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## Article

# Predictive Clinical Factors of in-Hospital Mortality in 506 Consecutive very Old Female Patients with Acute Ischemic Stroke

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**Abstract:** Background: The oldest old people ( $\geq 85$  years) represent the fastest growing age group in Western populations. Knowledge on early outcomes of acute ischemic stroke (AIS) in very old female patients remains limited. Methods: We assessed gender differences and female-specific clinical data and in-hospital mortality in very old patients with AIS. Acute cerebral infarction was diagnosed in 506 very old female patients from a total of 4,600 acute cerebrovascular infarctions available in an ongoing 24-year hospital stroke data bank. A comparative analysis of vital status at discharge (alive versus dead) was performed in terms of cardiovascular risk factors, clinical data, and early outcomes. Results: The overall in-hospital mortality rate was 20.4%. In multivariate analysis, sudden onset, altered level of consciousness, and neurological, respiratory, cardiological or hemorrhagic complications, and lacunar infarcts appeared to be independent predictors of in-hospital mortality. Conclusions: Female patients  $\geq 85$  years with AIS are an unfavorable subgroup of stroke patients with a high risk of early mortality, which may be due to comorbidity, stroke subtype distribution, and higher frequency of medical complications. However, the presence of lacunar infarcts showed a significant protective effect.

**Keywords:** Aged; 80 and over; ischemic stroke; cerebrovascular disorders; female; hospital mortality; patient blood management

## 1. Introduction

Stroke is one of the leading causes of increase in acquired disability and, in turn, acute cerebrovascular diseases, mostly ischemic in nature, are the second leading cause of death in wealthy countries in both men and women, although deaths have been reduced by 21% [1-4]. Early detection and treatments to respond to the acute phase of the disease are essential to prevent the effects associated with acute ischemic stroke, i.e. premature death, dependency, recurrence, epilepsy, and vascular dementia, all of which require rehabilitation and support, placing a considerable economic burden on the patient, his or her family and the health care system [6-10].

Changes in population structure by age and the aging of industrialized and developed populations, in which the very old (over 85 years) represent the fastest growing segment, increase the importance of studies on acute stroke in the elderly [11-14]. The selection of 85 years or older is an arbitrary cut-off point for the exclusion of stroke patients from clinical trials and this leads to the arbitrary exclusion of elderly patients from clinical trials to, for example, the study of recombinant tissue plasminogen activator (rtPA) or anticoagulant therapy as a secondary stroke prevention in presumed cardioembolic cerebral infarction. Increasing life expectancy projects a higher percentage of elderly stroke victims [14-15]. Stroke was the first global cause of death in the oldest old in Spain in 2017, the second in men and the first in women [16].

Studies focused on the incidence of stroke in elderly patients agree with our data-base (Sagrat Cor Registry) in pointing out a high in-hospital mortality rate, longer duration of admission and less aggressive therapeutics compared with younger patients [14,17-19]. A comparative study between patients older and younger than 85 years indicated that older age was an overall predictor of early mortality in acute cerebrovascular victims (27% vs. 13.5%), as well as in-hospital death (25% vs. 11.5%) [14]. However, knowledge on early outcomes and predictive data on in-hospital mortality of acute stroke in very elderly patients remains limited.

Likewise, it has been found that men and women differ with regard to acute stroke in general and cerebral ischemia in particular. It has been shown that women have specific risk factors, clinical data and a characteristic natural history, in addition to a worse prognostic outcome [20]. Some preclinical studies suggest the sex specificity of some cell death pathways, suggesting that sex-differentiated therapeutic interventions may hold promise for a neuroprotective role in adult ischemic brain injury [21-25]. Despite all of which the analysis of the clinical characteristics of acute is-chemic stroke in the subgroup of elderly women with acute ischemic stroke remains understudied.

Most studies agree on promoting healthy lifestyle habits that control modifiable risk factors, such as smoking, obesity and overweight, sedentary lifestyle, dyslipidemia, hypertension, diabetes mellitus, alcohol consumption, and previous heart disease [26-31], although there are cardiovascular risk factors that cannot be modified, such as age, sex (female), family history, thrombophilias, and previous strokes. All factors being equal, the physiology of women in their different reproductive stages makes them especially sensitive to cerebrovascular problems, especially coagulation problems, which can lead to stroke.

