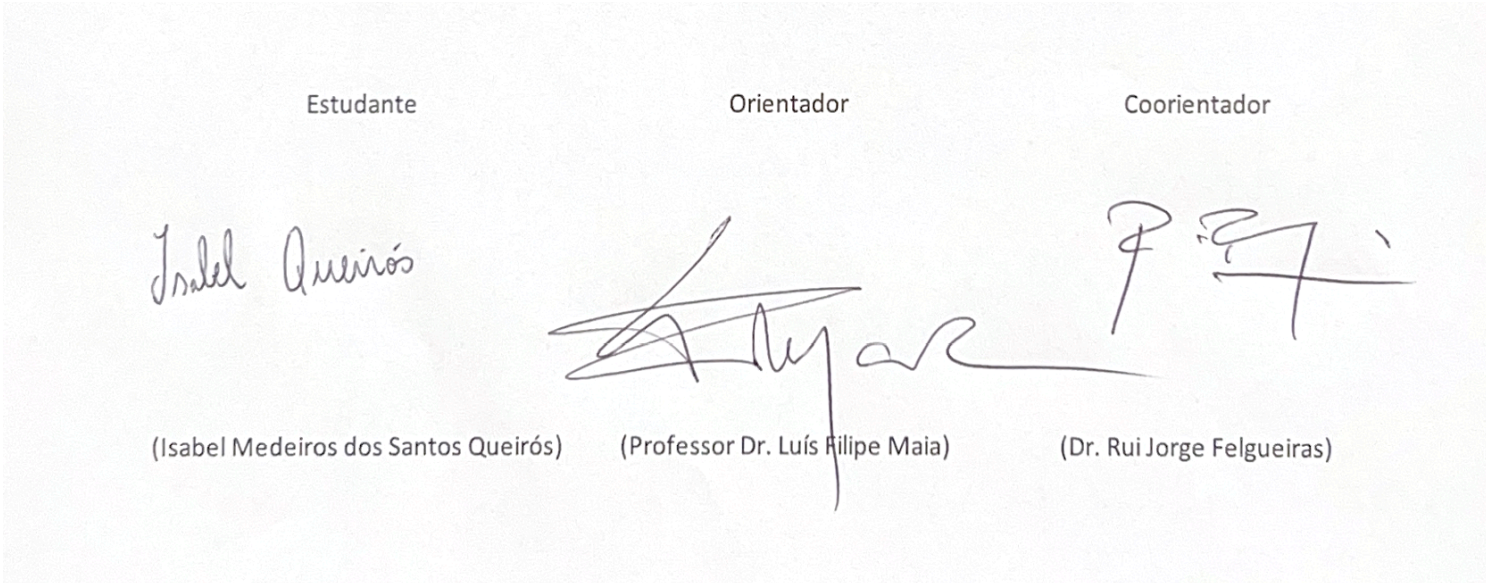

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RESUMO

Contexto e objetivos: O Acidente Vascular Cerebral (AVC) tem uma elevada incidência em Portugal e é a principal causa de morte e incapacidade em Portugal. O AVC é responsável por antecipar em dez anos o início de demência e a incidência é particularmente elevada no primeiro ano. A demência vascular é a segunda principal causa de demência a nível global e permanece subdiagnosticada. Por esse motivo, e tirando partido de um estudo prospetivo em curso no Hospital de Santo António, pretendemos determinar a frequência de demência, avaliar a incapacidade funcional nas atividades de vida diária e identificar preditores clínicos de incapacidade funcional e demência aos doze meses após o AVC isquémico.

Métodos: Coorte prospetiva de doentes admitidos consecutivamente na Via Verde AVC, entre setembro de 2022 e dezembro de 2023 incluídos no estudo StrokeSensor. Realizamos seguimento clínico, dos doentes com AVC isquémico, aos 3 e 12 meses. Aos 3 meses foi avaliada a recorrência do AVC e o estado funcional com a escala Rankin modificada (mRS). Os doentes foram convocados para consulta presencial, aos 12 meses, quando o mRs aos 3 meses era ≥3 e, para consulta telefónica, quando o mRS era ≥4. A avaliação dos 12 meses incluiu o mRS, o *Activities of Daily Living Questionnaire* (ADLQ) e o Mini Mental State Exam (MMSE) nas consultas presenciais. O ADLQ foi aplicado ao acompanhante do doente e avaliou a incapacidade funcional, classificando-a como ligeira (≤33%), moderada (34-66%) e grave (>66%). A avaliação clínica categorizou os doentes em dois grupos: sem demência e com demência. Aplicou-se um modelo de regressão logística para identificar preditores de incapacidade grave aos 12 meses.

Resultados: Foram admitidos 783 doentes, dos quais 533 tiveram AVC isquémico. O ADLQ foi aplicado em 273 doentes e a avaliação do estado cognitivo em 221 doentes, dos quais 48 doentes tinham demência. Aos 12 meses, 160 doentes (58,6%) apresentavam incapacidade funcional ligeira, 52 (19,0%) moderada e 62 (22,4%) grave. A incapacidade funcional grave está associada a uma idade média mais elevada e é mais prevalente nas mulheres. A fibrilação auricular, um baixo nível de escolaridade e um NIHSS>10 estão significativamente associados à incapacidade funcional grave. A demência aos 12 meses associa-se a uma idade média mais elevada, a um NIHSS>10 e é mais prevalente nos doentes com TACI e PACI.

Conclusões: A demência e a incapacidade funcional grave aos 12 meses estão associadas a uma idade média mais elevada, a um baixo nível de escolaridade e a um NIHSS>10. Um mRS prévio <3 associa-se a menores taxas de incapacidade funcional grave e demência. A escolaridade foi um preditor independente de incapacidade grave aos 12 meses. Estes achados destacam a importância de uma avaliação cognitiva e funcional abrangentes, identificando os doentes que apresentam maior risco de incapacidade funcional grave e demência, permitindo intervenções direcionadas.

