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Functional impairment and post-stroke depression: a 6-month longitudinal study

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Abstract

Background: In recent decades, considerable advances have been made in the treatment of acute ischemic stroke (IS) and its prevention. However, even after treatment, approximately two-thirds of patients with IS have some degree of disability that requires rehabilitation, along with an increased possibility of developing psychiatric disorders, particularly depression.

Objective: To determine the predictors of post-stroke depression in a 6-month period in patients with IS.

Method: Ninety-seven patients with IS without previous depression were included in the study. The study protocol was applied during hospitalization and at 30, 90, and 180 days after hospital discharge. A binary logistic regression was then used. Age, sex, marital status, occupation, education, thrombolysis, National Institute of Health Stroke Scale, modified Rankin scale (mRS) score, Barthel index, and Mini-Mental State Examination score were included as independent variables.

Results: Of the 97 patients, 24% of patients developed post-stroke depression. In the longitudinal follow-up, an mRS score of >0 was the lone significant predictor of depression development (odds ratio = 5.38; 95% confidence interval: 1.25–23.12; $p < 0.05$).

Conclusion: Our results showed that in patients without previous depression, functional impairment of any degree has a 5-fold greater chance of leading to depression development in the first 6 months post-stroke as compared to that in patients without functional impairment.

Keywords: Stroke, Post-stroke depression, Predictive factor.

Introduction

Stroke involves an interruption of blood flow in a particular area of the central nervous system. Symptoms of stroke appear suddenly, persist for more than 24 h, and are related to the brain territory affected by ischemia due to arterial blood flow obstruction or cerebral hemorrhage due to cerebral blood vessel disruption. The patient may show alterations in consciousness level, eye movements, face movements, muscle strength, sensitivity, speech, balance, gait, and attention.

Globally, stroke incidence rates have remained stable and mortality rates have declined in the last two decades. Consequently, there has been an increase in the number of stroke survivors with disability-adjusted years of life (DALYs) lost due to stroke[1] Stroke is one of the main factors of functional impairment. Six months after stroke, 26% of patients older than 65 years become dependent on others for performing their activities of daily living, and 46% of such patients have cognitive deficits[2].

Among the stroke survivors, despite treatment, approximately two-thirds of patients have some degree of disability that requires rehabilitation[3], along with an increase in the possibility of developing psychiatric disorders, particularly depression that can occur in up to one-third of patients at some point of clinical follow-up[4]. Mood disorders and cognitive impairment represent the main clinical manifestations of the so-called “invisible” deficiency post-stroke[5].

Patients with post-stroke depression have an increased risk of worse functional outcomes, recurrence of stroke events, worsening of quality of life, and increased mortality risk[4,6]. Studies have indicated a previous history of depression, cognitive deficits, earlier episodes of stroke, severe neurological deficits and disability, a family history of psychiatric disorder, and female gender as predictors of post-stroke depression[6,7,8]. Many studies also include hemorrhagic stroke and a previous history of mood disorders as predictors of post-stroke depression[7].

Our present study aimed to evaluate whether gender, age, functionality at hospital discharge after stroke, treatment with thrombolysis, and Mini-Mental State Examination (MMSE) score are predictors of depression in a period of 6 months following ischemic stroke (IS) in patients without a previous history of mood disorders.

Methods

Sample collection

Patients with the first-time diagnosis of IS who were admitted to the Stroke Unit (SU) of the Hospital de Clínicas of UFPR between May 2016 and August 2017 were selected. All patients underwent clinical evaluation for IS diagnosis, followed by a CT scan. Patients were indicated to undergo thrombolysis if they met the clinical criteria based on the onset of stroke symptoms: the patient's medical condition was good 4.5 h before the onset of symptoms, cranial tomography showed no signs of hemorrhage, absence of dysglycemia or blood pressure peaks above 185/110 mm Hg, and absence of contraindications.

The exclusion criteria for our study were: those with a history of previous IS; those under 18 years of age; those with a previous diagnosis of mental disorders, including mood disorders; and those with aphasia or language limitation and understanding of the consent form. The study was approved by the ethics committee of the Hospital de Clínicas do Paraná - CHC-UFPR.

Protocol for clinical and psychiatric evaluation

A sociodemographic interview of the included patients was conducted, and the following scales were administered: NIHSS, modified Rankin scale (mRS), Barthel index (BI), MMSE, and Mini-Plus. All participants signed the free and informed consent form previously approved by the Research Ethics Committee of the Hospital de Clínicas. The protocol was applied at hospital discharge after clinical stabilization of the patient's condition and at the Cerebrovascular Diseases Outpatient Clinic at 30, 90, and 180 days after hospital discharge.