It is essential to study and analyze the pathophysiological mechanisms of acute cerebrovascular disease from the different etiologies of the subtypes of ischemic stroke; this is intended to improve knowledge of the natural history of the disease, the expression of its clinical characteristics, with the result of increasing the therapeutic possibilities in cerebral reperfusion and neuronal protection, without forgetting secondary prevention. Thus, the validated subtypes of ischemic stroke are atherothrombotic, cardioembolic, lacunar, essential and cerebral infarction of unusual etiology [26-27]. Atherothrombotic and cardioembolic stroke are the subtypes with the most severe etiology [26-32]. In contrast, acute lacunar cerebral ischemia is caused by small infarcts (less than 20 mm in diameter) of the terminal branches of the perforating arteries, without anastomosis, that supply the subcortical region of the brain, the depth of the white matter, the basal ganglia and the pons, and approximately a quarter of acute strokes are of the lacunar type.

Emerging evidence suggests that acute lacunar cerebral ischemia, despite being a prevalent type of stroke with a favorable short-term prognosis, is not a benign entity and may represent the first clinical manifestation of cerebral small vessel disease, causing medium and long-term severe physical and vascular cognitive impairment or subcortical dementia [32-38]. However, there are no absolute data on the frequency and early prognosis of ischemic stroke subtypes in very elderly female patients.

Knowledge of the clinical and outcome differences between men and women could be of interest to improve prevention strategies and in-hospital treatment of very old women with acute cerebral infarction. To this end, we analyzed data from 4,600 consecutive patients with acute stroke included in our database, and compared the prevalence of demographics, cerebrovascular risk predictors, clinical features, and medical complications that developed during hospitalization, as well as neuroimaging data, in very elderly women with ischemic stroke on the basis of their vital condition at discharge (living versus dead) and by means of multiple regression analysis.

Although still controversial, the development of a predictive model of early in-hospital mortality in very elderly patients based on clinical neurological findings on admission would allow not only to establish the initial severity from bedside anamnesis, but also to identify those patients at high risk, with poor prognosis, in whom the relevance of new conventional treatments could be evaluated.

## **2. Materials and Methods**

### *2.1. Study Population*

We performed a retrospective analysis of data on stroke patients prospectively collected in the hospital stroke registry of the Hospital Universitari Sagrat Cor.

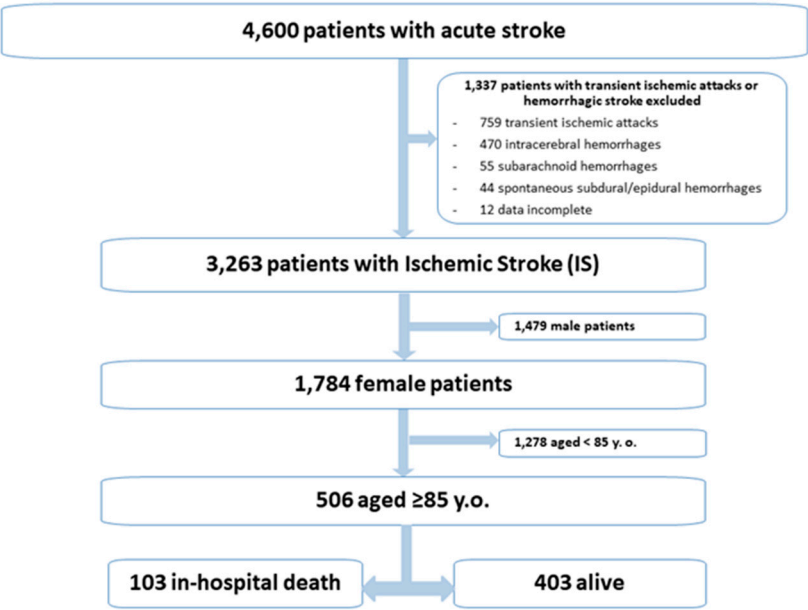
Our hospital is a 350-bed acute care university hospital in the city of Barcelona (Catalonia, Spain) serving an estimated population of 300,000 people [32]. For the present study, the data of all consecutive patients with cerebral infarction or primary cerebral hemorrhage admitted to the Department of Neurology, recorded over 24 years, were analyzed. This registry has been previously published and validated.