ABSTRACT

Context and Objectives: Stroke has a high incidence in Portugal and is the leading cause of death and disability in the country. Stroke is responsible for advancing the onset of dementia by ten years, with incidence particularly high in the first year. Vascular dementia is the second most common cause of dementia and remains underdiagnosed. Having this in mind and leveraging a prospective study currently underway at Hospital de Santo António, we aim to determine the frequency of dementia, assess functional disability in activities of daily living, and identify clinical predictors of functional disability and dementia twelve months after ischemic stroke.

Methods: Prospective cohort of patients consecutively admitted to the Acute Stroke Code Activation between September 2022 and December 2023, included in the StrokeSensor study. Clinical follow-up was conducted at 3 and 12 months for patients with ischemic stroke. At 3 months, stroke recurrence and functional status were assessed using the modified Rankin Scale (mRS). Patients were invited for an in-person consultation at 12 months if their 3-month mRS was less than or equal to 3, and for a telephone consultation if the mRS was greater than or equal to 4. The 12-month assessment included the mRS, the Activities of Daily Living Questionnaire (ADLQ), and the Mini Mental State Exam (MMSE) during in-person consultations. The ADLQ was administered to the patient's caregiver and assessed functional disability, classifying it as mild (≤33%), moderate (34–66%), or severe (>66%). Clinical evaluation categorized patients into two groups: with and without dementia. A logistic regression model was applied to identify predictors of severe disability at 12 months.

Results: A total of 783 patients were admitted, of whom 533 had ischemic stroke. The ADLQ was applied to 273 patients, and cognitive assessment was performed on 221 patients, of whom 48 had dementia. At 12 months, 160 patients (58.6%) had mild functional disability, 52 (19.0%) moderate, and 62 (22.4%) severe. Severe functional impairment was associated with a higher average age and was more prevalent among women. Low education attainment, atrial fibrillation and a NIHSS>10 were significantly associated with severe functional impairment. Dementia at 12 months was associated with higher average age, lower educational attainment, NIHSS>10, and was more prevalent in patients with TACI and PACI.

Conclusions: Dementia and severe functional impairment at 12 months are associated with higher average age and NIHSS>10. A prior mRS <3 is associated with lower rates of severe functional impairment and dementia. Education level was an independent predictor of severe disability at 12 months. These findings highlight the importance of comprehensive cognitive and functional assessments to identify patients at higher risk of severe functional disability and dementia, enabling targeted interventions.

LISTA DE ABREVIATURAS

ADLQ: Activities of Daily Living Questionnaire

BADL: Basic Activities of Daily Living

CVD: Cerebrovascular Disease

DSM-5: Diagnostic and Statistical Manual of Mental Disorders

IADL: Instrumental Activities of Daily Living

LACI: Lacunar Infarct

MCI: Mild Cognitive Impairment

MMSE: Mini-Mental State Exam

mRS: Modified Rankin Scale

mTICI: Modified Treatment in Cerebral Infarction

NIHSS: National Institutes of Health Stroke Scale

PACI: Partial Anterior Circulation Infarct

POCI: Posterior Circulation Infarct

PSD: Post-Stroke Dementia

TACI: Total Anterior Circulation Infarct

TIA: Transient Ischemic Attack

TOAST: Trial of Org 10172 in Acute Stroke Treatment

VCI: Vascular Cognitive Impairment

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Introduction

Stroke has a high incidence in Portugal and remains the leading cause of death and long-term disability in the country. Ischemic stroke accounts for approximately 80% of cases. The combination of high incidence and low lethality results in a substantial proportion of survivors experiencing functional impairment and long-term disability. Given that stroke predominantly affects the elderly population, the development of post-stroke cognitive impairment and dementia is a frequent and clinically relevant concern for both patients and caregivers. Stroke has been estimated to bring forward the onset of dementia by about ten years and the incidence is particularly high in the first year.[1] Dementia risk is related to individual clinical characteristics, and could depend on the acute lesion (severity, location, sub-type), pre-existing lesion burden, vascular risk factors, and other determinants of susceptibility, such as education and previous cognitive function. Although cognitive deficits following a stroke may be transient during the first year, evidence suggests that beyond this period, such impairments ultimately become permanent.

Dementia is defined as an acquired clinical syndrome characterized by the progressive decline of multiple cognitive domains. These deficits are persistent and severe enough to interfere with social functioning and the ability to perform Activities of Daily Living (ADL) independently. Diagnostic criteria require impairment in at least two cognitive domains, which may include memory, language, attention, executive function, social cognition, and visuospatial or perceptual-motor abilities.

Vascular Cognitive Impairment (VCI) and vascular dementia refer to cognitive decline resulting from cerebrovascular injury, characterized by damage to brain parenchyma due to ischemic or haemorrhagic events. Given the pathophysiological heterogeneity of VCI, it is typically classified into four distinct diagnostic entities: subcortical ischemic vascular dementia, post-stroke dementia (PSD), multi-infarct dementia, and mixed dementia.

Currently, an estimated 36 million individuals worldwide live with dementia, with projections suggesting a threefold increase by 2040.[2] Vascular dementia is recognized as the second most common cause of dementia, following Alzheimer's disease, and accounts for approximately 15–20% of the cases in Europe. The concept of mixed dementia encompasses cases in which both Alzheimer's pathology and cerebrovascular disease (CVD) coexist, with an estimated prevalence ranging from 20% to 27%. Despite its high prevalence, VCI remains underdiagnosed in clinical practice. Early identification and management of vascular risk factors are therefore critical to reducing the burden of cognitive impairment associated with CVD.[3]

In Portugal, epidemiological data on dementia remain scarce. In the study by Gonçalves Pereira *et al.*, 2017, which applied the 10/66 Dementia Research Group criteria, it was estimated that over 200,000 individuals are living with dementia in the community.[4]

Identifying predictors of PSD is essential for prognostic stratification, care planning, and potentially for selecting candidates for disease-modifying interventions. A comprehensive evaluation of patients' functional status at 12 months post-stroke provides critical insights into their long-term care needs. Beyond cognitive assessment, evaluating the level of dependence enables targeted strategies. The assessment of functional disability may reveal subtle changes that are not apparent during routine clinical evaluations, thereby creating opportunities for early cognitive intervention. In individuals with preserved cognitive status or with MCI, the assessment of functional disability can help identify early signs of decline and guide timely interventions to improve the quality of life of patients.[5]

Therefore, we aimed to: (i) determine the incidence of dementia at 12 months following ischemic stroke; (ii) evaluate functional impairment in activities of daily living at 12 months following ischemic stroke; and (iii) identify clinical predictors of functional impairment and dementia at the 12-month follow-up.

