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Predictive clinical features of cardioembolic infarction in patients aged 85 years and older

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Abstract

Objective To assess predictive clinical factors of cardioembolic infarction in very old patients (85 years of age and older). **Methods** Prospective hospital-based stroke registry ("The Sagrat Cor Hospital of Barcelona Stroke Registry") is an acute-care teaching hospital in Barcelona, Catalonia, Spain. From 956 first-ever cardioembolic stroke patients included in the stroke registry over a 24-year period, 639 were younger than 85 years of age and 317 were 85 years or older (mean age: 88.9 years). Demographics, clinical characteristics, risk factors and early outcome were compared. Predictors of cardioembolic infarction in the oldest age group were assessed by multivariate analyses. **Results** In a logistic regression model based on demographics, risk factors, clinical features and complications, female gender (odds ratio [OR] = 1.74, 95% confidence interval [CI]: 1.27–2.39), heart failure (OR = 2.27, 95% CI: 1.46–3.56), altered consciousness (OR = 1.76, 95% CI: 1.28–2.42), and infectious complications (OR = 2.01, 95% CI: 1.39–2.91) were predictors of cardioembolic stroke in the oldest age group. By contrast, heavy smoking, heart valve disease, hypertension, headache, early seizures, sensory deficit, and involvement of the posterior cerebral artery were independently associated with cardioembolic stroke in the younger group. **Conclusions** Identification of a differential clinical profile of cardioembolic stroke between patients aged 85 years or more and those younger than 85 years helps clinicians to the optimal management of ischemic infarction in the oldest segment of the population.

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Keywords: Cardioembolic stroke; Clinical features; Ischemic infarction; Stroke; Very old patients

1 Introduction

Twenty-six million people worldwide experience a stroke each year, making it the second-leading cause of mortality and a leading cause of long-term disability.[1,2] Atrial fibrillation, systolic heart failure, recent myocardial infarction, patent foramen ovale, aortic valve atheroma, and prosthetic heart valves are potentially emboligenous cardiac causes.[1] Septic emboli, fat embolism, and tumor embolism are unusual causes of cardioembolic infarction.[3] In different stroke registries, cardioembolic infarction accounts for 18% to 25% of all cases of ischemic stroke[4–6] and it is expected to increase as life expectancy continues to rise, with elderly subjects eventually constituting the majority of stroke victims.[7]

In a systematic review of stroke in the very old, subjects over 80 years contributed to 30% of strokes, with higher 30-day case fatality rate and occurrence of dependency as compared to younger patients.[8] In the Italian population-based L'Aquila registry of first-ever ischemic strokes occurring in a 5-year period (1994–1998), the burden of stroke in subjects 80 years old or older contributed to about one-third of health care utilization and 59.8% of deaths within 30 days.[9] Also, very elderly stroke patients are at risk of receiving suboptimal care and less active management in the hospital, which in fact appears to be one of the most important modifiable prognostic factors in older patients.[10,11]

A number of studies have examined clinical characteristics and outcome of stroke in the oldest old segment of the population,[12–16] but as far as we are aware no previous studies have focused on the stroke subtype of cardioembolic

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infarction in patients 85 years or older. Therefore, this study based of a large number of patients collected from a prospective hospital-based registry was designed to compare clinical features and early outcome of cardioembolic stroke between patients aged 85 years or more and those younger than 85 years. Identification of clinical predictors of cardioembolic stroke in very old patients will help clinicians to improve adequate and timely management of this stroke subtype in the oldest segment of the population.

2 Methods

2.1 Setting and study design

A retrospective clinical study based on prospectively collected data available from an ongoing hospital-based stroke registry was conducted. The objective of the study was to identify clinical characteristics of cardioembolic infarction in very old patients compared with younger patients. Identification of specific predictors of cardioembolic stroke in very old patients can be useful from a clinical perspective to contribute to improve the care of the elderly stroke patients.

Since 1986, the Sagrat Cor Hospital (an acute-care 350-bed teaching hospital in the city of Barcelona, Spain, serving a population of approximately 300,000 inhabitants) has an ongoing hospital-based stroke registry, the details of which have been previously described.[17] The Department of Neurology has 25 beds and an acute stroke unit. Data from first ever stroke patients are entered following a standardized protocol with 186 items detailing demographics, risk factors, clinical features, laboratory and neuroimaging findings, topography, diagnostic studies, complications, and outcome. The use of the same protocol for all patients ensures completeness of the information in the database. Stroke subtypes are classified according to criteria of the Cerebrovascular Study Group of the Spanish Society of Neurology,[18] which is similar to the National Institute of Neurological Disorders and Stroke classification.[19] The study protocol for exploitation of data of the stroke registry database was approved by the Clinical Research Ethics Committee of the Sagrat Cor University Hospital, Barcelona, Spain. Written informed consent has been obtained from each patient at the time of the index admission episode.