The NIHSS comprises 15 items that provide a quantitative measure of the main components of the standard neurological examination, including consciousness level, eye movements, visual fields, facial motricity, muscle strength, sensory function, language, coordination, speech, and attention[9,10]. Each deficiency was scored on an

ordinal scale ranging from 0 to 2, 0 to 3, or 0 to 4. Item scores were added to the total score ranging from 0 to 42; the higher the score, the more severe the stroke intensity[11].

The Rankin scale is used to evaluate stroke outcomes[12,13]. It assesses overall disability, in particular physical disability, functional disability, and the need for assistance. mRS has seven grades, from 0 to 6, where grade 0 indicates no symptoms, grades 1 to 5 indicate a progressive worsening of the patient's incapacity to conduct activities of daily living and thus requiring caregiver attention, and grade 6 indicates death [10].

The BI is commonly used to measure the disability or dependence of stroke victims on others for activities of daily living. The items evaluated are categorized into a self-care group (food, personal hygiene, and sphincter control) and a mobility-related group (ambulation, transference, and climbing stairs)[14].

The MMSE is used for screening and initial diagnosis of cognitive alterations. It can also be used to analyze disease progression and evaluate treatment responses in patients with dementia syndrome. It is also applied to understand the influence of schooling on the total MMSE score. The normal cutoff scores proposed by Brucki et al. (2003) were 20 for illiterate; 25 for age from 1 to 4 years of schooling; 26 for age from 5 to 8 years of schooling; 28 for age from 9 to 11 years of schooling; and 29 for individuals with more than 11 years of education[15].

The Mini-International Neuropsychiatric Interview (MINI) is a semi-structured interview for diagnosing psychiatric disorders mentioned in DSM-IV and ICD-10[16].through a short and accurate questionnaire that can be used for multicenter clinical trials and clinical practice in psychiatry[17].

Statistical analysis

Statistical analysis was performed using the JAMOVI 2.3.19 software. The results were expressed as mean, standard deviation, median, minimum, and maximum values (quantitative variables) or as frequency and percentage (categorical variables). To evaluate the predictors of post-stroke depression, a binary logistic regression was performed in which the dependent variable was the presence of depression at some point in the 6-month period after IS. The independent variables were age, gender, schooling, thrombolysis, MMSE score, low MMSE score according to schooling, NIHSS score at hospital discharge, mRS score, and BI. For regression analysis, the requirements of the absence of multicollinearity with tolerance greater

than 0.1 and variance inflation factor (VIF) less than 10 among the independent variables were followed.

Results

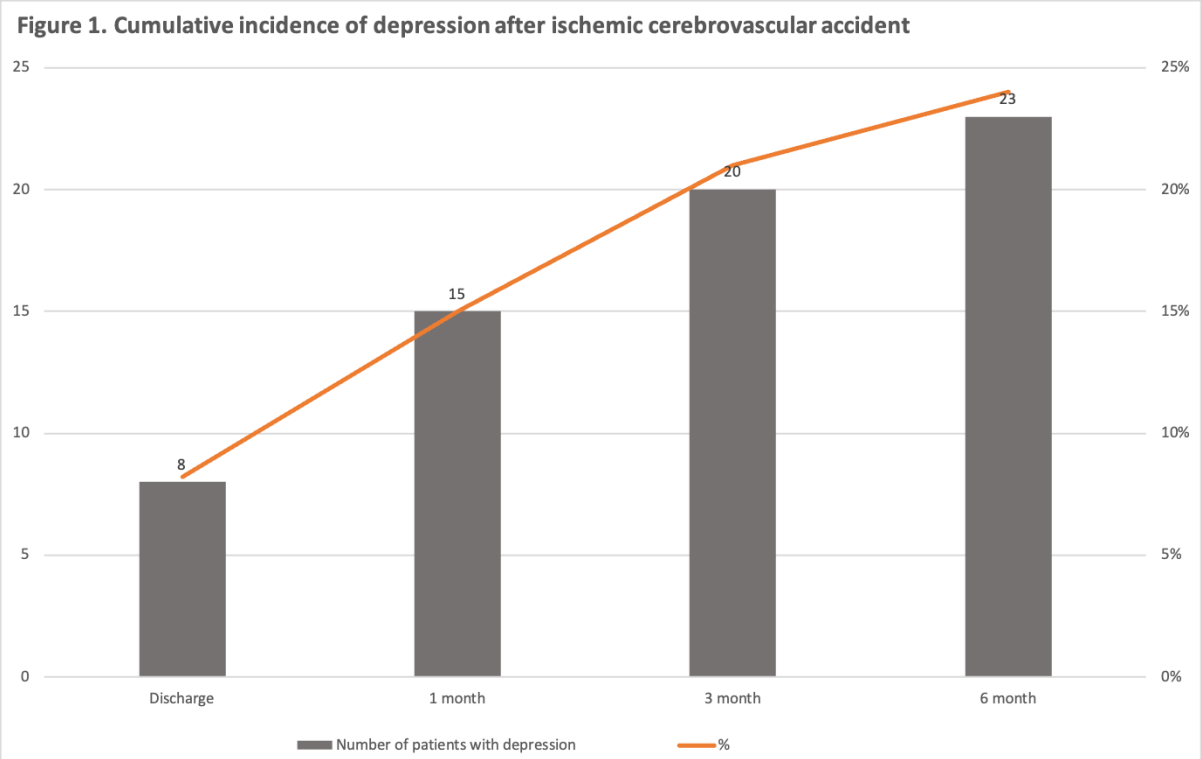
A total of 101 patients were selected. Three patients were excluded because of previous psychiatric history, and one patient diagnosed with hemorrhagic stroke was excluded. Finally, 97 patients were included in the study. Table 1 shows the sociodemographic data and clinical characteristics of the included patients.