Methods

The StrokeSensor study aims to develop a diagnostic platform based on a panel of molecular biomarkers for ischemic stroke. By integrating these biomarkers with clinical and neuroimaging data, the purpose is to establish a clinically relevant serum marker panel to support the stratification of patients with acute ischemic stroke.

We selected a consecutive series of patients with ischemic stroke admitted to the Acute Stroke Code Activation at Hospital de Santo António, between September 2022 and December 2023. Exclusion criteria comprised diagnoses of stroke mimic, transient ischemic attacks (TIA), and haemorrhagic stroke. Additional exclusion criteria were foreign nationality or non-residency in Portugal, absence of a legal representative, and a prior diagnosis of dementia. Clinical follow-up consisted of two time points: at 3 and at 12 months post-stroke. Cognitive assessments were conducted in patients followed at Hospital de Santo António.

At the 3-month follow-up visit, patients were evaluated for stroke recurrence, other significant vascular events, and functional status using the modified Rankin scale (mRS). Based on their functional status at this time point, patients with an mRS score ≤3 were invited for an in-person assessment at 12 months, while those with an mRS ≥4 were followed up via telephone.

During the 12-month clinical evaluation, in addition to the parameters evaluated at 3 months, further instruments were applied to assess cognitive and functional outcomes. These included the Activities of Daily Living Questionnaire (ADLQ), administered to the patient's companion and, during the face-to-face visit, the Mini-Mental State Exam (MMSE). In cases where the ADLQ could not be completed during the visit due to the absence of a companion, it was conducted by telephone within a maximum interval of one month.

Based on the 12-month clinical assessment, patients were categorized into two groups: with dementia and without dementia. Patients presenting with cognitive deficits underwent further diagnostic evaluation to investigate the underlying etiology. This included laboratory testing: complete blood count, fasting glucose, serum calcium, electrolytes, renal and hepatic function tests, thyroid function tests, serum levels of cyanocobalamin, homocysteine, folic acid, ceruloplasmin, and serological testing for syphilis and HIV, as well as a type II urine analysis. When clinically indicated, cranioencephalic imaging was performed. In patients whose cognitive status remained uncertain, a neuropsychological evaluation was performed, conducted according to a standardized protocol for this purpose, at the Neuropsychology Unit of Hospital de Santo António. The eligibility criteria for neuropsychological assessment were the presence of subjective cognitive complaints without clear functional impairment, and MMSE scores appropriate for the level of

education; and in cases of diagnostic uncertainty, particularly when differentiating between MCI vs. subjective cognitive complaints, and MCI vs. mild dementia.

Diagnosis of pre-existing dementia and post-stroke dementia:

The diagnosis of pre-existing dementia was established based on the clinical evaluation, reports from family members or caregivers, or evidence of a prior dementia diagnosis in the patient's medical records.

The diagnosis of post-stroke dementia was made by a neurologist during a follow-up consultation conducted 12 months after the stroke. Diagnostic criteria were based on the DSM-5, which require: evidence of significant decline from a previous level of cognitive functioning in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual motor abilities or social cognition); the decline must be reported by the individual, an informant, or observed by the clinician; objective documentation of cognitive impairment through neuropsychological testing; cognitive deficits must interfere with the individual's independence; the deficits must not occur exclusively in the context of delirium and be better explained by another mental disorder.[6]

Scales for cognitive and functional assessment

MMSE

The Mini-Mental State Examination is a standardized cognitive screening tool comprising thirty items, each scored either zero for an incorrect/absent response, or one for a correct one. These items are distributed across six cognitive domains. The orientation domain evaluates both temporal and spatial awareness. Registration involves the immediate repetition of three spoken words to assess short-term memory. Attention and calculation are tested using a subtraction task, typically involving five successive subtractions of three starting from thirty. The recall domain measures delayed memory by asking the individual to retrieve the previously registered words. Language abilities are assessed through tasks including object naming, sentence repetition, comprehension of a three-step verbal command, reading and executing a written instruction, and producing a spontaneous written sentence. Visuo-constructive skills are evaluated through a figure-copying task. The MMSE yields a maximum score of thirty points, with higher scores reflecting superior cognitive performance. Because both age and educational background influence performance, interpretation should be guided by normative data that account for these variables.[7] Cognitive impairment is typically suggested by a score of fifteen or below in individuals with no formal education, twenty-two or below in those with one to eleven years of schooling, and twenty-seven or below in individuals with more than eleven years of schooling.

ADLQ

The Activities of Daily Living Questionnaire is a comprehensive instrument designed to evaluate an individual's functional capacity across both basic and instrumental activities of daily living. The questionnaire is structured into six domains: Self-Care (6 items), Household Care (6 items), Employment/Recreation (4 items), Shopping/Money (3 items), Travel (4 items), and Communication (5 items). Each item is scored on a 4-point scale ranging from 0 (no difficulty) to 3 (no longer capable of performing the activity). A score of 9 is assigned in cases where the patient may never have performed that activity in the past, stopped the activity prior to the stroke, or for which the rater may not have information. Based on the total score, the functional impairment is categorized as mild (≤33%), moderate (34–66%), or severe (>66%).[8]

Modified Rankin Scale

The original Rankin scale was introduced by John Rankin in 1957 as a tool to categorize functional outcomes following a stroke and consisted of five grades, ranging from Grade I (no significant disability) to Grade V (severe disability).[9] The Modified Rankin Scale (mRS) was developed in the 1980s to enhance its clinical utility. It includes seven grades: Grade 0 (no symptoms); Grade 1 (no significant disability); Grade 2 (slight disability); Grade 3 (moderate disability); Grade 4 (moderately severe disability); Grade 5 (severe disability); and Grade 6 (death).

