# Predictors of Health-related quality of life of community-dwelling stroke survivors: a prospective longitudinal study

# Preditores de qualidade de vida relacionada à saúde em indivíduos após Acidente Vascular Cerebral (AVC) residentes na comunidade: estudo longitudinal prospectivo

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**ABSTRACT | INTRODUCTION:** Knowing the factors that contribute to health-related quality of life (HRQoL) and its changes over time is essential to understanding the extent of stroke impact. Our objective was to identify predictors of HRQoL in community-dwelling individuals after stroke. **METHODS:** Cohort of individuals with stroke followed up in an outpatient clinic. Sociodemographic and clinical data were collected at baseline evaluation and the following scales: National Institutes of Health Stroke Scale (NIHSS), Timed Up and Go Test (TUGT), Modified Barthel Index (MBI), Frenchay Activity Index (FAI). The HRQoL was assessed using the EuroQol-5 dimensions (EQ-5D). After univariate analysis, the variables were included in two logistic regression models. **RESULTS:** There were 100 subjects, and at baseline evaluation 55% were female, mean age of $54 \pm 13.9$ years old, 57% with marital life, and 91% with a support network. The median time stroke was 36 (16-48) months, median of the NIHSS of 3 (1-5.5), MBI with a median of 49 points (48-50). The median of TUGT time was 13.8 (11, 3-19) seconds and the performance in instrumental activities (FAI) was 20 (12-25). After one year of follow-up, 60% of the assessed individuals had favorable HRQoL, and the identified predictors were the level of functionality in daily life activities (OR = 1.21 per 1point increase in MBI; 95% CI = 1.03-1.42; P = 0.016), the vascular territory of the lesion (OR = 4.98 for posterior vs anterior circulation; 95% CI = 1.53-16.22; P = 0.008), and time since stroke onset (OR = 0.98 per month since stroke onset; 95% CI = 0.96-0.99; P = 0.016). **CONCLUSION:** A higher level of functionality in activities of daily living, posterior circulation vascular territory, and a shorter time since stroke onset at baseline evaluation were the predictors of a favorable HRQoL.

**KEYWORDS:** Stroke. Health-related quality of life. Community.

**RESUMO | INTRODUÇÃO:** Conhecer fatores que contribuem para a qualidade de vida relacionada à saúde (QVRS) e suas mudanças ao longo do tempo é essencial para compreender a extensão do impacto do Acidente Vascular Cerebral (AVC). Nosso objetivo foi identificar preditores de QVRS em indivíduos residentes na comunidade após AVC. **MÉTODOS:** Coorte de indivíduos com AVC acompanhados em ambulatório. Dados sociodemográficos e clínicos foram coletados na avaliação inicial e nas seguintes escalas: *National Institutes of Health Stroke Scale* (NIHSS), *Timed Up and Go Test* (TUGT), *Modified Barthel Index* (MBI), *Frenchay Activity Index* (FAI). A QVRS foi avaliada por meio das dimensões do EuroQol-5 (EQ-5D). Após análise univariada, as variáveis foram incluídas em dois modelos de regressão logística. **RESULTADOS:** Havia 100 indivíduos, na avaliação inicial 55% eram mulheres, média de idade de $54 \pm 13,9$ anos, 57% com vida conjugal, 91% com rede de apoio. Tempo médio de AVC foi 36 (16-48) meses, mediana NIHSS 3 (1-5,5), MBI mediana 49 pontos (48-50). Mediana do tempo de TUGT foi 13,8 (11, 3-19) segundos e o desempenho em atividades instrumentais (FAI) foi 20 (12-25). Após um ano de acompanhamento, 60% dos indivíduos avaliados apresentaram QVRS favorável e os preditores identificados foram o nível de funcionalidade nas atividades de vida diária (OR = 1,21 por 1 ponto de aumento no MBI; IC 95% = 1,03-1,42; P = 0,016), território vascular da lesão (OR = 4,98 para circulação posterior vs. anterior; IC 95% = 1,53-16,22; P = 0,008) e tempo desde o início do AVC (OR = 0,98 por mês desde o início do AVC; IC 95% = 0,96-0,99; P = 0,016). **CONCLUSÃO:** Um maior nível de funcionalidade nas atividades da vida diária, circulação posterior do território vascular e um menor tempo desde o início do AVC na avaliação inicial foram os preditores de uma QVRS favorável.