Table 1. Sociodemographic characteristics of the included patients at the baseline

	Patients with Ischemic Cerebrovascular Accident (n = 97)
Age	59.6 ±14.6
Sex (M/F)	57 (58.8%)/40 (41.2%)
Marital Status (Partner/No Partner)	65 (67%)/30 (31%)
Education Level	
up to 4 years:	46 (47.4%)
5–11 years:	32 (33%)
> 11 years	19 (19.6%)
Thrombolysis (Yes/No)	36 (37.1%)/60 (61.9%)
Mini-Mental State Examination (MMSE) scores	24.2 ±3.7
Mini-Mental State Examination (MMSE) scores according to education levels (normal/low)	40 (40.2%) 55 (56.7%)
National Institutes of Health Stroke Scale (NIHSS)*	1 ±2
Ranking Scale (mRS)	

	Patients with Ischemic Cerebrovascular Accident (n = 97)
Age	59.6 ±14.6
0:	42 (43%)
1:	25 (25.8%)
2:	19 (19.3%)
3:	4 (4.1%)
4:	7 (7.2%)
5:	0 (0%)
6:	0 (0%)
Barthel Scale	99.2 ±2.1

Among the included patients, 23 patients (24%) experienced depression at some point of time in the 6-month period (Figure 1). Thirteen patients (13%) were lost to follow-up, of which 6 (6%) were lost at the first follow-up; 4 (4%) were lost at the second follow-up, and 3 (3%) were lost at the third follow-up. We followed the Last Observation Carried Forward (LOCF) approach for maintaining the data of the patients.



We performed a logistic regression analysis with depression at any time in the 6-month period as a dependent variable. Age, gender, schooling, thrombolysis, NIHSS score, BI, MMSE score, low MMSE score according to schooling, marital status, and Rankin score were included as independent variables. However, because of the sample size, we modified the Rankin score for the presence or absence of functional impairment (binomial variable), wherein a score of 0 represented the absence of functional impairment. In contrast, a score of 1 or more represented some functional impairment. The binary logistic regression analysis revealed that only an mRS score greater than 0 was statistically significant as a predictor of depression development in the longitudinal follow-up of patients after IS [odds ratio (OR) = 5.38; 95% confidence interval (CI) = 1.25–23.12; $p < 0.05$). The other independent variables were not statistically significant in predicting depression development (Table 2). None of the included variables showed multicollinearity.