Stroke classification scales

TOAST

The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system is widely used to classify the etiology of ischemic stroke. It defines five distinct categories based on pathophysiological mechanisms: (1) large-artery atherosclerosis, (2) cardioembolism, (3) small-vessel occlusion, (4) stroke of other determined etiology, and (5) stroke of undetermined etiology, including those with more than one etiology. The classification requires a complete diagnostic workup, which includes clinical evaluation, neuroimaging (CT or MRI), electrocardiography and transthoracic echocardiography, carotid Doppler ultrasonography, cerebral arteriography, and relevant laboratory investigations.[10]

OCSP

The Oxfordshire Community Stroke Project classification is a clinically oriented system for categorizing ischemic strokes based on presenting neurological signs and symptoms. It delineates four subtypes: Lacunar Infarcts (LACI), Total Anterior Circulation Infarcts (TACI), Partial Anterior Circulation Infarcts (PACI), and Posterior Circulation Infarcts (POCI).

LACI is characterized by small subcortical strokes presenting with pure motor, pure sensory, sensorimotor, or ataxic hemiparesis syndromes. TACI involves extensive cortical and subcortical damage and presents with higher cortical dysfunction (such as aphasia or neglect), a homonymous visual field defect, and ipsilateral motor and/or sensory deficits affecting at least two of the following regions: face, upper or lower extremities. PACI is diagnosed when only two of the three TACI criteria are met, or when there is isolated higher cortical dysfunction or more restricted motor/sensory impairment than typically seen in LACI. POCI encompasses infarcts in the vertebrobasilar territory and may present with features such as ipsilateral cranial nerve palsy with contralateral or bilateral motor and/or sensory deficits, oculomotor disturbances, cerebellar signs, or isolated homonymous visual field loss.[11]

NIHSS

The National Institutes of Health Stroke Scale is a standardized 15-item instrument designed to quantify the severity of neurological deficits in individuals experiencing an acute stroke. It evaluates the level of consciousness, ocular motility, visual field integrity, facial symmetry, motor strength in both upper and lower extremities, sensory perception, limb coordination, language abilities, speech articulation, and the presence of neglect. Each item is scored on a graded scale, ranging from 0 to 2, 0 to 3, or 0 to 4, depending on the domain assessed. The cumulative score, which can range from 0 to 42, reflects the overall severity of the stroke, with higher scores representing more severe neurological impairment.[12]

Statistical analysis

Unless otherwise stated, continuous variables are reported as means and standard deviations, while categorical variables are reported as count or percentage. Student's t-test was used to compare age according to cognitive status. To examine age differences across the three functional impairment categories, a one-way analysis of variance (ANOVA) was employed. Associations between categorical variables and either cognitive status or functional impairment groups were assessed using Pearson's chi-square test. Furthermore, a Receiver Operating Characteristic (ROC) curve was constructed to evaluate the discriminative capacity of the ADLQ in identifying dementia at 12 months, with the area under the curve (AUC) serving as the primary metric. Logistic regression analysis was subsequently performed to identify independent predictors of dementia and impairment at the 12-month follow-up. Statistical significance was set at a p-value of <0.05. All analyses were conducted using IBM SPSS Statistics, version 29.

Results

Between September 2022 and December 2023, a total of 783 patients were admitted to the Acute Stroke Code Activation at Hospital de Santo António. Of these, 250 patients were excluded from the analysis due to alternative diagnosis: 143 Stroke mimic, 56 TIA and 51 haemorrhagic strokes. This resulted in a total of 533 patients with ischemic stroke. Among these, 163 patients were not included in the 12-month follow-up for the following reasons: 119 deaths, 22 patients with a pre-existing diagnosis of dementia, 16 lost to follow-up, 3 refusals to participate, 2 duplicate records, and 1 non-resident. Thus, 370 patients were evaluated at 12 months, with 296 assessed at Hospital de Santo António and 74 at other affiliated hospitals. Clinical follow-up at Hospital de Santo António comprised 195 in-person visits and 101 telephone consultations. Cognitive status was successfully assessed in 74.7% (n=221), while functional impairment, as measured by the ADLQ, was evaluated in 92.2% of patients (n=273) (Figure 1).

Cognitive status at 12 months

Among the 221 patients for whom cognitive status was assessed, the mean age was 68.8 years (SD=12.2), and 40.7% were female. At the 12-month follow-up, 48 individuals (21.7%) met the diagnostic criteria for dementia. Patients diagnosed with dementia were older (mean age 74.8 vs. 67.1 years; $p<0.001$), had lower educational attainment ($p=0.014$), and exhibited a higher prevalence of pre-stroke disability (16.7% vs. 6.3%; $p<0.001$).

In terms of stroke characteristics, dementia was more frequent in patients presenting with TACI (35.4%) and PACI (39.6%) ($p = 0.047$), as well as in those with NIHSS>10 (37.1% vs. 25.1%; $p=0.031$). Regarding stroke etiology, cardioembolic events were more common among patients with dementia (50.0% vs. 35.8%), although this difference did not reach statistical significance ($p=0.058$) (Table 1).

Univariate analysis identified age, pre-stroke disability, and NIHSS as significant risk factors for the development of dementia at 12 months, whereas higher educational attainment emerged as a protective factor. In the multivariate logistic regression model, adjusted for sex, education remained the only independent protective factor against the development of dementia (Table 2).

A subgroup analysis was conducted on patients who underwent mechanical thrombectomy to evaluate the potential influence of vessel recanalization on cognitive outcomes. Supplementary table 1 presents the distribution of Modified Treatment in Cerebral Infarction (mTICI) scores among 96 individuals who underwent endovascular therapy, stratified by the presence or absence of

dementia at 12 months. Most patients did not have a diagnosis of dementia (79.2% vs. 20.8%). The distribution of mTICI recanalization grades was comparable between the two groups, with no statistically significant differences observed (p=0.701).

Functional assessment at 12 months

Among the 273 patients evaluated for functional impairment, the mean age was 71.1 years (SD=12.3), and 50.9% were female. At the 12-month visit, 160 patients (58.6%) had mild functional impairment, 52 (19.0%) had moderate functional impairment, and 62 (22.4%) had severe functional impairment. Patients in the severe impairment group were older (mean age 76.8 years) compared to those with mild (67.8 years) and moderate (74.9 years) impairment (p<0.001) and were more frequently female than those with mild impairment (60.7% vs. 41.9%; p=0.001).

