

# Infectious disease is the most common cause of death among stroke patients: two-years of follow-up

Doença infecciosa é a causa mais comum de morte entre pacientes com AVC: dois anos de acompanhamento

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## ABSTRACT

Stroke represents the second common cause of death in adults. **Objective:** It was to evaluate the incidence and causes of mortality after 30 days in a group of patients with an atherothrombotic ischemic stroke who were followed-up for a period of up to two years. **Methods:** We analyzed retrospectively the medical records of patients with ischemic stroke, who did not undergo thrombolysis, of the Santa Marcelina Hospital. We applied a research protocol to obtain information about risk factors and the etiology of death. **Results:** They were followed 337: mean age was 66.6 years (SD 9.05) and 43.9% were females. The mortality rate was 11.9% with most deaths (37.5%) occurring due to infectious causes. The age was correlated with the risk of death, which was five times higher in patients older than 80. **Conclusion:** The most important cause of death after 30 days was infectious disease, and advanced age was predictor of mortality among patients with an atherothrombotic stroke etiology.

**Key words:** stroke, cause of death, respiratory tract infections.

## RESUMO

O acidente vascular cerebral (AVC) representa a segunda causa de morte em adultos. **Objetivo:** Foi avaliar a incidência e causas de mortalidade após 30 dias num grupo de pacientes com AVC isquêmico aterotrombótico acompanhados por dois anos. **Métodos:** Analisaram-se retrospectivamente os prontuários de pacientes com AVC isquêmico (AVCi), não submetidos à trombólise, atendidos no Hospital Santa Marcelina, aos quais se aplicou um protocolo de pesquisa para obter informações sobre fatores de risco e etiologia do óbito. **Resultados:** Acompanharam-se 337 pacientes: a idade média foi de 66,6 anos (desvio padrão (DP) 9,05) e 43,9% eram mulheres. A taxa de mortalidade foi de 11,9% e a maioria dos óbitos (37,5%) ocorreu por infecção. A idade correlacionou-se ao risco de morte, o qual foi cinco vezes maior em pacientes acima de 80 anos. **Conclusão:** A principal causa de mortalidade após 30 dias foi por infecção, e a idade avançada foi preditor de mortalidade entre pacientes com AVCi aterotrombótico.

**Palavras-Chave:** acidente vascular cerebral, causa de óbito, infecções respiratórias.

Stroke is a public health problem worldwide, representing the second most common cause of death and a major cause of disability in adults<sup>1</sup>. It is a heterogeneous disease with three main types: ischemic, intracerebral hemorrhage and subarachnoid hemorrhage. The first type can in turn be sub-classified according to clinical syndromes and the presence of cardiac sources of embolism, atherosclerotic arterial disease and disease of small penetrating arteries or multiple rare causes<sup>2</sup>.

According to the Pan American Health Organization (PAHO), in 2002, there were approximately 272,000 deaths from stroke in 27 Latin American countries<sup>2</sup>. In Brazil, it is the

leading cause of death in adults, with mortality rates that can reach up to 40% at the end of the first year after the occurrence of the event<sup>3</sup>.

Nevertheless, there has been a significant reduction in mortality related to disease in the USA and many other developed countries, especially since the 20<sup>th</sup> century<sup>3</sup>. This has led to a large regional variation in mortality associated with stroke worldwide, so that, currently, about two-thirds of cases occur in developing countries<sup>4</sup>. Even in these places, the rates can differ widely, ranging from 3% in Peru to 11% in Trinidad and Tobago<sup>2</sup>. This variation is not only because of the differences existing in the general health of the populations

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**Conflict of interest:** There is no conflict of interest to declare.

Received 22 May 2012; Received in final form 19 November 2012; Accepted 26 November 2012.

and the socioeconomic conditions of the regions but also the fact that mortality estimates are based on death certificates, which, in many cases, have low accuracy<sup>2</sup>.

Thus, an early risk stratification of patients with stroke, by applying simple and reliable prognostic models, could provide important clinical estimates of mortality rates, promoting guidelines for decision-making in caring for the disease and economic evaluation, to allow a better allocation of health resources<sup>1</sup>. However, there is little research funding directed to this area compared with heart disease or neoplasia<sup>5</sup>.

Our objective was to evaluate the incidence and causes of late mortality (after 30 days) in a group of patients with ischemic stroke followed for a period of up to two years.

