

Factors Associated With In-Hospital Mortality in Very Elderly Patients With Ischemic Stroke: A Cohort Study

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Introduction: The highest mortality rates associated with ischemic stroke occur in patients of advanced age. However, studies of factors that establish the increase in hospital mortality are scanty in this population. *Material and Methods:* Epidemiologic, clinical and laboratory data, etiology and ischemic stroke subtype and complications during hospitalization were analyzed in 195 patients aged 80 years or older. In attempt to associate prognostic factor with the in-hospital mortality during first 28 days from admission, the death and survivor groups were compared. *Results:* Among the 195 patients evaluated, the age was 85.3 ± 4.6 years with a mortality of 26.1%. Following the multivariate model, the factors associated with in-hospital mortality were: age (OR = 1.07, 95% CI = 1.00-1.20), the score less than or equal to 8 on Glasgow coma scale (OR = 22.87, 95% CI = 3.55-148.76), diabetes mellitus (OR = 3.40, 95% CI = 1.30-8.87), total anterior clinical subtype (OR = 5.15, 95% CI = 1.82-14.52) and infectious complications (OR = 8.38, 95% CI = 3.28-21.43). *Conclusions:* The following risk factors were associated with a higher in-hospital mortality rate in patients over 79 years of age with ischemic stroke: older age, Glasgow coma score less than or equal to 8, total anterior circulation infarction, infection, and diabetes mellitus.

Key Words: Ischemic stroke—elderly—mortality—prognosis—outcome
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Introduction

Stroke is the second commonest cause of death in the world.¹ In addition, most deaths due to cerebrovascular disease occur in individuals over 75 years of age and, worldwide, in low and middle-income developing countries.² Furthermore, an increase in overall mortality is estimated, with a predicted 12 million deaths a year by 2030.²

The clinical presentation and the etiology of the ischemic stroke present differently with aging. In the respect,

older individuals have more cerebrovascular risk factors, in addition to increased numbers of clinical comorbidities.³⁻⁷ Recently, there has been an increasing interest in the behavior of ischemic stroke in patients of advanced ages with the breaking of paradigms and changes in conduct.^{8,9} In this context, further information on the characteristics of stroke in very old patients is essential for assessment during hospital sojourn and possible improvement in treatment.

Previous studies have demonstrated different factors associated with in-hospital mortality in patients with ischemic stroke and advanced age. Clinical subtype,⁴ etiology,⁵ level of consciousness at hospital admission,^{3,4} NIHSS score,^{3,5,10} degree of prior disability,^{3,10} hyperglycemia, and changes in white blood cell count¹¹ have all been associated, with increased mortality in this particular group of elderly patients.

In this cohort, we specifically studied very elderly patients with ischemic stroke to determine the clinical characteristics and cerebrovascular risk factors that are associated with in-hospital mortality.

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Material and Methods

A retrospective cohort study was performed in 332 patients aged 80 years or older, with the Disease Identification Code, in its tenth edition (ICD 10), corresponding to the ischemic stroke or stroke of undetermined cause (I63-I69), admitted from January 2014 to January 2016.

Twenty-two patients with transient ischemic stroke, 28 patients with hemorrhagic stroke and 87 patients transferred to other units leading to loss of follow-up were excluded, leaving a sample of 195 patients. All patients underwent a CT scan, an electrocardiogram, serum tests at hospital admission and vascular studies, ie, vertebral and carotid ultrasound, angiography of intra and extra-cranial vessels or cerebral angiography, depending on clinical presentation.

The study was conducted at the Pelopidas Silveira Hospital, a tertiary public hospital, regional reference in cerebrovascular disease that offers a 24-hour neurology and neurosurgery service, including TC scan, stroke unit, and interventional hemodynamic team.

The study was approved by the Human Research Committee of the University of Pernambuco (CAE number 53612016.1.0000.5192) and authorized by the Board of Education and Research of Pelopidas Silveira Hospital.

The ischemic stroke and the deaths attributed to it were defined according to the criteria of the WHO. The primary outcome was in-hospital mortality up to the twenty-eighth day of hospitalization.

The variables studied included: demographic data (age and sex), risk factors for cerebrovascular disease, hospital admission data, laboratory tests, etiology, clinical syndrome of the ischemic stroke, and complications during hospitalization.