A significant inverse association was observed between educational attainment and functional impairment (p=0.007), with individuals in the mild impairment group demonstrating higher levels of education compared to those in the moderate impairment group (28.8% vs. 6.7%). Moreover, patients with mild impairment were more likely to have been functionally independent prior to the stroke (98.8%) compared to those with moderate (78.8%) and severe (70.5%) functional impairment (p<0.001) (Table 3).

Patients classified with severe functional impairment exhibited a higher prevalence of atrial fibrillation compared to those with mild impairment (42.6% vs. 24.4%; p=0.019). Also, the severe impairment group demonstrated a greater proportion of individuals with a NIHSS>10 (55.1%; p<0.001) and a higher frequency of TACI (45.9%; p=0.025).

A significant positive association was observed between functional impairment, as measured by the ADLQ, and the mRS scores at both 3 and 12 months (p<0.001), with higher levels of impairment corresponding to higher mRS scores. This relationship was further supported by a strong positive correlation between mRS at 12 months and ADLQ scores (Spearman's rho=0.80; p<0.001).

Consistently, patients with mild functional impairment had higher mean scores on the MMSE (27.2 vs. 22.5 and 17.6 for moderate and severe impairment, respectively; p<0.001) and were less frequently diagnosed with dementia at 12 months (8.3% vs. 41.2% and 62.9%; p<0.001) (Table 3).

Discriminative ability of the ADLQ ROC for dementia

To evaluate the discriminative capacity of the ADLQ in identifying PSD, a Receiver Operating Characteristic (ROC) curve analysis was performed. The AUC was 0.858 (95% CI: 0.804-0.911), indicating a high level of diagnostic accuracy. The optimal cut-off point was determined using the Youden Index, which identified a threshold of 34.06% functional impairment. This cut-off yielded a

sensitivity of 75.0% and a specificity of 81.9%, supporting the ADLQ as a reliable instrument for distinguishing individuals with dementia at 12 months post-stroke.

Discussion

In this prospective study involving a consecutive cohort of patients admitted to the Stroke Code, we observed a 12-month prevalence of dementia of 21.7% among stroke survivors who were able to undergo clinical evaluation. Similarly, 22.4% of patients exhibited severe functional impairment. These findings align with previously reported prevalence rates of PSD, which range from approximately 7% in population-based studies to 40% in hospital-based cohorts that include individuals with pre-existing dementia and recurrent strokes.[1,13] To the best of our knowledge, this is one of the first studies conducted in Portugal that have specifically examined the relationship between functional impairment and PSD at 12-month follow-up. Moreira *et al.* have examined cognitive performance 15 months after stroke/TIA and found that MMSE scores were significantly lower among women and individuals with lower educational attainment.[14]

Our findings suggest that stroke severity and TACI were significantly associated with both dementia and severe functional impairment at 12 months, in line with previous research. While common vascular risk factors such as hyperlipidaemia, diabetes mellitus, and arterial hypertension were not linked to an increased incidence of dementia, atrial fibrillation was notably associated with severe functional impairment at follow-up. Others have previously reported several predictors of PSD, including demographic variables such as advanced age, lower educational attainment, and pre-existing cognitive decline, as well as diabetes mellitus and atrial fibrillation. In contrast, arterial hypertension, hyperlipidaemia, ischemic heart disease, and smoking history have not consistently shown significant associations. In fact, many of the strongest predictors of PSD are directly related to the stroke event itself, particularly stroke severity, recurrence, and involvement of the left cerebral hemisphere. In this study, left hemisphere strokes were the most frequently observed, especially among individuals diagnosed with PSD. Despite this, the association between lesion lateralization and the presence of dementia did not reach statistical significance within this cohort, a finding that contrasts with existing literature.

It is hypothesized that the cumulative effect of multiple strokes plays a central role in the progression from post-stroke cognitive impairment to vascular dementia. However, other studies have emphasized the contribution of white matter changes and amyloid deposition in both the brain parenchyma and cerebral vasculature as predominant factors.[15] Although exposure to vascular risk factors increases susceptibility to cognitive dysfunction, the occurrence of a stroke itself appears to be the primary precipitating event in the development of cognitive decline.[16]

Regardless of stroke severity, post-stroke cognitive impairment is recognized as an independent risk factor for functional dependence and institutionalization, with substantial implications for patients, caregivers, and healthcare systems.[17] In this study, we found that 22.4% of patients

experienced severe functional impairment and 19.0% had moderate impairment at 12 months post-stroke. Although ADLQ was structured across multiple domains, allowing for the distinction between BADL and IADL, impairment was not analysed separately. Appelros *et al.* reported that dependence in BADL affects approximately 35% of stroke survivors within the first year, while around 59% require assistance with IADL.[18] Changes in IADL are strong predictors of progression to dementia. Individuals with MCI who exhibit deficits in IADL are at significantly greater risk of developing dementia compared to those without such impairments. Greater levels of incapacity are typically observed in older patients, those with comorbid conditions, pre-existing cognitive decline, and more severe strokes. However, it is important to note that even individuals who experience minor strokes may develop functional dependence, indicating that prognosis cannot be determined solely based on stroke severity.[19]

The mRS is widely used in cross-sectional studies to assess post-stroke recovery. However, variability in the interpretation of its parameters across clinical trials may contribute to the multidimensional nature of post-stroke disability. In this study, we observed that approximately 30% of patients with an mRS score ≤3 still exhibited moderate to severe impairment, measured by the ADLQ. These findings highlight the need to incorporate specific measures of functional status when evaluating long-term outcomes. Some studies have reported a reduction in cognitive deficits during the first year following stroke, which is attributed to neuroplasticity and the effects of rehabilitation. Nevertheless, these deficits may persist and become permanent. The ability to predict functional and cognitive outcomes is highly relevant for the clinical management and long-term care of stroke patients.[20,21] In individuals with established or at-risk of developing cognitive decline, functional assessment offers a more nuanced understanding of impairment, facilitates better environmental adaptation, supports caregiver training, and enables targeted intervention strategies. In this study, the ADLQ showed good discriminatory ability in identifying patients with dementia. This tool may prove valuable in optimizing resource allocation, particularly by enabling telephone-based screening to identify patients who require in-person evaluation. Moreover, functional impairment alone may hold prognostic value for dementia risk, as deficits in IADL often emerge earlier than abnormalities detected through standard neuropsychological testing.[22]

Our findings suggest that the grade of reperfusion achieved during the acute phase of endovascular recanalization does not significantly influence the presence of dementia at 12 months. This may have important implications for both the selection and prognostic evaluation of patients undergoing endovascular therapy.