A protocolized 186-item questionnaire was used for each and every patient. Demographic data, cardiovascular risk factors, history and physical examination findings, laboratory data, chest x-ray, 12-lead electrocardiogram, neuroimaging data (noncontrast CT, CT angiography, angiography or MRI), complications and outcomes were collected.

For the classification of stroke subtypes, we used the criteria of the Catalan Society of Neurology and the Guidelines of the Cerebrovascular Study Group of the Spanish Society of Neurology [39,40]; both are similar to the classification of the National Institute of Neurological Disorders and Stroke [41] and have been used by our group in previous studies. The study obtained approval from the hospital's Clinical Research Ethics Committee.

A total of 4,600 consecutive patients with acute stroke were analyzed, with the following distribution of stroke subtypes: 955 cardioembolic strokes (20.8%), 944 atherothrombotic strokes (20.5%), 863 lacunar strokes (18.8%), 128 cerebral strokes of unusual etiology (2.8%), 373 cerebral strokes of unknown etiology (8.1%), 761 transient ischemic attacks (TIAs) (16.5%), 473 intracerebral hemorrhagic strokes (10.3%), 52 subarachnoid hemorrhages (1.1%), and 44 spontaneous subdural hemorrhages/spontaneous epidural hemorrhages (1%).

For the purposes of this study, and as shown in the flow-chart in Figure 1, from the initial sample of patients diagnosed with acute cerebrovascular disease, only very elderly ( $\geq 85$  years) women diagnosed with acute cerebral infarction (cardioembolic infarction, atherothrombotic infarction, lacunar infarction, cerebral infarction of unusual etiology, or cerebral infarction of unknown etiology) were selected from the stroke registry.



**Figure 1.** Schematic flow-chart of the patients included in the study considering the early outcome in the very old female patients with acute cerebral infarction.

Thus, a total sample of 503 very old female with acute cerebral infarction was obtained, of whom 103 died and 403 dismissed alive.

Medical complications (neurological and non-neurological: infectious, hemorrhagic, vascular, respiratory, cardiac, urinary, sudden death) during the acute phase were assessed as well as the

causes of early mortality. Neurological causes included recurrence of focal brain ischemia, cerebral herniation, or brain hemorrhage. Vascular complications were peripheral arterial embolism and deep venous thrombosis. Cardiac complications were arrhythmia, heart failure, and acute myocardial infarction. Pulmonary complications included aspiration pneumonia, superinfection, and pulmonary embolism. Mortality after stroke was assessed according to Silver et al criteria [42]. Modified Rankin Scale (mRs) for Neurologic disability was applied for evaluating the patient's clinical status and degree of disability at discharge and scored as spontaneous neurological improvement or good prognosis (mRS grades 0-2) and poor prognosis or in-hospital death [43,44].

## 2.2. Statistical Analysis

Deceased and living very old women patients were analyzed comparatively. For univariate analysis, analysis of variance (ANOVA) and t-Student test for continuous variables and Chi-square test (with Yates correction) for categorical variables were used to assess demographics, frequency of risk factors, clinical and neuroimaging data, and outcome in relation to vital status at discharge (alive or dead). The level of statistical significance was established at  $p < 0.05$ .

Next, a multivariate analysis was performed on those variables that were significantly related to vital status in the univariate analysis plus age. Age was used as a continuous variable, with a constant odds ratio [OR] for each year. In order to evaluate the independent predictive effect of each variable on in-hospital mortality, when  $p < 0.10$ , a logistic regression procedure and forward stepwise selection were used.

Three predictive models were designed, and in all of them, the dependent variable was in-hospital mortality coded as "alive=0" and "dead=1".

The first model was structured on the basis of cardiovascular risk factors and clinical characteristics collected during the examination on admission. In the second model, variables related to medical complications occurring during the acute phase were added to cardiovascular risk factors and clinical characteristics and, finally, in the third model, the presence of lacunar infarction was evaluated together with the previous variables (cardiovascular risk factors, clinical characteristics, and medical complications).

In the analyses performed, the statistical significance threshold for remaining in the model was 0.15, and the tolerance threshold was set at 0.0001. The weight estimates of the variables in the model were based on the maximum likelihood method [45]. Odds ratios (OR) and confidence intervals (CI) were calculated from beta coefficients and standard deviations. The Chi-squared test was used to assess the goodness of fit of the logistic regression model. Each predictive model was evaluated using the receiver operating characteristic (ROC) curve and the area under the curve (AUC). The SPSS-PC+ and BMDP programs were used for statistical analysis [46].