The risk factors studied were: systemic arterial hypertension (prior diagnosis, ongoing treatment or two measurements greater than 140/90 mmHg 72 hours post ictus), diabetes mellitus (prior diagnosis, ongoing treatment, or at least two measurements of capillary glucose > 200 mg/dL 72 hours post ictus), cardiopathy (evidence of acute or prior coronary disease, acute myocardial infarction in the last 6 months, angina pectoris, history of myocardial revascularization or congestive heart failure, history of chronic or paroxysmal atrial fibrillation (AF) or demonstration through electrocardiogram during hospitalization, echocardiogram with disease or low ejection fraction below 35%, and prior ischemic stroke (previous event occurred in the same distribution after 28 days or previous event in an unequivocally different brain area in less than 28 days). The variables at the time of hospital admission were: level of consciousness measured by the Glasgow coma scale, mean systemic arterial pressure, oxygen saturation levels, and capillary glycemia.

The etiology of the ischemic stroke was classified as previously reported¹²: large vessels, small vessels, cardioembolic, undetermined and other causes. The Oxfordshire

Community Stroke Project¹³ classification was used to define the clinical syndrome of the ischemic stroke: ie, total anterior circulation infarction (TACS), partial anterior circulation infarction (PACS), posterior circulation infarction and lacunar infarction. We also analyzed the following laboratory data: hemoglobin levels, nitrogenous lags and leukocyte and platelet counts. Complications during hospitalization such as: chest infections (inspiratory crackles and fever, radiographic evidence or purulent sputum), including aspiration pneumonia, urinary infections (clinical symptoms, such as dysuria or foul urine and fever or positive urine culture) were recorded. Epileptic seizures were also registered.

The institutional protocol contraindicated thrombolysis in patients arrived at the medical service after 3 hours of stroke as well as decompressive craniectomy in patients older than 80 years.

The variables are described as mean \pm standard deviation or in percentages. Logistic regression was used to investigate the association between the outcome of the study and the characteristics of the patients. Using a univariate model, the variables of both death and survivor groups, were compared, the Student's t-test or Pearson's chi-square test, depending on the analysis. Potential predictor variables were eligible for the multivariable model when *P* is less than .200. For the evaluation of the outcome, independent predictors were identified by the multivariable logistic regression model using *P* less than .05 as the criterion for the final model. Results were expressed with odds ratio (OR) and their corresponding 95% confidence intervals (CI). The analyses were performed using the software STATA / SE 12 and EXCEL 2013.

Results

There were 195 patients in the studied sample. The average hospital stay was 15.4 ± 13.0 days, with in-hospital mortality of 26.1% (*n* = 51) of the sample.

The age of the patients was 85.3 ± 4.6 years with 51% (*n* = 99) of women. The main risk factor found was systemic arterial hypertension (90.8%, *n* = 177), followed by cardiopathies (44.6%, *n* = 87), with emphasis on atrial fibrillation (25.1%, *n* = 49). 30.8% (*n* = 60) of the patients were diabetic and about one in three patients had a previous history of ischemic stroke. Considering the etiology of the event, we observed an almost proportional division among cardioembolic (29.7%, *n* = 58), undetermined (27%, *n* = 51), and lacunar (27.4%, *n* = 53) etiologies. Large vessels were recorded as etiology in 14.3% (*n* = 29) and other causes in only 1.5% (*n* = 3) of the patients. The partial anterior clinical subtype (45.1%, *n* = 88) was the one most frequently found, in almost half of the cases, followed by the lacunar (25.3%, *n* = 50), anterior total (18%, *n* = 35) and, finally, posterior (11.3%, *n* = 22).

The most used secondary prophylactic treatment was platelet antiaggregation. Only 1.5% (*n* = 3) of the patients went through angioplasty. There was no record of carotid

endarterectomy or decompressive craniectomy. All patients received statin and rehabilitation physical therapy. Despite the frequency of cardioembolic events (about 1/3 of the sample), only 16.4% of eligible patients received anticoagulant therapy. The most frequent clinical complication found was infection. Epileptic seizures were described in 10.2% (n = 20) of the patients. Twelve patients (6.15%) arrived at the medical service within 3 hours of the beginning of the neurological deficit, thrombolytic treatment was performed in 5 patients (four intravenous and one intraarterial), only one survivor.

Table 1 shows the comparison between the death group (n = 51) and survivors (n = 144) of the variables: cerebrovascular risk factors, etiology and clinical syndrome of ischemic stroke, as well as clinical complications during hospitalization. The frequency of patients with the TACS (47.1%, 24/51 versus 7.6% 11/144; $P < .001$) and the undetermined etiology was higher in the death group (47.1% 24/51 versus 18.8% 27/144; $P < .001$) compared to the survivor group. As expected, complication rates during hospitalization were higher among patients who died, with a greater difference being observed when considering infectious complications.