Strengths of our study include its prospective design based on real-world data, the use of neurologist-led cognitive assessments, supported by consensus discussions or formal neuropsychological evaluations, a structured annual follow-up and low loss to follow-up. However,

our study also had some limitations. The predominant use of the MMSE may have led to underdiagnosis of vascular dementia or overdiagnosis in individuals with lower education. Despite this, MMSE remains a widely accepted tool for diagnosing dementia in both stroke and non-stroke populations.[23] Also, this study did not differentiate between dementia subtypes, which may limit the specificity of our findings. Finally, we did not investigate the association between 12-month cognitive outcomes and neuroimaging findings at admission, which might have revealed underlying white matter lesions or strategic lesions, both recognized as hallmarks of VCI.

The pathological mechanisms underlying CVD remain poorly understood and challenges arise from its heterogeneity. This can result from variations in lesion burden, type, and location, as well as secondary neurodegeneration caused by coexisting neuropathologies, and resilience mechanisms. Throughout the lifespan, risk factors interact with factors that exert a protective influence on the brain and cognition. Cognitively stimulating activities likely contribute to preserving cognitive function through two resilience mechanisms: brain maintenance and cognitive reserve. Brain maintenance refers to the relative absence of neuropathological changes. Cognitive reserve represents the discrepancy between the extent of the brain damage from decades of accumulating neuropathological changes and the absence of clinical manifestation of dementia. Both concepts are dynamic, as exposure to protective factors can enhance brain resilience. This neuroplasticity enables individuals to better withstand the progressive cerebrovascular damage associated with aging. In this study, the association between lower educational attainment and dementia suggests that individuals with limited formal education may have reduced brain resilience, thereby increasing their susceptibility to cognitive decline. Currently, the investigation of such variables rely on the development of advanced algorithms capable of estimating brain age through neuroimaging data.[24, 25]

Future research in the field of CVD should adopt a multidimensional approach, integrating plasma biomarkers and neuroimaging findings with demographic and clinical variables, such as those identified in this study, to enhance the identification of individuals at risk for PSD. This integrative strategy improves prognostic accuracy and supports the development of personalized follow-up plans, facilitates clinical stratification for future trials, and may contribute to the discovery of novel therapeutic targets.

Conclusions

Our findings demonstrate that advanced age, lower educational attainment, stroke severity, and TACI are significant predictors of both severe functional impairment and dementia at 12 months following ischemic stroke. Conversely, a premorbid mRS score below 3 and higher MMSE scores are associated with more favourable functional and cognitive outcomes. The ADLQ, easily administered via telephone to a patient's familiar, appears to be a valuable tool for distinguishing individuals diagnosed with dementia. These results emphasize the importance of comprehensive assessment in stroke patients to identify those at elevated risk for poor long-term outcomes, thereby enabling targeted interventions. Besides, patients' educational background and pre-stroke functional status emerge as critical considerations in the planning of post-stroke rehabilitation strategies.

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TABLES

Table 1. Cognitive outcome 12 months after ischemic stroke.

	Total *n=221* *n (%)*	***No dementia*** *n=173* *n (%)*	***Dementia*** *n=48* *n (%)*	***p***
Mean (SD) age, years	68.8 (12.2)	67.1 (12.4)	74.8 (9.5)	<0.001
Female sex	104 (47.1)	77 (44.5)	27 (56.3)	0.149
Premorbid mRS <3	207 (93.7)	167 (96.5)	40 (83.3)	<0.001
Education, years				0.014
0	9 (4.7)	6 (3.8)	3 (8.8)	
1-11	137 (71.0)	108 (67.9)	29 (85.3)	
>11	47 (24.4)	45 (28.3)	2 (5.9)	
Clinical classification				0.047
TACI	60 (27.1)	43 (24.9)	17 (35.4)	
PACI	70 (31.7)	51 (29.5)	19 (39.6)	
LACI	74 (33.5)	66 (38.2)	8 (16.7)	
POCI	17 (7.7)	13 (7.5)	4 (8.3)	
Lateralization (n=220)				0.239
Right	83 (37.7)	67 (39.0)	16 (33.3)	
Left	130 (59.1)	98 (57.0)	32 (66.7)	
Bilateral	7 (3.2)	7 (4.1)	0 (0)	
Etiology				0.058
Large vessel atherosclerosis	39 (17.6)	31 (17.9)	8 (16.7)	
Cardioembolic	86 (38.9)	62 (35.8)	24 (50.0)	
Small vessel occlusion	42 (19.0)	38 (22.0)	4 (8.3)	
Other determined	14 (6.3)	13 (7.5)	1 (2.1)	
More than one cause	7 (3.2)	6 (3.5)	1 (2.1)	
Undetermined	16 (7.2)	10 (5.8)	6 (12.5)	
Incomplete study	16 (7.2)	13 (7.5)	3 (6.3)	
Not investigated	1 (0.5)	0 (0)	1 (2.1)	
Stroke severity (n=170)				0.031
NIHSS < 3	30 (17.6)	27 (20.0)	3 (8.6)	
NIHSS 3-5	56 (32.9)	49 (36.3)	7 (20.0)	
NIHSS 6-10	37 (21.8)	25 (18.5)	12 (34.3)	
NIHSS > 10	47 (27.6)	34 (25.2)	13 (37.1)	
Reperfusion treatment				0.634
No treatment	95 (43.0)	75 (43.4)	20 (41.7)	
Thrombolysis	30 (13.6)	22 (12.7)	8 (16.7)	
Thrombectomy	67 (30.3)	51 (29.5)	16 (33.3)	
Thrombolysis + thrombectomy	29 (13.1)	25 (14.5)	4 (8.3)	

Table 2. Univariate and Multivariate Analysis of the variables associated with clinical outcome in patients with ischemic stroke.