## 3. Results

### 3.1. General Data

Overall, acute ischemic stroke in oldest old women was diagnosed in 506 patients, mean age of 88.6 years (SD 3.2 years), and the most frequent cardiovascular risk factors were hypertension in 56.5% of cases, atrial fibrillation in 42.9%, diabetes in 17.8 %, ischemic heart disease in 15%, heart failure in 13.8%, and hyperlipidemia in 12.8% of cases.

The frequency by different ischemic stroke subtypes was 37.7% of cardioembolic infarcts, 30.8% of atherothrombotic infarcts, 26.1% of cerebral infarcts of unknown cause, 26.1% of lacunar infarcts, and 11.5% of cerebral infarctions of unusual cause.

One hundred and three died, representing an in-hospital mortality of 20.4%. By subtype of ischemic stroke, in-hospital mortality rates were highest in cardioembolic infarct (30.4%) and the lowest frequency was observed in cerebral lacunar infarcts (1.2%) (Table 1).

**Table 1.** Mortality rates in the different ischemic stroke subtypes in oldest old female patients ( $\geq 85$  years).



Ischemic stroke subtypes	Alive	Dead	Total
Atherothrombotic infarct	119 (82.1)	26 (17.9)	145
Lacunar infarct	81 (98.8)	1 (1.2)	82
Cardioembolic infarct	158 (69.6)	69 (30.4)	227
Cerebral infarcts of unknown cause	39 (88.6)	5 (11.4)	44
Cerebral infarctions of unusual cause	6 (75)	2 (25)	8
Total	403 (79.6)	103 (20.4)	506

Causes of mortality recorded were –from highest to lowest frequency- the following: brain herniation in 31%, pneumonia in 19.5%, infection in 19.5%, myocardial infarction in 5.5%, sudden death in 5.5%, recurrent cerebral ischemia in 3%, pulmonary thromboembolism in 1.5%, and unknown in 5%.

### 3.2. Comparative Clinical Study According to Vital Status at Discharge

Table 2 shows the distribution of statistically significant variables or clinically relevant data between deceased and discharged alive patients. Patients who died showed significantly more frequent presence of atrial fibrillation, sudden onset, consciousness disorders, limb weakness, sensory deficit, and neurological, respiratory, cardiac, hemorrhagic, and infectious complications in the univariate analysis.

**Table 2.** Results of univariate analysis in 506 female very old patients ( $\geq 85$  years) with acute stroke according to vital status at discharge.

Variable, coded	Alive (n=403)	Deceased (n=103)	P value
Cerebrovascular risk factors (%)			
Hypertension			
Absent	174 (79.1)	46 (20.9)	0.786
Present	229 (80.1)	57 (19.9)	
Diabetes Mellitus			
Absent	333 (80)	83 (20)	0.628
Present	70 (77.8)	29 (22.2)	
Coronary heart disease			
Absent	340 (79.1)	90 (20.9)	0.445
Present	63 (82.9)	13 (17.1)	
Atrial fibrillation			
Absent	244 (84.4)	45 (15.6)	0.002
Present	159 (73.3)	58 (26.7)	
Congestive heart failure			
Absent	353 (81)	83 (19)	0.066
Present	50 (71.4)	20 (28.6)	
Previous cerebral stroke			
Absent	363 (80.3)	89 (19.7)	0.282
Present	40 (74.1)	14 (25.9)	
History of Transient Ischemic attack (TIA)			
Absent	359 (80.3)	88 (19.7)	0.304
Present	44 (74.6)	15 (25.4)	
Chronic obstructive pulmonary disease			
Absent	381 (80.2)	94 (19.8)	0.216
Present	22 (71)	9 (29)	
Obesity			
Absent	385 (79.1)	102 (20.9)	0.169