## METHODS

A retrospective analysis was performed of all of the medical records of patients with ischemic stroke who did not undergo thrombolytic therapy or patients in the Transitory Ischemic Attack (TIA) outpatient Neurology clinic during the period from 1<sup>st</sup> January 2006 to 1<sup>st</sup> January 2008.

The classification of the subtype of ischemic stroke was performed by applying the criteria of TOAST (Trial of ORG 10172 in Acute Stroke Treatment).

The patients met the following inclusion criteria: over 18 years of age, first clinical ischemic stroke, only atherothrombotic strokes (TOAST 1 and 3) and a diagnosis of ischemic stroke established by corresponding focal symptoms, confirmed by computed tomography (brain parenchymal hypodensity) or magnetic resonance imaging (hyperintensity on T2 and FLAIR or hypointensity on T1-weighted) performed in the acute phase.

The degree of functional impairment of the patient was evaluated by applying the modified Rankin scale (mRS) at the first appointment. For scores of 0–2, the patients were classified as independent, whereas for scores of 3–5, they were classified as dependent<sup>6</sup>.

For all of the records, we used a research protocol to obtain information on the demographics (e.g., age, education, gender), risk factors (modifiable and non-modifiable) for ischemic stroke (such as diabetes mellitus, hypertension, dyslipidemia, smoking), etiology and, if applicable, the time elapsed in months between the cerebrovascular event and death.

The patient information was used to assign patients based on the following criteria: (a) hypertension: any patient who made use of oral anti-hypertensive medication or had a systolic blood pressure (SBP)  $\geq 140$  or diastolic blood pressure (DBP)  $\geq 90$  mm Hg at the onset; (b) diabetes: use of oral hypoglycemic agents or insulin or a fasting glucose level  $\geq 126$  mg/dL in at least two different measures; (c) hypercholesterolemia: use of oral lipid-lowering agents or with

an isolated LDL  $\geq 160$  mg/dL; (d) hypertriglyceridemia: triglyceride levels  $\geq 150$  mg/dL; (e) smoker: when a patient considered himself a smoker or, in the case of an inability to respond due to a language barrier, for example, which was also observed by the informant, through a spontaneous “yes” answer to a question about a smoking habit<sup>7–9</sup>.

We calculated the body mass index (BMI) to assign patients to the following categories: underweight ( $< 18.5$ ), normal weight (18.5–24.9), overweight ( $\geq 25$ –29.9) and obese ( $\geq 30$ )<sup>10</sup>.

The monitoring begun after the confirmation of a cerebrovascular event, which occurred within the first 30 to 60 days after stroke, depending on the case, and was followed-up every 6 months by outpatient visits, contact via telephone in the case of a lack of transportation or the inability to access transport, or an active search of the patient's home in the case of a lack of consultations without justification and no response to telephone contact. The determination death causes was performed in two ways: in the case of death that occurred in the hospital, by reviewing the patient's medical records; or, otherwise, the verification of the death certificate presented by the family.

The statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 16.0. The chi-squared ( $\chi^2$ ) test was used to evaluate the continuous variables ( $p < 0.05$ ), and the differences in variables between the survivors and deaths were evaluated using the Mann-Whitney test. A logistic regression was performed to determine the odds ratios for significant variables.

The study was conducted with the approval of the Ethics Committee of Santa Marcelina Hospital, and patients were included after signing an informed consent.

## RESULTS

During the study period, we followed 337 patients (mean age of  $66.60 \pm 9.05$  years), 148 females (43.9%) and 189 males. Our sample was characterized by a very low level of education, with a median value of one year of schooling. The demographic and clinical variables are shown in Table 1. In Table 2, we show the odds ratios for the presence of each factor.

The mortality rate was 11.9% and its main cause was infection (Table 3). There were no differences in the risk factors between the deceased and surviving patients except for the ones with 80 years or more of age.