	Univariate			Multivariate		
	OR	**95% CI**	*p*	**OR**	**95% CI**	*p*
Age	1.06	1.03-1.10	<0.001	1.04	0.99-1.10	0.121
Male vs. Female	0.62	0.33-1.19	0.151	1.65	0.59-4.65	0.341
Premorbid mRS ≥2 vs. 0-2	5.57	1.83-16.9	0.003	5.04	0.81-31.5	0.222
Education	0.81	0.72-0.92	<0.001	0.80	0.68-0.94	0.008
Clinical classification			0.059			
TACI vs. LACI	3.26	1.30-8.22	0.012			
PACI vs. LACI	3.07	1.25-7.58	0.015			
POCI vs. LACI	2.54	0.67-9.69	0.173			
Left vs. right	1.34	0.70-2.70	0.364			
Etiology			0.085			
LAA vs. SVO	2.45	0.67-8.91	0.173			
CE vs. SVO	3.68	1.18-11.4	0.024			
Other/+1 cause vs. SVO	1.00	0.17-5.96	1.000			
nInv/Und vs. SVO	4.13	1.16-14.7	0.029			
NIHSS	1.06	1.00-1.12	0.049	0.99	0.91-1.08	0.861
Reperfusion treatment						
Thrombolysis vs. No reperfusion	1.36	0.53-3.52	0.521			
Thrombectomy vs. No reperfusion	1.18	0.56-2.48	0.670			
Both vs. No reperfusion	0.60	0.19-1.921	0.390			

LAA, large-artery atherosclerosis; CE, cardioembolic; Und, undetermined; nInv, not investigated; SVO, small-vessel occlusion; +1 cause, more than one cause.

Table 3. Functional Impairment 12 months after ischemic stroke.

		Impairment			
	Total	*Mild*	*Moderate*	*Severe*	
	n=273	*n=160*	*n=52*	*n=61*	
	n (%)	*n (%)*	*n (%)*	*n (%)*	*p*
Mean age (SD), years	71.1 (12.3)	67.8 (12.1)[a]	74.9 (11.8)[b]	76,8 (10.2)[b]	<0.001
Female sex	139 (50.9)	67 (41.9)[a]	35 (67.3)[b]	37 (60.7)[b]	0.001
Premorbid mRS <3	242 (88.6)	158 (98.8)[a]	41 (78.8)[b]	43 (70.5)[b]	<0.001
Recurrent stroke	36 (13.2)	20 (12.5)[a]	6 (11.5)[a]	10 (16.4)[a]	0.692
Education, years (n=190)					0.007
0	10 (5.3)	4 (2.9)[a]	3 (10.0)[a]	3 (14.3)[a]	
1-11	136 (71.6)	95 (68.3)[a]	25 (83.3)[a]	16 (76.2)[a]	
>11	44 (23.2)	40 (28.8)[a]	2 (6.7)[b]	2 (9.5)[a, b]	
Vascular risk factors					
Hypertension	189 (69.2)	104 (65.0)[a]	40 (76.9)[a]	45 (73.8)[a]	0.185
Diabetes mellitus	79 (28.9)	43 (26.9)[a]	18 (34.6)[a]	18 (29.5)[a]	0.561
Hyperlipidaemia	151 (55.3)	90 (56.3)[a]	30 (57.7)[a]	31 (50.8)[a]	0.714
Current smoker	26 (9.5)	20 (12.5)[a]	4 (7.7)[a]	2 (3.3)[a]	0.095
Atrial fibrillation	84 (30.8)	39 (24.4)[a]	19 (36.5)[a, b]	26 (42.6)[b]	0.019
Peripheral arterial disease	4 (1.5)	3 (1.9)[a]	0 (0)[a]	1 (1.6)[a]	0.615
Stroke severity (n=213)					<0.001
NIHSS < 3	32 (15.0)	27 (21.8)[a]	2 (5.0)[b]	3 (6.1)[b]	
NIHSS 3-5	61 (28.6)	44 (35.5)[a]	11 (27.5)[a,b]	6 (12.2)[b]	
NIHSS 6-10	45 (21.1)	19 (15.3)[a]	13 (32.5)[a]	13 (26.5)[a]	
NIHSS > 10	75 (35.2)	34 (27.4)[a]	14 (35.0)[a,b]	27 (55.1)[b]	
Clinical classification					0.025
TACI	88 (32.2)	42 (26.3)[a]	18 (34.6)[a, b]	28 (45.9)[b]	
PACI	84 (30.8)	49 (30.6)[a]	21 (40.4)[a]	14 (23.0)[a]	
LACI	80 (29.3)	55 (34.4)[a]	12 (23.1)[a]	13 (21.3)[a]	
POCI	21 (7.7)	14 (8.8)[a]	1 (1.9)[a]	6 (9.8)[a]	
mRS at 3 months (n=257)					<0.001
0-2	149 (58.0)	129 (84.9)[a]	17 (33.3)[b]	3 (5.6)[c]	
3	65 (25.3)	21 (13.8)[a]	28 (54.9)[b]	16 (29.6)[c]	
4-5	43 (16.7)	2 (1.3)[a]	6 (11.8)[b]	35 (64.8)[c]	
mRS at 12 months					<0.001
0-2	145 (53.1)	128 (80.0)[a]	14 (26.9)[b]	3 (4.9)[c]	
3	74 (27.1)	31 (19.4)[a]	28 (53.8)[b]	15 (24.6)[a]	
4-5	54 (19.8)	1 (0.6)[a]	10 (19.2)[b]	43 (70.5)[c]	
Mean MMSE (SD) (n=191)	25.4 (5.7)	27.2 (3.5)[a]	22.5 (6.8)[b]	17.6 (7.7)[b]	<0.001
Dementia at 12 months	48 (22.4)	12 (8.3)[a]	14 (41.2)[b]	22 (62.9)[b]	<0.001

Supplementary table 1. Distribution of cognitive outcome at 12 months, in patients who underwent endovascular treatment, according to the mTICI score.