**PALAVRAS-CHAVE:** AVC. Qualidade de vida relacionada à saúde. Comunidade.

## Introduction

Comorbidities and sudden changes in lifestyle associated with stroke can contribute to the impact on health-related quality of life (HRQoL).[1] Most investigations in individuals after stroke focus on epidemiological aspects or measurement of clinical outcomes, focusing on the limitation of functional activities.[2-4] Although quality of life and functional status may be related concepts, they represent different components of the individual's health condition and are not sufficient to be considered substitutes.[5,6]

Information on HRQoL allows a better understanding of adaptation to the condition.[1,7] The concept of HRQoL is multidimensional and is fundamental in the interpretation of changes in health status.[7] Considering the relevance of the topic, few longitudinal studies have investigated HRQoL after stroke.[8-14] In Brazil, only three studies describe the impact of stroke on HRQoL, and none of them have a longitudinal analysis.[12-14] Knowing the factors that contribute to the quality of life and their changes over time is essential to understand the extent of the impact of stroke in the community[9], for planning the resources allocated to rehabilitation and acute care services, as well a source of information for survivors and their families to confront with the individual's new condition.[15] This study aimed to identify predictors of HRQoL in individuals living in the community after stroke and to describe the domains of quality of life

## Methods

### Study design and population

This is a prospective cohort of post-stroke patients recruited from the stroke outpatient clinic of the Federal University of Bahia, Brazil. All subjects had a clinical diagnosis of ischemic or hemorrhagic stroke confirmed by neuroimaging (CT scan or magnetic resonance imaging), regardless of the number of events, with or without walking, using or not using orthoses or walking aids. Individuals with less than six months of the event, low vision, carriers of vestibular diseases and other associated neurological or orthopedic diseases, as well as individuals unable to understand the test instructions and perform the requested activities, were excluded.

Upon admission of patients to the study, demographic data such as age, gender, education, presence of a spouse, occupation after stroke, support network, and clinical data such as comorbidities, self-report of urinary incontinence, time from the last stroke to admission to study, use of medication, use of orthoses or assistive devices were collected. Affected cerebral hemisphere and vascular territory lesions were collected through radiological examination reports.

Then the following scales were applied to all patients: National Institutes of Health Stroke Scale (NIHSS)[16], Modified Barthel Index (MBI)[16], Frenchay Activity Index (FAI)[17], and The European Quality of Life - 5 Dimensions (EQ -5D).[8,18]

The NIHSS was used to measure stroke severity by assessing the level of consciousness, language, neglect, visual field loss, extraocular movements, muscle strength, ataxia, dysarthria, and sensory loss. The score ranges from 0 to 42, and the higher the score, the more severe the stroke.[16]

To assess the level of functionality of basic activities of daily living, IBM was applied. The results are categorized into groups of functionality: MBI of 50 - complete independence, 46-49 slightly dependent, 31-45 moderate dependence, 11-30 greater dependence, and 0-10 complete dependence.[16]

The FAI assesses performance in instrumental activities, subdivided into categories of domestic activity, work/leisure, and outdoor activity. The FAI score is based on the frequency with which activities were performed in the last 3 or 6 months, ranging from 0 (inactive) to 45 (very active). Ranked 0-15, inactive; 16-30, moderately active and 31-45, very active. It has a cutoff point ≥ 18 as a predictor of mild disability after stroke.[17] This instrument was used to assess instrumental activities of daily living at the time of assessment, after six and twelve months.

Only individuals who presented independent gait performed the Timed Up & Go Test (TUGT), which quantifies the time in seconds that the individual takes to get up from a standardized chair, walk 3 meters and sit down. The individual is instructed to walk at their usual pace, with or without the use of orthoses/assistive devices. TUGT results greater than or equal to 14 seconds indicate compromised functional mobility.[19]

The EQ-5D was used to assess the quality of life in five domains (mobility, self-care, usual activities, pain, anxiety/depression) and calculated based on previously published criteria, whose sum of dimensions results in a score ranging from 0 to 1, with death considered 0, and value 1 the perfect state of health.[12,18]

This project was approved by the local ethics committee with the following CAEE number: 51737515000005544, and all participating individuals signed an informed consent form.