Table 2 compares the clinical and laboratory data from hospital admission, demonstrating that patients who died showed, on average, higher levels of capillary glycemia at admission, lower score on the Glasgow coma scale, and a higher peripheral white blood cell count.

The multivariable model was built from the variables that were P less than .20, starting with those with greater association power in the bivariate model. Thus, the following variables were included in the model: hospital infection, TACS, ischemic stroke of undetermined etiology, hyperglycemia at hospital admission, low Glasgow coma scale, age, diabetes mellitus, epileptic seizures, leukocyte increase. The hemoglucotest variables from admission and number of leukocytes were withdrawn from the model because they presented collinearity with diabetes mellitus and hospital infection, respectively. The variables that determined, in a significant and independent way, the increase of in-hospital mortality with their respective

odds ratio and confidence interval are presented in Table 3.

Discussion

Our cohort determines the factors associated with in-hospital mortality in very elderly patients, ie, aged 80 years or older, with ischemic stroke, a population often excluded from clinical trials due to the lack of specific information in this age group. The distribution of cerebrovascular risk factors is in agreement with that described in epidemiological studies^{5,6} with emphasis on the high frequencies of hypertensive patients and cardiopathies, especially patients with AF. Thus, the most common etiology was cardioembolic. On average, one in every four patients presented AF confirming its high prevalence in an older population.

A considerable part of the sample had undetermined etiology, particularly due to the concomitance of potential causes. Considering the high prevalence of AF in the elderly, it is possible that some of these patients had undocumented paroxysmal AF during the ischemic event. The low percentage of patients with cardioembolic ischemic stroke who received anticoagulant therapy is also highlighted. The decision to anticoagulate very old patients is challenging since aging increases the risk of bleeding complications.

Our study shows a low percentage of patients arrived within 3 hours, a difficulty access to referral services associated a lack of awareness of stroke as an emergency by the victim or family justify such a situation. In addition, the high percentage of deaths in thrombolytic patients underscores the importance of careful evaluation at the more advanced ages. The increased 30-day mortality rate post-thrombolysis in elderly patients was suggested.^{14,15}

Most of the patients presented the PACS clinical subtype. The major involvement of the anterior circulation is possibly due to the high frequency of cardioembolic events. There is disagreement in the literature regarding the distribution of clinical syndromes in patients of advanced age with a record of a higher number of PACS

Table 1. Cerebrovascular risk factors, etiology, clinical subtype, and complications according to whether or not death occurred*

Variables, % (n)	Deaths		P value
	Yes (51)	No (144)	
Hypertension	84.3 (43)	93.1 (134)	.116
Diabetes Mellitus	41.2 (21)	27.1(39)	.101
Previous ischemic stroke	37.5 (18)	27.5 (39)	.259
Cardiopathy	49.0 (25)	43.1 (62)	.567
OCSF subtype TACS	47.1 (24)	7.6 (11)	.0001
Etiology Undetermined	47.1 (24)	18.8 (27)	.0001
Infection	82.4 (42)	29.2 (42)	<.0001
Epileptic seizure	19.6 (10)	6.9 (10)	.022

*Results expressed in percentagens and absolute numbers

Table 2. Hospital and laboratory admission data according to whether or not death occurred*

Variables, % (n)	Deaths		P value
	Yes (51)	No (144)	
Hospital admission data			
Mean blood pressure (mmHg)	161.6 ± 34.7	155.8 ± 29.2	.264
Hemoglucoest (mg/dL)	164.1 ± 12.4	135.1 ± 4.0	.031
Oxygen saturation (%)	94.1 ± 4.3	94.8 ± 4.3	.481
Glasgow coma score			
≤8	21.7 (10)	1.6 (2)	<.0001
Laboratory data			
Leukocytes (cel/mm ³)	9118 ± 602	7658 ± 320	.025
Serum creatinine (mg/dL)	.9 ± .08	.8 ± .04	.284
Hemoglobin	11.2 ± .6	11.5 ± .4	.654
Platelets	179.647 ± 12.836	176.780 ± 10.325	.880

*Results expressed in means and standart deviation

subtype by some authors,⁵ lacunar syndromes,¹⁰ or even TACS syndromes by others.⁴

The Oxfordshire Stroke Community Project (OSCP) scale and Trial of Org 10172 in Acute Stroke Treatment (TOAST) etiology criteria have shown prognostic capacity in older patients.^{4,5} In general, the TACS clinical subtype, commonly found in older patients, is classified as the most severe with high mortality rates¹⁶ because of the superficial and deep involvement of the cerebral parenchyma. In our analysis, the TACS subtype was associated with increased mortality in the elderly, after adjustment of variables. The same was not observed when considering the group of undetermined etiology.