Present	18 (94.7)	1 (5.3)	
Anticoagulants			
Absent	388 (80.2)	96 (19.8)	0.274
Present	15 (68.2)	7 (31.8)	
Hyperlipidemia			
Absent	346 (78.5)	95 (21.5)	0.084
Present	57 (87.7)	8 (12.3)	
Clinical features (%)			
Sudden onset			
Absent	220 (85.6)	37 (14.4)	0.001
Present	183 (73.5)	66 (26.5)	
Acute onset (hours)			
Absent	279 (78.4)	77 (21.8)	0.273
Present	124 (82.7)	26 (17.3)	
Headache			
Absent	836 (78.6)	100 (21.4)	0.047
Present	35 (92.1)	3 (7.9)	
Early seizures			
Absent	399 (80)	100 (20)	0.310
Present	4 (57.1)	3 (42.9)	
Altered consciousness			
Absent	327 (89.3)	39 (10.7)	0.000
Present	76 (54.3)	64 (45.7)	
Limb weakness			
Absent	87 (88.8)	11 (11.2)	0.012
Present	316 (77.5)	92 (22.5)	
Sensory deficit			
Absent	293 (83)	60 (17)	0.004
Present	110 (71.9)	43 (28.1)	
Hemianopia			
Absent	339 (81.1)	24 (27.3)	0.076
Present	64 (72.7)	103 (20.9)	
Extrapyramidal disorders			
Absent	391 (79.1)	103 (20.9)	0.159
Present	12 (100)	0	
In-hospital outcome (%)			
Neurological complications			
Absent	374 (84.8)	67 (15.2)	0.000
Present	29 (44.6)	36 (55.4)	
Respiratory complications			
Absent	361 (86.6)	56 (13.4)	0.000
Present	42 (47.2)	47 (52.8)	
Digestive complications			
Absent	391 (80.5)	95 (19.5)	0.052
Present	12 (60)	8 (40)	
Cardiac events			
Absent	390 (81.8)	87 (18.2)	0.000
Present	13 (44.8)	16 (55.2)	
Hemorrhagic events			
Absent	399 (80.8)	95 (19.2)	0.000
Present	4 (33.3)	8 (66.7)	

Infectious complications			
Absent	335 (84.6)	61 (15.4)	0.000
Present	68 (61.8)	42 (38.2)	

### 3.3. Multivariate Analysis

The results of multivariate analysis for each predictive model indicated that sudden onset, altered consciousness, and limb weakness appeared to be independent clinical predictors of hospital death in the first predictive model based on cerebrovascular risk factors and clinical characteristics (Table 3). In addition to these variables, neurological, respiratory, cardiac, and hemorrhagic complications were selected in the second predictive model based on cerebrovascular risk factors, clinical features and medical complications. In the third model, lacunar infarcts were selected in association with sudden onset, altered consciousness, neurological, respiratory, cardiac, and hemorrhagic events.

For the three predictive models analyzed, the establishment of a cutoff point of 0.50 to predict vital status at hospital discharge yielded the following results: sensitivity of 62%, 77.7% and 80.6%; specificity of 81.1%, 83.1% and 80.4%; positive predictive values of 45.7%, 54% and 51.2%; negative predictive values of 89.3%, 93.6% and 94.2%; and total correct classifications of 77.3%, 82% and 80.4%.

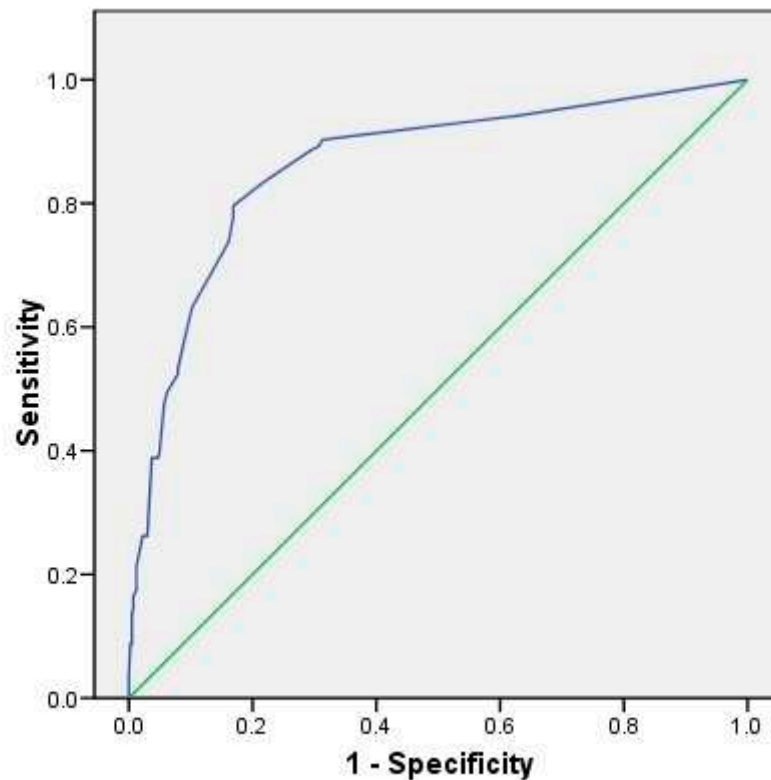
**Table 3.** Multivariate logistic regression.