Table 2. Logistic regression analysis with depression as the dependent variable

Variable	Coefficient	Wald	P value	Odds Ratio (OD)	95% CI for OD
Age	0.003	0.175	0.90	1.00	0.96 - 1.05
Sex	-0.552	0.881	0.35	0.55	0.18 - 1.67
Marital Status	0.178	0.088	0.77	1.20	0.37 - 3.87
Education Level (up to 4 years/5–11 years)	1.088	1.190	0.28	2.97	0.42 - 20.95
Education Level (up to 4 years/> 11 years)	0.256	0.75	0.79	1.29	0.21 - 23.12
Thrombolysis	-0.21.9	0.138	0.711	0.80	0.25 - 2.55
Rankin Scale (0/>0)*	1.682	5.105	0.02	5.375	1.25 - 23.12
NIHSS scale	-0.009	0.005	0.95	0.99	0.76 - 1.29
Barthel Scale	-0.072	0.354	0.55	0.93	0.73 - 1.18
Mini-Mental State Examination (MMSE) scores	0.120	0.862	0.35	0.93	0.88 - 1.46
Mini-Mental State Examination (MMSE) scores according to education levels (normal/low)	-0.434	0.285	0.593	0.65	0.13 - 3.18

Discussion

According to the results of our present study, the cumulative incidence of depression at 6 months in patients with IS was 24%. This finding was similar to the frequency of mood disorders reported in previous literature[3,4,6]. Studies that evaluated patients after stroke showed that degree of disability, stroke severity, previous history of depression, and cognitive deficits are the factors related to the risk of developing subsequent depression[8,18,19,20]. The association between depression and stroke

severity supports the hypothesis of a direct relationship between neurological damage and mood disorder[8].

In our study, in patients with functional impairment, an mRS score of >0 increased the likelihood of developing depression during the first 6 months after IS occurrence by more than 5-fold as compared to that in patients without functional impairment. A similar result was reported by Schwab-Malek et al. (2010), wherein depressive symptoms were present in 16% of patients with mRS scores of 0–2 at 3 months after stroke[21]. The prospective study of Snaphaan et al. (2009) evaluated 420 patients, and an increased risk of post-stroke depression was observed in patients with an unfavorable functional result represented by an mRS score of ≥2 (OR = 4.54; 95% CI = 2.29–9.01)[22].

The present study did not find associations between other sociodemographic factors and stroke symptoms and depression development. Previous studies have reported that gender and age show divergent results regarding their association with depression development[18,23]; however, a meta-analysis by Shi et al. (2017) showed that gender and age > 70 years were predictors of depression development after stroke[24].

In our study, no significant association was observed between depression and stroke severity (reflected by the NIHSS score), and between depression and impact on activities of daily living (assessed by the BI). A possible explanation for this finding is that our sample population had low severity of the stroke and low functional impairment; this is because only patients with IS and lower NIHSS scores were included in our study. When patients with extensive severity of IS and hemorrhagic stroke and those with greater functional impairment are included in the study cohort, then the NIHSS score and BI, in addition to mRS, also seem to predict depression development[25].

Thrombolysis, MMSE scores, and cognitive performance below the schooling level were also not associated with depression development within the 6 months of follow-up. In a meta-analysis published by Perrain et al. (2020), cognitive impairment was not found to be a risk factor associated with depression development in longitudinal studies[7]. The causes for the increased frequency of depressive episodes after stroke are currently under investigation. Factors such as functional impairment and increased brain inflammatory processes have been suggested as the causes[26].

Our study has some limitations, including follow-up in a single hospital and a limited number of patients. The selection of patients without aphasia for diagnostic interviews reduced the stroke severity level of the enrolled patients and probably led to lower rates of depressive episodes and we did not include stroke localization in the brain as independent variable in our analysis. The strengths of our study are the longitudinal follow-up of patients, low rates of follow-up losses, and the use of structured interviews for diagnosing depression.

Post-stroke depression is a common condition and may affect up to one-third of survivors at any time during clinical follow-up. The clinical course of post-stroke depression is dynamic, and its pathophysiology is poorly understood. Post-stroke depression is associated with worse functional outcomes, poor treatment, and increased mortality risk. The identification of risk and treatment factors may improve the patients' quality of life and outcomes after stroke[3,4,20].