2.2 Patient selection and study procedures

The present study is based on data included in the registry during a 24-year period (1986–2009), a time at which 4597 patients had been entered into the database. For the purpose of the study, consecutive patients diagnosed with cardioembolic infarction were selected. To classify a patient as having cardioembolic infarction required the presence of a medium-sized (maximal diameter of the lesion 1.5–3 cm) or large (> 3 cm) cerebral infarction, cerebral cortex involvement on the brain computer tomography (CT) and/or magnetic resonance imaging (MRI) scans, sudden (minutes) or acute (hours) onset, stroke onset during ordinary daily activities, peak of deficit at onset, duration of focal neurological deficit > 24 h, absence of lacunar clinical syndrome, and identification of a commonly accepted cardiac source of embolus in the absence of confirmatory clinical (ipsilateral carotid bruit) or investigative results (Doppler ultrasonography, carotid angiography, or angio-MRI) of lesions (stenosis ≥ 50%) in the ipsilateral supra-aortic trunks.

All patients were admitted to the hospital within 48 h of the onset of symptoms. On admission, demographic characteristics; salient features of clinical and neurological examination and results of laboratory tests (blood cell count, biochemical profile, serum electrolytes, urine analysis), chest radiography, 12-lead electrocardiography, and brain CT and/or MRI were recorded. Other investigations, such as angio-MRI, echo-Doppler of the extracranial carotid and vertebral arteries, arterial digital subtraction angiography, two-dimensional echocardiography and lumbar puncture were performed at the discretion of the neurologist in charge.

For each patient, demographic data, vascular risk factors, clinical features, neuroimaging findings, and outcome were recorded. Medical complications (respiratory, urinary, cardiac, vascular, and infectious) and mortality during the acute phase of the disease were recorded. Respiratory complications included aspiration pneumonia, respiratory superinfection and pulmonary embolism. Cardiac complications were arrhythmia, heart failure and acute myocardial infarction. Vascular complications were deep venous thrombosis and peripheral arterial embolism. The degree of clinical disability at discharge from the hospital was evaluated according to modified Rankin Scale (mRS).[20]

2.3 Statistical analysis

Categorical variables are expressed as frequencies and percentages, and continuous variables as mean ± SD. The distribution of variables in patients aged 85 years and older and in those younger than 85 years was compared with the chi-square (χ^2) test or the Fisher's exact test for categorical variables, and the Student's *t* test for quantitative variables. Statistical significance wat set at $P < 0.05$. Covariates with a P value < 0.20 in the univariate testing were then entered into multivariable logistic regression models with a stepwise selection method, in which age of 85 years or more (versus age under 85 years) was the dependent variable. Three re-

gression models based on data collected from the medical history, including clinical manifestations, signs on physical examination, and clinical course during stay in the hospital, were constructed. Model 1 was based on demographics and cardiovascular risk factors, to which clinical features and vascular topography (model 2) and complications (model 3) were added. The odds ratio (OR) and 95% confidence interval (CI) were calculated for the final statistically significant variables independently associated with cardioembolic stroke in patients aged 85 years or more as well as in those younger than 85 years. The accuracy of model 3 to identify cardioembolic infarction in subjects aged 85 years or older was assessed using the receiver operating characteristics (ROC) curve. The sensitivity, specificity and positive and negative predictive values were calculated. Statistical analysis was performed using the SPSS software package.

3 Results

The study population included 956 patients with first-ever cardioembolic infarction, 317 (33.2%) of which aged 85 years or more, with a mean age of 88.9 ± 3.3 years. The remaining 639 patients were younger than 85 years, with a mean age of 77.5 ± 7.7 years. The percentage of women was significantly higher in the oldest old group as compared to younger patients where there was a predominance of males.

Results of univariate analysis are shown in Table 1. In relation to cardiovascular risk factors, hypertension, valve heart disease, peripheral vascular disease, hyperlipidemia, and heavy smoking were significantly more frequent in the younger age group, whereas congestive heart failure was significantly more frequent in the older age group. Regarding clinical features, sudden onset, headache, and early seizures were significantly more frequent in the younger age group. By contrast, decreased consciousness was more common among older patients. The distribution of lesions according to the vascular topography was similar. Complications including respiratory, urinary and infectious events were more frequent in the oldest age group. Early outcome was better in the younger age group, with a significantly higher percentage of patients free of symptoms at hospital discharge and with mild neurological deficit as compared to older patients. Also, the mortality rate was significantly higher in the older age group.