## DISCUSSION

In our sample, the late mortality rate was 11.9%, with most deaths (52.6%) occurring after the first year of

**Table 1.** Demographic and clinical variables in 337 patients with stroke, according to the death and survival rates.

	Deaths				Total		$\chi^2$	p-value
	No		Yes					
	n	%	n	%	n	%		
	297	88.1	40	11.9	337	100		
Gender								
Male	171	57.6	18	45.0	189	56.1	2.264	0.174
Female	126	42.4	22	55.0	148	43.9		
Age								
40–60 years	86	29.0	8	20.0	94	27.9		
61–70 years	116	39.1	16	40.0	132	39.2	11.248	0.010
71–80 years	78	26.3	8	20.0	86	25.5		
Greater than 80 years	17	5.7	8	20.0	25	7.4		
Education								
<4 years	196	79.0	26	83.9	222	79.6	0.397	0.359
>4 years	52	21.0	5	16.1	57	20.4		
No information	49	–	9	–	58	–		
Nutricional status								
Eutrophic	137	46.6	17	42.5	154	46.1		
Overweight	122	41.5	16	40.0	138	41.3	1.02	0.599
Obese	35	11.9	7	17.5	42	12.6		
No information	3	–	–	–	3	–		
Smoking								
Yes	151	50.8	16	40.0	167	49.6	1.658	0.239
Hypertension								
Yes	267	89.9	38	95.0	305	90.5	1.067	0.399
Diabetes								
Yes	105	35.4	16	40.0	121	35.9	0.331	0.600
Hypercholesterolemia								
Yes	73	29.6	12	38.7	85	30.6	1.088	0.306
Hypertriglyceridemia								
Yes	63	25.9	10	32.3	73	26.6	0.564	0.518
Ranking score								
0	55	19.0	6	15.4	61	18.5		
1	68	23.4	8	20.5	76	23.1		
2	108	37.2	13	33.3	121	36.8	3.089	0.543
3	27	9.3	7	17.9	34	10.3		
4	32	11.0	5	12.8	37	11.2		
No information	7	–	1	–	8	–		

cerebrovascular insult. In Brazil, the results seem to vary slightly, depending on other factors such as the sample size and the region where the study was conducted, varying from 5 to 24.6%<sup>4,11,12</sup>. These data confirm a global trend of a significant reduction in the death rates related to disease<sup>13</sup>. In Oxfordshire, United Kingdom, during the periods between 1981 and 1984 and between 2002 and 2004, the death rates decreased by 20 to 40%. Other countries have gone through reductions, in what can be considered an epidemic pattern of the disease, i.e., a period of increased incidence and/or mortality, followed by a decline. Current mortality rates range from 100 deaths per 100,000 inhabitants (Japan) to 50–53 per 100,000 (United States, Canada and Israel) and reaching 24 per 100,000 (Australia)<sup>14</sup>.

Brazil has also followed this trend and, in the last three decades, it showed the highest rate of reduction among Latin American countries: mortality rates by disease, according to André et al.<sup>3</sup>, declined consistently between 1980 to 1982 and 2000 to 2002 from 68.2 to 40.9 per 100,000 inhabitants. The causes for this decline in Brazil are not completely understood, but may be explained in part by improvements in the

control of cardiovascular risk factors, as well as the secular trend of improvement in general health care and technological advances in the treatment of acute stroke. However, it should be emphasized that this result cannot be extrapolated to the entire Brazilian population, considering the discrepancies in general health and socioeconomic conditions that exist across the country<sup>15</sup>.

The region of residence of the deceased can be used as an indicator of the quality of care and access to health services<sup>16</sup>. The eastern part of São Paulo is an area of 194 km<sup>2</sup> covering six subregions, among them, Itaquera, where the Santa Marcelina Hospital is located. It is one of the most populous areas of the State, with approximately one million inhabitants with an average income of US\$ 2273.61 and an educational level of 4–7 years; only 26.47% of the population has access to sanitary sewers<sup>17</sup>. Therefore, it is possible that these unfavorable social conditions may have contributed to the level of mortality rates found in the region.

Most deaths occurred due to non-neurological causes, and an infectious etiology, especially pneumonia, was the primary cause in 37.5% of the cases. Davenport et al.<sup>18</sup>