After entering the cohort, individuals were followed for one year to assess their quality of life. The reassessment every six months occurred as a way to ensure greater adherence by the participants, and those who did not attend the clinic regularly were contacted by telephone. Data were collected using a standard form used by the researchers, which included, in addition to the quality of life questionnaire, information to control complications after individuals entered the cohort, such as emergency room visits, hospitalizations, and new episodes of stroke, falls, or deaths. The evaluators responsible for the follow-up remained blind to the information contained in the evaluation of the patients when entering the cohort.

### Sample size calculation

In the literature, nine predictors of quality of life in individuals after stroke were identified: stroke severity (NIHSS)[8], age[9], gender[9], functional mobility[8,20], educational level[21], incontinence[22,23], level of instrumental activities[24], level of functionality in activities of daily living (ADLs)[25] and support network.[11] Considering ten individuals for each independent variable[26], the total sample was 90 participants, and to minimize possible follow-up losses, 20% was added to the sample.

### Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences Program (SPSS Inc., Chicago, Illinois, United States) version 14.0 for Windows. Descriptive statistics included means and standard deviations for continuous variables with normal distribution; median and interquartile range for non-normally distributed continuous variables; and proportions for categorical variables.

Sociodemographic factors and clinical and functional data secondary to the stroke were considered independent variables. HRQoL assessed by the EQ-5D at 12 months of entry into the cohort was considered the dependent variable, being dichotomized for this analysis into favorable (EQ-5D > 0.78) or unfavorable (EQ-5D < 0.78).

Univariate analysis using the chi-square test or Fisher's exact test was performed for categorical variables and Student's t-test or Mann-Whitney test when the independent variable was continuous. After univariate analysis, the variables were included ($P < 0.05$) in a logistic regression model considering the favorable HRQoL dependent variable (EQ-5D $\geq$ 0.78)[23], using the stepwise backward selection process, which places the potential predictor variables according to the statistical significance of the univariate analysis and eliminates the least significant in each round. In the final model, only those that were statistically significant ($P < 0.05$) remained.

## Results

A total of 112 patients were evaluated between March 2016 and November 2017. During follow-up, there were 12 losses, including five deaths and seven lost contacts. The clinical and demographic characteristics of patients with stroke at baseline data are described in Table 1. A total of 55% of the individuals were female, with a mean age of study participants of 54 ± 13.9 years, 93 (93%) declaring non-white and presenting a median of 9 years of study (5-12 years). In 95 subjects (95%), the stroke was classified as ischemic, and the median time from stroke onset at study entry was 36 months (interquartile range 16-48 months). It was observed that the patients had a median of stroke severity, measured by the NIHSS, of three points (interquartile range from 1 to 5.5), representing a mild to moderate deficit.

The median level of ADL functionality in the MBI was 49 points (interquartile range 48-50), with individuals being classified as mildly dependent. Participants were classified as moderately active as measured by the FAI, median 20 (interquartile range 12-25), and no change in mobility assessed by TUGT with a median 13.8 (interquartile range 11, 3-19).

When analyzing the HRQoL at the beginning of the cohort, the average of the EQ-5D was 0.57 ± 0.03, while at twelve months of follow-up, the quality of life in the total sample reached 0.73 ± 0.03. When stratified into unfavorable (< 0.78) and favorable (> 0.78) at the end of twelve months, a median of 0.36 (0-0.77) and 1.0 (0.79-1.0) was found, respectively.

In Table 1, in addition to sample characterization, univariate analyzes identified factors associated with HRQoL at the end of one year. It was found that 40% of the patients had an unfavorable HRQoL. The following variables were significantly associated with a favorable HRQoL: marital life, shorter time since stroke onset, lower stroke severity, compromised posterior vascular territory, less compromised functional mobility and functional capacity in basic activities of daily living, and a higher level of functionality in activities instrumental.

In Table 2, we present two multivariate logistic regression models using all variables that reached possible significance in the univariate analysis (Model 1) and the variables that remained in the final model after stepwise backward analysis (Model 2).