Results of multivariate analysis are shown in Table 2. In the first logistic regression model based on demographics and cardiovascular risk factors, congestive heart failure (OR = 2.26) and female gender (OR = 1.75) were independently associated with cardioembolic stroke in older patients, whereas hypertension, valve heart disease and smoking were predictors of cardioembolic stroke in younger patients. In the second regression model in which clinical features and vascular topography were added, congestive heart failure (OR = 2.29), altered consciousness (OR = 1.90) and female gender (OR = 1.74) were predictors of cardioembolic stroke in the older age group, whereas sensory deficit, hypertension, infarction in the territory of the posterior cerebral artery, valve heart disease, headache, early seizures and smoking were variables independently associated with cardioembolic stroke in the younger age group. In the final model in which complications were added, congestive heart failure (OR = 2.27), infectious complications (OR = 2.01), altered consciousness (OR = 1.76) and female gender (OR = 1.74) were predictors of cardioembolic stroke in older patients. Other variables including hypertension, sensory deficit, posterior cerebral artery, valve heart disease, headache, early seizures and smoking were associated with cardioembolic stroke in younger patients. According to these models, cases of cardioembolic infarction in subjects aged 85 years or older versus less than 85 years were correctly classified in 58% of the cases for model 1, 66% of the cases for model 2, and 66% of the cases for model 3.

Figure 1 shows the ROC curve of the accuracy of the regression model based on demographics, cardiovascular risk factors, clinical features, vascular topography and complications to differentiate cardioembolic infarction between subjects aged 85 years or older and subjects less than 85 years of age. The area under the curve (AUC) was 0.715. The sensitivity was 75%, specificity 61%, positive predictive value 49% and negative predictive value 83%.

4 Discussion

This study adds interesting information to clinicians for a better characterization of the clinical profile of cardioembolic infarction in the population segment of very old patients (aged 85 years or more). Cardioembolic stroke accounts for 14%–30% of ischemic strokes and is generally the most severe ischemic stroke subtype, with a high rate of neurological disability at hospital discharge, high mortality and prone to early and late embolic recurrences.[21] Although the general characteristics of cardioembolic stroke are well known, there are no specific studies of this subtype of cerebral infarction in very elderly patients.

In our study, female gender was associated with cardioembolic stroke in very old patients, which is explained by the longer life expectancy of women as compared to men. Women generally live longer than males, on average by 6 to 8 years, in relation to women's biological advantage, sex

Table 1. Results of univariate analysis: differences between patients with cardioembolic infarction according to age.

	Age ≥ 85 yrs (*n* = 317)	Age < 85 yrs (*n* = 639)	*P* value
Demographics			
Male patients	90 (28.4%)	264 (41.3%)	0.001
Female patients	227 (71.6%)	374 (58.5%)	
Age, yrs	88.9 ± 3.3	75.5 ± 7.7	0.001
Risk factors			
Hypertension	154 (48.6%)	358 (56.0%)	0.018
Diabetes mellitus	52 (16.4%)	125 (19.6%)	0.136
Valve heart disease	30 (9.5%)	126 (19.7%)	0.001
Ischemic heart disease	60 (18.9%)	139 (21.8%)	0.177
Atrial fibrillation	246 (77.6%)	464 (72.6%)	0.056
Congestive heart failure	51 (16.1%)	49 (7.7%)	0.001
History of TIA	37 (11.7%)	59 (9.2%)	0.143
History of cerebrovascular disease	56 (17.7%)	118 (18.5%)	0.418
Previous cerebral hematoma	4 (1.3%)	7 (1.1%)	0.523
COPD	28 (8.8%)	56 (8.8%)	0.530
Chronic renal disease	23 (7.3%)	34 (5.3%)	0.148
Peripheral vascular disease	16 (5.0%)	52 (8.1%)	0.05
Chronic liver disease	5 (1.6%)	10 (4.8%)	0.001
Hyperlipidemia	32 (10.1%)	98 (15.3%)	0.015
Heavy smoking (> 20 cigarettes/day)	3 (0.9%)	39 (6.1%)	0.001
Clinical features			
Sudden onset	195 (61.5%)	429 (67.1%)	0.050
Headache	11 (3.5%)	62 (9.7%)	0.001
Vegetative symptoms	11 (2.5%)	36 (17.1%)	0.001
Early seizures	2 (0.8%)	15 (2.3%)	0.044
Nausea/vomiting	16 (5.0%)	46 (7.2%)	0.128
Altered consciousness	118 (37.2%)	146 (22.8%)	0.001
Motor symptoms	261 (82.3%)	500 (78.2%)	0.081
Sensory symptoms	103 (32.5%)	242 (37.9%)	0.059
Visual disturbances	62 (19.6%)	140 (21.9%)	0.226
Speech disturbances	192 (60.6%)	396 (62.0%)	0.363
Ataxia	12 (3.8%)	28 (4.4%)	0.403
Cranial nerve palsy	13 (4.1%)	30 (4.7%)	0.407
Vascular topography			
Middle cerebral artery involvement	209 (65.9%)	411 (64.3%)	0.623
Posterior cerebral artery involvement	15 (4.7%)	62 (9.7%)	0.212
Anterior choroidal artery	3 (0.9%)	1 (0.2%)	0.495
Vertebral artery	3 (0.9%)	16 (2.5%)	0.168
Basilar artery	6 (1.9%)	17 (2.7%)	0.466
Posteroinferior cerebellar artery	2 (0.6%)	7 (1.1%)	0.730
Superior cerebellar artery	3 (0.9%)	5 (0.8%)	1.000
Complications			
Neurological	41 (12.9%)	85 (13.3%)	0.481
Respiratory	68 (21.5%)	70 (11.0%)	0.001
Renal	4 (0.9%)	6 (3.8%)	0.01
Urinary	36 (11.4%)	50 (7.8%)	0.048
Cardiac events	30 (9.5%)	56 (8.8%)	0.403
Vascular	9 (2.8%)	18 (2.8%)	0.566
Infectious	81 (25.6%)	91 (14.2%)	0.001