	Total	***No dementia***	***Dementia***	
	n=96	*n=76*	*n=20*	***p***
	n (%)	*n (%)*	*n (%)*	
mTICI				0.701
0	5 (5.3)	3 (4.0)	2 (10.0)	
2A	3 (3.2)	3 (4.0)	0 (0.0)	
2B	23 (24.2)	18 (24.0)	5 (25.0)	
2C	16 (16.8)	12 (16.0)	4 (20.0)	
3	48 (50.5)	39 (52.0)	9 (45.0)	

FIGURES

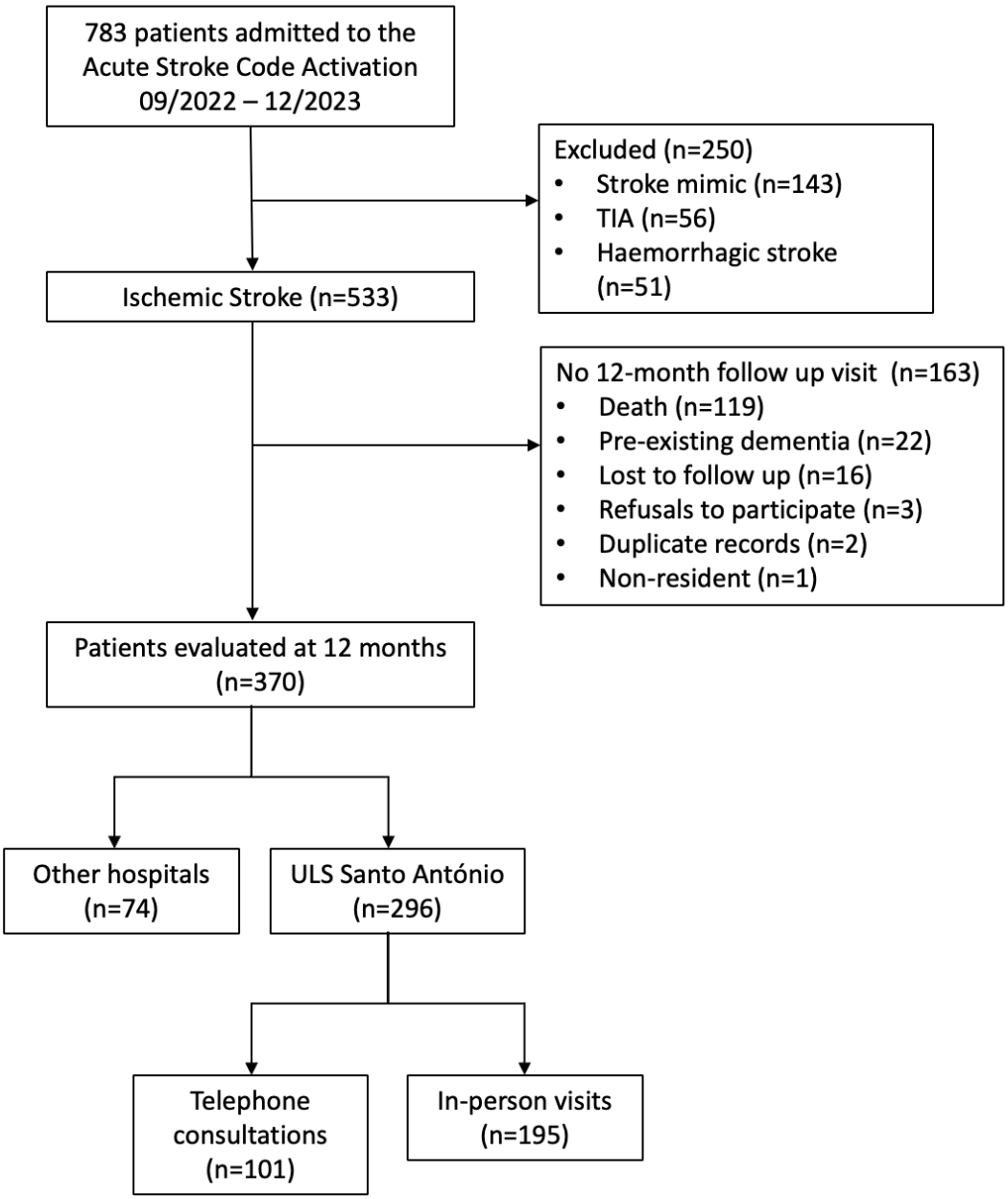

Figure 1. Flowchart of patient´s selection.

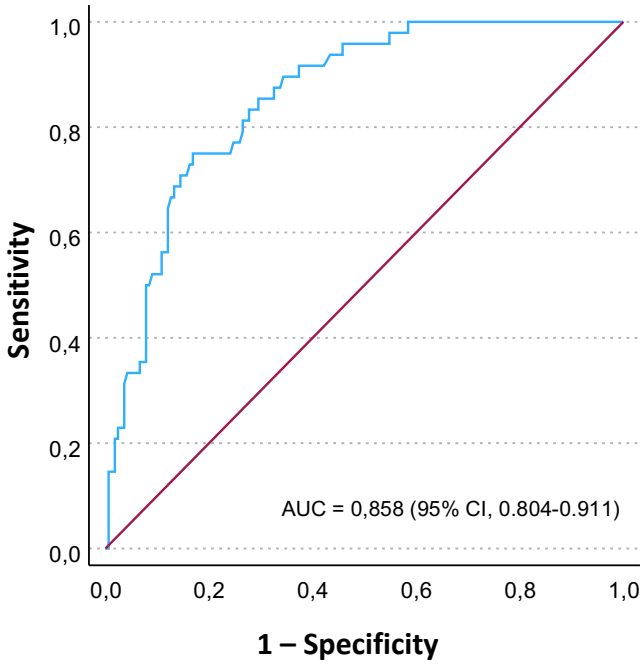

Figure 2. ADLQ ROC for discriminating patients with dementia vs. controls.

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