When analyzing the impact of each domain on HRQoL assessed by the EQ-5D, it was found that individuals with favorable quality of life (QoL) did not have mobility problems and did not need help for their personal care. In individuals with unfavorable HRQoL, anxiety/depression and pain were reported as domains that most impacted this result. (Figure 1)

**Table 1.** Sociodemographic, clinical and functional characteristics of individuals with favorable and unfavorable quality of life after stroke, followed in an outpatient clinic of an educational institution in the city of Salvador (BA), Brazil (to be continued)

| Variables | Total (n = 100) | EQ-5D ≥ 0.78 (n = 60) | EQ-5D < 0.78 (n = 40) | P value |
|---|---|---|---|---|
| **Female**. n (%) | 55 (55) | 33 (55) | 22 (55) | 1.000* |
| **Age**. mean (SD) | 54 ± 13.9 | 53.8 ± 14.8 | 55.1 ± 13 | 0.673** |
| **Number of years studied**. median (IQ) | 9 (5-12) | 9 (0-12) | 6 (0-16) | 0.099*** |
| **With marital life**. n (%) | 57 (57) | 39 (65) | 18 (45) | 0.048* |
| **With support network**. n (%) | 91 (91) | 53 (90) | 37 (92) | 0.650* |
| **Time since stroke onset in months**. median (IQ) | 36 (16-48) | 22 (6-96) | 37 (6-396) | 0.029*** |
| **Severity of stroke (NIHSS score)**. median (IQ) | 3 (1-5,5) | 2 (0- 7) | 4 (0-23) | 0.024*** |
| **Posterior vascular territory injury. n (%)** | 32 (32) | 26 (44) | 6 (16) | 0.004* |
| **Previous stroke**. n (%) | 26 (26) | 13 (22.0) | 13 (34) | 0.186* |
| **Occupation after stroke**. n (%) | | | | 0.281* |
|   Not modified. n (%) | 21 (21) | 12 (22) | 9 (25) | |
|   Modified Function. n (%) | 23 (23) | 17 (31) | 6 (17) | |
|   Retired. n (%) | 46 (46) | 25 (46) | 21 (58) | |
| **Comorbidities**. n | | | | |
| Hypertension n % | 70 (70) | 38 (65) | 32 (80) | 0.119* |
| Diabetes n% | 23 (23) | 11 (19) | 12 (30) | 0.222* |
| Hypercholesterolemia n% | 28 (28) | 17 (16) | 11 (31) | 0.506* |
| Heart failure n% | 11 (11) | 7 (16) | 4 (11) | 0.568* |
| Chagas n% | 10 (10) | 7 (16) | 3 (9) | 0.330* |
| Report of Urinary Incontinence n% | 9 (9) | 5 (9) | 4 (10) | 0.816* |

**Table 1.** Sociodemographic, clinical and functional characteristics of individuals with favorable and unfavorable quality of life after stroke, followed in an outpatient clinic of an educational institution in the city of Salvador (BA), Brazil (conclusion)

| Variables | Total (n = 100) | EQ-5D ≥ 0.78 (n = 60) | EQ-5D < 0.78 (n = 40) | P value |
|---|---|---|---|---|
| Received physical therapy. n% | 30 (30) | 18 (30) | 12 (30) | 1.000* |
| Functional Mobility (TUGT) median (IQ) (did not perform = 4) | 13.8 (11.3-19) | 12.6 (7-38) | 16.7 (7-98) | 0.004*** |
| Level of functionality in ADLs (MBI). median (IQ) | 49 (48-50) | 50 (42-50) | 49 (16-50) | 0.007*** |
| Instrumental Activity Level (FAI) median (IQ) | 20 (12-25) | 21 (3-36) | 15 (2-35) | 0.005*** |