References

1. Hankey GJ. Stroke. *Lancet*. 2017;389:641–654.
2. Meschia JF, C, B, Braun LT, Bravata DM, Chaturvedi S, et al. Guidelines for the primary prevention of stroke: A statement for healthcare professionals from the American heart association/American stroke association. [s.l: s.n.]. v. 45.
3. Altieri M, Maestrini I, Mercurio A, Troisi P, Sgarlata E, Rea V, et al. Depression after minor stroke: prevalence and predictors. *Eur J Neurol*. 2012;19:517–521
4. Towfighi A, Ovbiagele B, El Husseini N, Hackett ML, Jorge RE, Kissela BM, et al. Poststroke Depression: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2017;48:e30–e43.
5. Sagnier S, Munsch F, Bigourdan A, Debruxelles S, Poli M, Renou P, et al. The Influence of Stroke Location on Cognitive and Mood Impairment. A Voxel-Based Lesion-Symptom Mapping Study. *Journal of Stroke and Cerebrovascular Diseases*. 2019, 28:1236–1242
6. Tsai CS, Wu CL, Hung TH, Chou SY, Su JA. Incidence and risk factors of poststroke depression in patients with acute ischemic stroke: A 1-year prospective study in Taiwan. *Biomedical Journal*. **2016**; 39:195–200

7. Perrain, R., Mekaoui, L., Calvet, D., Mas, J.-L., & Gorwood, P. A meta-analysis of poststroke depression risk factors comparing depressive-related factors versus others. *International Psychogeriatrics*. 2020; 1–14
8. Ayerbe L, Ayis S, Rudd AG, Heuschmann PU, Wolfe CDA. Natural history, predictors, and associations of depression 5 years after stroke: the South London Stroke Register. *Stroke*. 2011;42:1907–1911.
9. Brott T, Adams HP, Olinger CP, Marler JR, Barsan WG, Biller J, Spilker J, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*. 1989;20:864–870
10. Kasner SE. Clinical interpretation and use of stroke scales. *Lancet Neurol*. 2006;5:603–612.
11. Kwah LK, Diong J. National Institutes of Health Stroke Scale (NIHSS). *Journal of Physiotherapy*. 2014; 60-61
12. Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. *Scott Med J*. 1957;2:200–215
13. Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988; 19: 604–607
14. Sulter G; Steen C; Keyser JDE. Acute Stroke Trials. *Stroke*. 1999:1538–1541
15. Brucki, S, NItrini R, Caramelli P, Bertolucci HF, Okamoto IH. Suggestions for utilization of the mini-mental state examination in Brazil. *Arquivos de Neuro-Psiquiatria*. 2003; 61: 777–781
16. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview for DSM-IV and ICD-10. *J Clin Psychiatry*, v. 59, p. 22–33, 1998.
17. Amorim, P. Mini International Neuropsychiatric Interview (MINI): validação de entrevista breve para diagnóstico de transtornos mentais. *Revista Brasileira de Psiquiatria*. 2000; 22: 106–115
18. Hackett ML.; Anderson CS. Predictors of depression after stroke: A systematic review of observational studies. *Stroke*. 2005; 36:2296–2301
19. Kutlubaev MA, Hackett ML. Part II: Predictors of depression after stroke and impact of depression on stroke outcome: An updated systematic review of observational studies. *International Journal of Stroke.* 2014; 9: 1026–1036

20. Allan LM, Rowan EN, Thomas AJ, Polvikoski TM, O'Brien JT, Kalaria RN. Long-term incidence of depression and predictors of depressive symptoms in older stroke survivors. *Br J Psychiatry*. 2013;203:453–460
21. Schwab-Malek S, Vatankhah B, Bogdahn U, Horn M, Audebert HJ. Depressive symptoms and quality of life after thrombolysis in stroke: the TEMPIS study. *J Neurol* 2010; 25: 1848–1854
22. Snaphaan L, Van der Werf S, Kanselaar K, de Leeuw FE. Post-stroke depressive symptoms are associated with post-stroke characteristics. *Cerebrovascular Diseases*. 2009; 28: 551–557
23. Das J, Rajanikant GK. Post stroke depression: The sequelae of cerebral stroke. *Neuroscience and Biobehavioral Reviews.* 2018, 90: 104–114
24. Shi Y, Yang D, Zeng Y, Wu W. Risk Factors for Post-Stroke Depression: a Meta-analysis. *Front Aging Neurosci*. 2017; 9: 218
25. Espuela FL, Roncero-Martín R, Canal-Macías ML, Moran JM, Vera V, Gomez-Luque A, et al. Depressed Mood after Stroke: Predictive Factors at Six Months Follow-Up. *Int. J. Environ. Res. Public Health*. 2020; 17: 9542
26. Wijeratne T, Sales C. Understanding Why Post-Stroke Depression May Be the Norm Rather Than the Exception: The Anatomical and Neuroinflammatory Correlates of Post-Stroke Depression. *J. Clin. Med*. 2021; 10, 1674.