Age influences not only the emergence of stroke but also the prognosis of the disease. Studies indicate a higher frequency of deaths from ischemic stroke in very elderly patients than in younger patients.^{3,4} We observed a slight increase in the risk of death associated with age even in this advanced age group (over 79 years), even after adjustment of variables, corroborating the idea that age alone is capable of influencing the outcome, regardless of other risk factors. Such evidence had already been found in other cohorts.^{4,5}

The alteration of consciousness at the time of patient admission, measured in our work by the Glasgow Coma Scale, was shown to be a predictor of mortality. Weir and colleagues¹⁷ demonstrated a good predictive value of this scale

for mortality in patients with ischemic stroke, even in dysphasic patients. Other studies^{3,4} point to changes in the level of consciousness measured by GSC as a factor associated with mortality from ischemic stroke in very old patients.

A history of DM was associated as a factor for the increase of mortality in our evaluation. Glycemic changes are known to be associated with a worse functional outcome in patients with stroke.¹⁸ Hyperglycemia increases both brain lactate production and the oxidative stress, stimulates systemic inflammation, and alters the permeability of the blood-brain barrier, thereby reducing the area of penumbral tissue and causing an increase in the area of infarction.¹⁹ Tziomalos and colleagues²⁰ studied the influence of DM on the functional outcome and in-hospital mortality in patients with ischemic stroke, and, after adjusting for cardiovascular risk factors, conclude that DM is associated with a worse functional outcome, although it has not influenced an increase in patient mortality in the present study. The influence of acute hyperglycemia in the mortality of patients with ischemic stroke is controversial. The GIFA study¹¹ evaluated factors associated with in-hospital mortality and in its analysis; patient's glycemia at admission was a predictor of mortality. However, Tziomalos and colleagues,²¹ when prospectively monitoring ischemic stroke patients and assessing the influence of stress

Table 3. Multivariable analysis for predictors of mortality in ischemic stroke patients*

Variables	Analysis		P value
	OR	95% CI	
Age	1.097	[1.00-1.20]	.047
Diabetes Mellitus	3.409	[1.30-8.87]	.012
Clinical subtype TACS [†]	5.151	[1.82-14.52]	.002
GCS ≤ 8 [‡]	22.874	[3.55-148.76]	<.001
Infection	8.384	[3.28-21.43]	<.001

*Results expressed with their odds ratio and their respective confidence intervals.

[†]Total anterior clinical syndrome.

[‡]Glasgow Coma score.

hyperglycemia (high capillary blood glucose levels in the first 72 hours after the vascular event), found a worse functional outcome and increase in-hospital mortality in hyperglycemic patients. Nonetheless, this association did not persist after adjusting for the severity of the ischemic stroke. These studies, however, evaluated populations of different age groups and did not restrict their analysis to very old populations. Our work suggests a negative influence exerted by a chronic hyperglycemic condition in the outcome of patients of advanced age.

Among the complications presented during hospitalization, infection was one that significantly influenced the outcome. Infectious complications occur in 23%-65% of stroke patients (CVA), depending on the definition used. A meta-analysis study estimated a prevalence of around 30% of infection after ischemic stroke, where respiratory and urinary infections are more prevalent.²² Boehme et al²³ studied the infections acquired during the hospitalization of patients with ischemic stroke, observing a strong influence on neurological deterioration and worse functional outcome. The infection rate during hospitalization was 43.1% in our sample. It is known that elderly patients are more susceptible to infections during hospitalization, but studies have shown differences in the care offered to ischemic stroke patients in different age groups²⁴ and this could, to a certain extent, influence the emergence of complications. Invasive procedures, such as parenteral treatment, vesical urinary catheterization, and ventilatory assistance, might contribute to infection in stroke patients.

Our work has some methodological limitations because it is a retrospective study with secondary and single-center data analysis. Furthermore, we used mortality as the outcome, which, despite its obvious importance, is certainly not the only relevant outcome in ischemic stroke patients.

Aging promotes a series of physiologic and morphologic changes that affect cerebral vascularization and metabolism, making the elderly more vulnerable to stroke and mortality attributed to the diseases.²⁵⁻²⁷ Patients over 79 years of age are a neglected population and studies are scanty. Identification of prognostic factors may contribute to better clinical management. Future research may show the influence of each factor specifically on increased mortality. The presence of comorbidities, medication costs, hospitalizations, and end-of-life aspects make treatment challenging, with its clinical, economic, and cultural implications.

In conclusion, our data indicate that older age, diabetes mellitus, TACS syndrome, Glasgow coma score less than or equal to 8 and infection may be predictors of death.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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