*Chi square; **Independent Test T; ***Mann-Whitney.
EQ-5D = European Quality of Life-5 Dimensions; MBI = Modified Barthel Index; NIHSS = National Institutes of Health Stroke Scale; TUGT = Timed Up and Go Test; FAI = Frenchay Activity Index; SD = standard deviation; IQ = interquartile range; ADLs = activities of daily living.
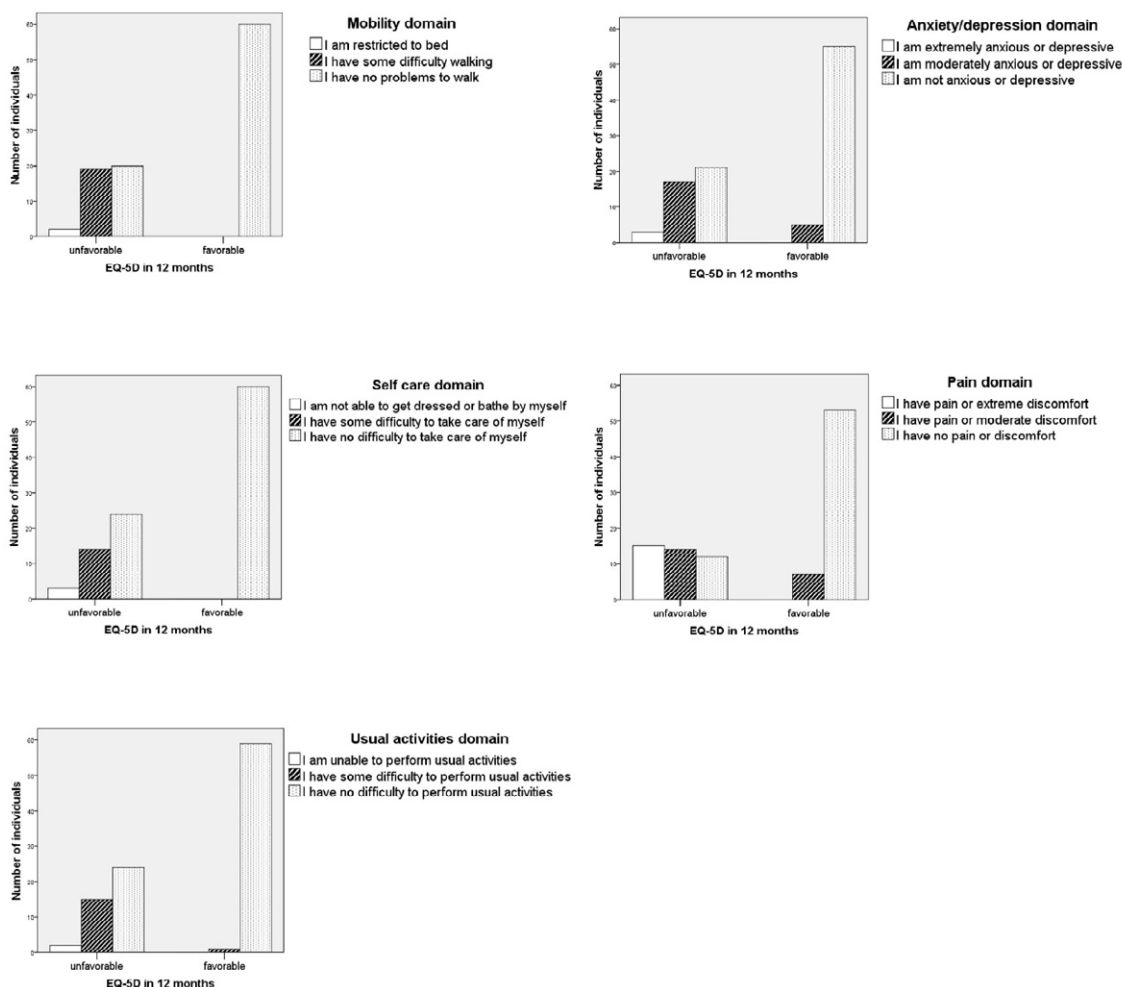Source: The authors (2022).

**Table 2.** Predictors of favorable health-related quality of life* (European Quality of Life-5 Dimensions, EQ-5D ≥ 0.78) in individuals after stroke, followed in an outpatient clinic of an educational institution in the city of Salvador (BA), Brazil

| Variables | OR (95% CI) | P value |
|---|---|---|
| **Model 1** | | |
| With marital life | 2.17 (0.776-6.04) | 0.140 |
| NIHSS | 1.01 (0.99-1.02) | 0.603 |
| Time since stroke onset | 0.98 (0.98-0.99) | **0.017** |
| Posterior vascular territory | 3.89 (1.15-13.17) | **0.028** |
| TUGT | 0.98 (0.90-1.05) | 0.518 |
| MBI | 1.15 (0.94-1.41) | 0.172 |
| FAI | 1.03 (0.96-1.10) | 0.427 |
| **Model 2** | | |
| Time since stroke onset** | 0.98(0.96-0.99) | **0.016** |
| Posterior vascular territory*** | 4.98 (1.53-16.22) | **0.008** |
| MBI**** | 1.21 (1.03-1.42) | **0.024** |