**Table 2.** Logistic regression analysis to evaluate the predictors of mortality.

	Deaths				OR (95%CI)
	No		Yes		
	n	%	n	%	
	297	88.1	40	11.9	
Gender					
Male	171	57.6	18	45.0	1
Female	126	42.4	22	55.0	1.66 (0.85–3.22)
Age					
40–60 years	86	29.0	8	20.0	1
61–70 years	116	39.1	16	40.0	1.48 (0.61–3.62)
71–80 years	78	26.3	8	20.0	1.10 (0.40–3.08)
Greater than 80 years	17	5.7	8	20.0	5.06 (1.67–15.3)
Education					
<4 years	196	79.0	26	83.9	1.38 (0.51–3.77)
>4 years	52	21.0	5	16.1	1
Nutricional status					
Eutrophic	137	46.6	17	42.5	1
Overweight	122	41.5	16	40.0	1.06 (0.51–2.18)
Obese	35	11.9	7	17.5	1.61 (0.62–4.19)
Smoking					
Yes	151	50.8	16	40.0	0.65 (0.33–1.26)
Hypertension					
Yes	267	89.9	38	95.0	2.14 (0.49–9.31)
Diabetes					
Yes	105	35.4	16	40.0	1.22 (0.62–2.41)
Hypercholesterolemia					
Yes	73	29.6	12	38.7	1.51 (0.71–3.26)
Hypertriglyceridemia					
Yes	63	25.9	10	32.3	1.36 (0.61–3.04)
Ranking score					
0	55	19.0	6	15.4	
1	68	23.4	8	20.5	
2	108	37.2	13	33.3	1.16 (0.88–1.53)
3	27	9.3	7	17.9	
4	32	11.0	5	12.8	

OD: odds ratio; CI: confidence interval.

**Table 3.** Causes of mortality.

	Female		Male	
	n	%	n	%
Infection	8	20	7	17.5
Pulmonary	5	12.5	4	10
Urinary	3	7.5	3	7.5
Cardiac*	5	12.5	8	20
Cancer	4	10	2	5
New Stroke	2	5	–	–
Others#	3	7.5	1	2.5

\*Acute myocardial infarction, cardiogenic shock, congestive heart failure, sudden death; #Chronic renal failure, cirrhosis.

found that the most common complications after a stroke were infections of the urinary tract (16%) or lung (12%). These complications are important because they may predispose patients to death. In a study by Hamidon et al.<sup>19</sup>, the overall mortality rate for stroke was 11.7%, of which 12.3% died due to pneumonia. Precarious socioeconomic conditions, as experienced by the population of this study, may contribute to the disadvantages in access to health information and to rehabilitation motor therapies and in the purchase of healthy foods, low availability of suitable sites for physical activity and access and/or use of assistive health technology<sup>20</sup>. Therefore, these disadvantages may contribute

to a reduced quality of care for these patients and thus increase the risk of infection.

According to Kimura et al.<sup>6</sup>, infectious causes (22.6%) are the second cause of death after the first year of the stroke insult, following cerebrovascular disease (24.1%). For them, cardioembolic stroke had a high cumulative incidence of deaths after one year (12.5%) compared with other etiologies (4% in lacunar stroke, 7.8% in atherothrombotic, 8.1% in other types and 3% in TIA,  $p < 0.001$ ).

In this study, it was also observed that age was directly correlated with the risk of death, as the mortality rate was five times higher in patients older than 80 years of age. This had been verified by means of a survey conducted by the Ministry of Health, in which it appeared that for all regions of Brazil, there is a trend of increasing mortality rates with age and a much higher rate from 80 years and beyond. Among the elderly, there is a high prevalence of hypertension, a factor that contributes to the incidence of cerebrovascular diseases, in addition to frequent drinking and smoking, especially among males<sup>21</sup>.

It is no coincidence that in our sample hypertension was the main risk factor for atherothrombotic disease, and 95% of patients who died were hypertensive, although

this variable was not statistically predictive of the risk of death in patients with an atherothrombotic etiology stroke. In another study, conducted in another region of country, the researchers found that hypertension was one of the main risk factors associated with cerebrovascular disease<sup>11</sup>.

An inverse association between adverse socioeconomic conditions (indicated by income, education and housing), such as that observed in our sample, cerebrovascular disease mortality and hypertension, has also been observed in Brazil<sup>21</sup>. Associated with this observation is the influence of Portuguese heritage on the Brazilian diet, one of whose main characteristics is the high consumption of salt<sup>22</sup>. We infer that this plays an important role, regardless of the socioeconomic structures (the differences between

Portugal and Brazil), because the inhabitants of the two countries have high mortality rates from stroke.

The limitations of the study included a lack of characterization of neurological symptoms, such as global aphasia, because, once present in the acute phase of stroke, they may contribute to increased mortality from the disease<sup>23</sup>. In addition, the research was retrospective and conducted in a region with specific characteristics, and thus should be extrapolated with caution to other regions of Brazil, due to the socioeconomic and health discrepancies across the entire country.

In our study, the late death rate was 11.9%, and an infectious etiology was the leading cause of death. Advanced age was the main predictor of mortality among patients with an atherothrombotic stroke etiology.

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