Variable	$\beta$	SE ( $\beta$ )	OR (CI 95%)	p
Cerebrovascular risk factors and clinical features <sup>1</sup>				
Sudden onset	0.627	0.252	1.871 (1.143-3.065)	0.013
Altered consciousness	1.953	0.245	7.049 (4.365-11.384)	0.000
Limb weakness	0.757	0.367	2.132 (1.038-4.378)	0.039
Cerebrovascular risk factors, clinical features and medical complications <sup>2</sup>				
Sudden onset	0.680	0.278	1.974 (1.144-3.406)	0.015
Altered consciousness	1.739	0.280	5.693 (3.290-9.850)	0.000
Neurological complications	1.374	0.334	3.950 (2.053-7.601)	0.000
Respiratory complications	1.752	0.304	5.765 (3.177-10.460)	0.000
Cardiac events	1.107	0.503	3.025 (1.128-8.109)	0.028
Hemorrhagic events	1.829	0.738	6.227 (1.466-26.440)	0.013
Cerebrovascular risk factors, clinical features, medical complications and presence of lacunar infarct <sup>3</sup>				
Sudden onset	0.671	0.281	1.957 (1.128-3.394)	0.017
Altered consciousness	1.583	0.282	4.868 (2.800-8.466)	0.000
Neurological complications	1.380	0.336	3.895 (2.017-7.521)	0.000
Respiratory complications	1.725	0.305	5.610 (3.084-10.207)	0.000
Cardiac events	0.987	0.497	2.709 (1.023-7.177)	0.045
Hemorrhagic events	1.685	0.733	5.392 (1.281-22.698)	0.022
Lacunar infarct	-2.264	1.058	0.104 (0.013-0.828)	0.032

<sup>1</sup> $\beta$  = -3.104, SE( $\beta$ ) = 0.376, Hosmer-Lemeshow goodness-of-fit test  $\chi^2$  = 1.926, df = 4, p = 0.749, percentage correctly classified = 77.3%. <sup>2</sup> $\beta$  = -3.271, SE( $\beta$ ) = 0.286, Hosmer-Lemeshow goodness-of-fit test  $\chi^2$  = 5.396, df = 4, p = 0.249, percentage correctly classified = 82%. <sup>3</sup> $\beta$  = -3.063, SE( $\beta$ ) = 0.296, Hosmer-Lemeshow goodness-of-fit test  $\chi^2$  = 6.468, df = 7, p = 0.486, percentage correctly classified = 80.4%.

Figure 2 illustrates the ROC curve for the accuracy of the regression model for predicting vital status at discharge, including the variables of cardiovascular risk factors, clinical data, medical complications and presence of lacunar infarct. The area under the receiver operating characteristic curve was 0.872. The sensitivity was 80.6%, the specificity was 80.4%, the positive predictive value was 51.2% and the negative predictive value was 94.2%.





**Figure 2.** ROC curve for the regression model. Variables adjusted for cerebrovascular risk factors, clinical features, medical complications, and presence of lacunar infarct. Area under the curve = 0.872. ROC: receiving operating characteristics.

#### 4. Discussion

The results of the present study, based on the analysis of 506 very elderly female patients with ischemic stroke, according to data from our hospital registry, showed that they constituted a subgroup of stroke patients at high risk of early fatal outcome, revealing an in-hospital mortality rate of 20.4%. This higher risk seems to be related to comorbidity, the presence of subtypes of cerebral infarction with worse prognosis and a higher frequency of medical complications.

There are few studies and little published information on the clinical predictors of in-hospital mortality in the oldest old patients with acute cerebral infarction, so the optimal management of these patients remains a dilemma. Also, we have been unable to identify any previous studies that specifically examine the association between ischemic stroke in very elderly women and clinical predictors of in-hospital mortality.