*The outcome considered was a score ≥ 0.78 in the EQ-5D; **For every 1 months less; ***Posterior circulation impairment; ****For every 1-point increase.
NIHSS = National Institutes of Health Stroke Scale; TUGT = Timed Up and Go Test; MBI = Modified Barthel Index; FAI = Frenchay Activity Index; OR = odds ratio; CI = confidence interval.
Source: The authors (2022).

**Figure 1.** Impact of European Quality of Life-5 Dimensions (EQ-5D) domains on the quality of life of individuals after stroke followed at an outpatient clinic of an educational institution in the city of Salvador (BA), Brazil, 2018



Source: The authors (2022).

## Discussion

In the present study, the level of functionality in activities of daily living, the vascular territory of the lesion, and the time since the stroke were identified as predictors of HRQoL in the post-stroke population living in the community. These findings corroborate the results of two cohorts with individuals after stroke; one study followed 65 individuals in Nigeria for one year[25], and another followed 226 individuals in four European rehabilitation centers for five years.[27] In both, the authors concluded that functional performance and HRQoL are negatively impacted by stroke.[25,27] Predicting functional outcomes and quality of life is considered essential for the treatment of stroke patients[28,29], and it is essential to monitor changes in HRQoL over time to identify predictors and implement possible measures aimed at treating modifiable factors.[30]

Advances in the treatment of acute stroke have resulted in more survivors, but many of them have long-term difficulties.[31,32] HRQoL is of growing interest, but the results of studies on its evolution over the years are divergent. Some studies found an improvement in HRQoL six months after the stroke[28,33], while others concluded that, although HRQoL increased during hospitalization for rehabilitation, it decreased in the subsequent six months.[34] In the sample presented here, at the end of one year of follow-up, all had better scores on the EQ-5D, but a significant number of individuals remained with unfavorable HRQoL. Although the entire sample was composed of individuals after six months of stroke, the inconsistency of the findings may be related to the dynamic process of recovery after the stroke and heterogeneous results, characterized by individual recovery patterns, as well as different ways of coping.[29] Despite the relevance of the outcome, this study did not seek to identify the different forms of coping.

A multicenter prospective cohort study carried out in 2017 concluded that when HRQoL is recovered, most of it occurs in the first months after the stroke, and this was attributed to the recovery process after the injury, highlighting that most of the functional recovery occurs in the first six months, reaching a plateau at an average of three to six months after the stroke.[29] In the present investigation, with participants 6 months or more after the event, the time since the onset of the stroke at baseline was an independent predictor of HRQoL, with a longer time since stroke onset found in individuals with unfavorable HRQoL. As stroke recovery is a dynamic process, it is likely that individuals who entered the cohort with longer times since stroke onset had already reached a plateau in stroke recovery, while those who entered with shorter times since stroke onset were still recovering to a higher functional status.

In this study, although the majority of the population was classified as mildly dependent, there was a higher concentration of individuals with a lower MBI value among individuals with unfavorable HRQoL. Compromised functional capacity leads the individual to incapacity for self-care and important implications that fall on the family, the community, the health system, and the individual's life.[25] Disability leads to greater vulnerability and dependence, leading to a decrease in well-being, and a decline in quality of life.[15] The assessment of functional capacity allows meeting the specific demands of the individual, guiding their care plan, identifying risks, and preventing losses in quality of life.[4,15]

The involvement of the vascular territory was a predictor in the present study, and the presence of lesions in the posterior territory was associated with a favorable HRQoL. A study in the United States, which investigated the NIHSS scale as a predictor of stroke prognosis, found that individuals with posterior circulation involvement had lower NIHSS scores than individuals with anterior circulation involvement[35], demonstrating greater severity in individuals with anterior circulation involvement.[36-38] One of the most relevant findings of this study is that 15% of patients with NIHSS scores ≤ 4 had death or disability within three months as a direct consequence of the stroke.[35] Corroborating the present study, the researchers suggest the involvement of the posterior circulation as a protective prognostic factor.

In discussing impaired HRQoL dimensions, a study using data from the European Registers of Stroke (EROS) on 1,023 patients followed for one year[10] found large variations between populations in all dimensions covered by the EQ-5D. A study with records from different populations found that half of the stroke survivors report symptoms of anxiety, depression, and mobility and activity limitations, while 70% report feeling pain or discomfort.[10] When investigating the EQ-5D domains in the present study, the pain was the most frequently affected domain.

Pain is one of the subjective symptoms frequently reported, and the frequency of pain varies between 11% and 55% in stroke studies.[39-42] Pain favors secondary disabilities, reduced function, and, in addition to the impact on patient recovery after stroke, can substantially impair HRQoL leading to lower participation and gains during rehabilitation.[43] In a study that compared the dimensions of HRQoL assessed by the EQ-5D among individuals with heart failure, individuals after stroke, and their caregivers, found a similarity between these three groups in the psych-oaffective dimensions.[12] The authors highlight the prevalence of pain in the general population and report that mainly musculoskeletal pain is frequent and independent of the activity performed, not always justified by biological aspects.[12] As already mentioned in another study[41], it cannot be said that pain reported by the participants is associated with stroke, as we did not investigate in the present study whether the report of pain came from the stroke or if there was a history of previous pain.

In this study, another domain that impacted the quality of life score assessed by the EQ-5D was reporting anxiety/depression. A one-year cohort that followed 134 individuals after stroke to assess changes in HRQoL, as well as identify predictors of HRQoL, identified a relationship between a history of depression, low social participation, and lower functional capacity with compromised HRQoL.[9] Findings of anxiety and depression symptoms and their impact on HRQoL lead to a discussion on the importance of tracking psychological morbidity, as well as monitoring changes in HRQoL[12] and the need to include anxiety management strategies in rehabilitation services.[44,45]

As already mentioned, a large list of post-stroke QoL predictors is identified in the literature[12,28,46]; possibly, differences in the sample profile justify the heterogeneity of the results found in these studies.[46] Study with 233 individuals followed up at six months and one year after the stroke, which aimed to identify predictors of HRQoL and measure changes in the functional status of Nigerians after the stroke, found that the involvement of family members as caregivers was the key factor for those survivors who had improved functional status.[11] In this study, no relation was found between support networks and HRQoL, probably because almost 100% of the sample reported having a support network.

It is noteworthy that many of the decisions about treatment and interventions, especially in chronic patients, are often taken based on the professionals' perception of the patients' expected quality of life, and it is necessary to know the individual's perception of their living conditions[7], using reliable and validated measures. In the present study, the authors recognize that the selection of tested variables, although based on the results of longitudinal studies carried out in different populations after stroke, may not be sufficiently representative of the individuals' life histories, mainly due to the broad spectrum of symptoms and disabilities, as well as the associated subjective aspects.

## Conclusion

A higher level of functionality in activities of daily living, a compromised posterior vascular territory, and a shorter time since the onset of the stroke in the initial assessment were the predictors of a favorable HRQoL in this study. The pain and anxiety/depression domains were the most affected in individuals with unfavorable HRQOL, and no problems were found in the mobility and self-care domains in patients who achieved favorable HRQOL in one year of follow-up.
In addition, the study was carried out with an accessible sample in a single reference outpatient clinic, thus not being possible to extrapolate results to another population, as well as limiting its external validation.

## Authors' contributions

Pinheiro LOR participated in conceptualization, data curation, formal analysis, investigation, methodology, project management, software, supervision, validation, visualization, and writing-revision. Guimarães M participated in data curation, writing-revision, investigation, methodology, validation, and visualization. Baía M participated in the investigation, data curation, methodology, validation, and visualization. Carvalho ME participated in the investigation, data curation, methodology, validation, and visualization. Oliveira-Filho J participated in conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, supervision, validation, visualization, and writing-revision. Pinto EB participated in the conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, supervision, validation, visualization, and writing-review.

## Conflicts of interest

No financial, legal or political conflicts involving third parties (government, companies and private foundations, etc.) were declared for any aspect of the submitted work (including, but not limited to grants and funding, participation in an advisory board, study design, preparation manuscript, statistical analysis, etc.).

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