Currently, one third of all patients with a first-ever acute cerebral infarction are 85 years of age or older [11,47,48]. Ischemic stroke causes great health and social impact due to its high incidence and prevalence, and because it is the leading cause of adult acquired disability and the second cause of dementia after Alzheimer's disease. It is a great burden, not only from the public health point of view, but also from the personal and family point of view, due to its impact on the lives of the people who suffer from it and their caregivers. The percentage of stroke patients among the elderly is increasing due to longer life expectancy and changes in the population pyramid in developed societies and it is becoming a major public health problem [49,50].

Analysis of our data, in line with other studies [51-54], reveals that the short-term prognosis of these patients with acute or hemorrhagic cerebrovascular infarct is poor compared to non-very old patients, showing higher in-hospital mortality (20.9% vs. 8.9%) and a lower percentage of symptom-free patients at discharge (9% vs. 13.7%), the latter being an indicator of disease burden.

The analysis of demographic data specifically related to female sex in the oldest old patients with acute ischemic cerebrovascular infarction is also limited. In this regard, the results based on the multivariate analysis presented here are novel.

The risk of acute cerebrovascular disease is lower in premenopausal women than in men of the same age [55-57]. It is known that endogenous estrogen acts as a protective factor, contributing to the maintenance of cardiovascular health through direct and indirect effects. During the climacteric period there is a decrease in ovarian estrogen levels, which causes an increase in the incidence of hypertension, diabetes, dyslipidemia and metabolic syndrome. In addition, there are alterations in weight, insulin sensitivity, lipid profile, sympathetic tone and vascular function. These changes interact with each other and increase the risk of cardiovascular disease in postmenopausal women [58,59]. Thus, gender-specific differences in the incidence of cerebrovascular disease disappear in the age group 65-84 years, increasing in women in the age range equal to or above  $\geq 85$  years, in acute strokes analyzed globally [60].

Data on the prognosis of ischemic infarction in oldest-old patients are scarce. In previous studies by our group we found that women were 67.2% of patients in the very old subgroup with first-ever acute stroke with a mean (SD) age of 88.6 (3.2) years [14] and that women differed from men in the distribution of risk factors and stroke subtypes, stroke severity, and outcome [61].

However, little is known about mortality rates in the different ischemic stroke subtypes in oldest old female patients ( $\geq 85$  years) and we are not aware of a published predictive model of early in-hospital mortality in very elderly female patients.

One of the objectives of this study was to determine the existence of predictors of in-hospital mortality based on clinical data obtained after diagnosis of focal neurological deficit in the emergency department or within 48 hours of stroke onset. Our results confirm the existence of some predictors of early mortality during hospital admission. Multivariate analysis showed that using only clinical variables, the percentage of correct classification was 80.2%, contributing our clinical investigation to the knowledge of the little known natural history of this subgroup of very old female victims.

Specifically, our study highlights the dominant relevance of medical complications developed during hospital care in the prediction of in-hospital mortality in acute stroke victims. Neurological, respiratory, cardiac, and hemorrhagic complications were independent clinical factors, easily diagnosed at the patient's bedside, associated with in-hospital death.

Contracting an infection of any type or origin is associated with severe neurological deterioration, which in turn increases both mortality and morbidity in acute stroke patients [62-64]. Stroke-associated infection, particularly pneumonia or respiratory superinfection, has been shown to be independently associated with poor functional outcome after cerebral infarction [65,66]. Urinary complications, whether urinary tract infection, incontinence, or urinary retention, are the most frequent in stroke patients and, in turn, can lead to bloodstream infection. Among the vascular complications, deep vein thrombosis stands out, which can cause pulmonary thromboembolism, which in turn is a common cause of death during the acute phase of cerebrovascular disease.

In view of these medical conditions, early diagnosis and appropriate pharmacological treatment are imperative, as they improve the prognosis of patients, as has been observed in other studies [65,66].

It should be emphasized that in-hospital mortality, as an independent variable, has been shown to decrease in hospitals that offer acute stroke unit services. These findings endorse the importance of careful and detailed cardiac and respiratory screening, together with the early institution of early therapy for cardiac and respiratory diseases and concurrent cardiopulmonary episodes.

In our study, altered consciousness was another clinical predictor related to in-hospital mortality, coinciding with the results of other studies [15,26,67,68]. In the study by Lee et al [51], very old Asian patients had the highest proportion of conscious impairment on admission and medical complications.

Motor neurological deficit was also a predictor of early mortality in our series. Appelros [69], in his study on predictors of length of admission in stroke patients, showed that the NIH stroke scale items that correlated with worse prognosis and longer length of stay were paresis, unilateral neglect,

and level of consciousness. Most interestingly, lacunar infarction was the only acute infarction subtype that was inversely associated with in-hospital mortality. These patients have a good potential for recovery that may be due to the small infarct size (<2 cm in diameter) and the generally favorable short-term prognosis of lacunar cerebral infarction compared to other subtypes of non-lacunar ischemic stroke [34, 70]. Consequently, the presence of lacunar stroke showed a significant protective effect versus other ischemic cerebral infarct subtypes.

Specifically in the objectives of the study, the data on elderly women reflect a greater probability of cardioembolic cerebrovascular infarction, together with a greater frequency of heart disease as comorbid condition. In this regard, it should be noted that cardioembolic cerebral infarction is the subtype of infarction associated with the highest in-hospital mortality (30.4%) in the acute phase of cerebral ischemia. It has been speculated that this may be due, on the one hand, to the high risk of early recurrence of infarction and, on the other, to the large infarct volume in cardiogenic cerebral embolism.

The possible limitations of the present study should be noted. A first limitation would be the potential bias of the retrospective design in a single center, which could contribute to selection bias. Although recruitment to the database was consecutive, this possibility cannot be dismissed out. It would therefore be desirable to design future multicenter studies that allow the study of a large sample size. The second limitation of the study is the lack of analysis of the prognostic value of sex in very old female patients with acute ischemic stroke in the medium or long term. And, finally, a third limitation would consist of not having analyzed the etiology of ischemic infarction of unusual cause in the sample [71], nor the relevance of vascular cognitive impairment in prognosis, with a negative predictive role in the older age group [72-74]. These points would represent interesting lines of research to be developed in future studies.

However, our study also has strengths and these are a large, homogeneous and well-characterized cohort, along with complete baseline and initial clinical outcomes with minimal loss to follow-up. In addition, the methods used in this study based on a stroke registry database on a large sample of 506 female patients older than 85 years collected over a 24-year period is more than less objective.

In summary, the poor health status prior to stroke and the greater disability and medical complications immediately following stroke might partly explain the poor clinical prognosis and high in-hospital mortality in oldest old women with acute ischemic stroke.

## 5. Conclusions

Acute ischemic cerebrovascular infarction in the oldest old ( $\geq 85$  years) is more frequent in female patients and is a devastating situation that is associated with an increased risk of premature death.

In these patients, who constitute a subgroup with severe conditions and poorly understood natural history, the most determinant relevant clinical factors influencing in-hospital mortality after acute ischemic stroke are in-hospital medical complications, whether respiratory, cardiac, neurological, and hemorrhagic. However, the presence of lacunar infarcts showed a significant protective effect. This fact should condition clinicians to establish an early prognosis with greater precision.

The relevance of these findings lies in the fact that most medical complications are potentially avoidable and/or treatable conditions whose prevention, early diagnosis and aggressive treatment should be pursued. Doing so may reduce mortality and improve the prognosis of the oldest old female patients. Therefore, prevention and therapeutic management of avoidable risk factors for medical complications is essential in the early management of the oldest old female patients with acute cerebral ischemia.

As life expectancy increases, the elderly will constitute the majority of cerebrovascular casualties. Identifying particular patterns in cardiovascular factors of risk and outcomes in different age groups of patients with acute stroke has important preventive implications, in part because of the enormous challenges that demographic changes pose to both health and social care systems. A

better understanding of the impact of sex-specific characteristics on acute cerebral infarction will improve out-comes for the entire population.

Finally, mention should be made of some of the most promising current lines of research, such as stroke genomics, possible determinant of recurrence in cerebral infarct, and biomarker-based diagnosis of subtypes of acute cerebral infarction. Not to mention the consolidation of new oral anticoagulants in long-term daily treatment of cardioembolic infarction in oldest old patients as the safest and most effective therapeutic management.

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