Table 1. Cont.

Variables	Age ≥ 85 yrs (*n* = 317)	Age < 85 yrs (*n* = 639)	*P* value
Outcome			
At hospital discharge			
Symptom free	32 (10.1%)	91 (14.2%)	0.043
Degree of disability/dependence, mRS			
0–1, no symptoms, no significant disability	41 (12.9%)	127 (19.9%)	0.005
2, slight disability	48 (15.1%)	154 (24.1%)	0.001
3, moderate disability	50 (15.8%)	118 (18.5%)	0.174
4 or 5, severe neurological impairment	54 (17.0%)	81 (17.7%)	0.044
Length hospital stay, days, median (IQR)	14 (10–24)	13 (8–22)	0.013
In-hospital mortality	97 (30.6%)	121 (18.9%)	0.001

Data are presented as mean ± SD or *n* (%). COPD: chronic obstructive pulmonary disease; IQR: interquartile range; mRS: modified Rankin Scale; TIA: transient ischemic attack.

Table 2. Results of multivariate analysis: variables independently associated with cardioembolic infarction in subjects aged 85 years or older.

Regression models	Coefficient (β)	Standard error	Odds ratio (95% confidence interval)	*P* value
Model 1: demographics and risk factors				
Congestive heart failure	0.816	0.221	2.26 (1.47–3.48)	0.001
Female gender	0.559	0.156	1.75 (1.29–2.37)	0.001
Hypertension	–0.428	0.144	0.65 (0.49–0.86)	0.003
Valve heart disease	–1.042	0.223	0.35 (0.23–0.55)	0.001
Smoking	–1.703	0.613	0.18 (0.06–0.60)	0.005
Model 2: demographics, risk factors, clinical features and vascular topography				
Congestive heart failure	0.827	0.227	2.29 (1.47–3.56)	0.001
Altered consciousness	0.645	0.161	1.90 (1.39–2.61)	0.001
Female gender	0.554	0.160	1.74 (1.27–2.38)	0.001
Sensory deficit	–0.367	0.157	0.69 (0.51–0.94)	0.019
Hypertension	–0.376	0.148	0.69 (0.51–0.92)	0.011
Posterior cerebral artery	–0.702	0.317	0.50 (0.27–0.92)	0.027
Valve heart disease	–0.959	0.227	0.38 (0.25–0.60)	0.001
Headache	–1.014	0.347	0.36 (0.18–0.72)	0.003
Early seizures	–1.629	0.793	0.20 (0.04–0.93)	0.040
Smoking	–1.676	0.622	0.19 (0.05–0.63)	0.007
Model 3: demographics, risk factors, clinical features, vascular topography and complications				
Congestive heart failure	0.822	0.228	2.27 (1.46–3.56)	0.001
Infectious complications	0.700	0.188	2.01 (1.39–2.91)	0.001
Altered consciousness	0.566	0.163	1.76 (1.28–2.42)	0.001
Female gender	0.552	0.161	1.74 (1.27–2.38)	0.001
Hypertension	–0.370	0.149	0.69 (0.52–0.93)	0.013
Sensory deficit	–0.468	0.161	0.63 (0.46–0.86)	0.004
Posterior cerebral artery	–0.671	0.319	0.51 (0.27–0.95)	0.035
Valve heart disease	–0.957	0.229	0.38 (0.24–0.60)	0.001
Headache	–1.004	0.348	0.37 (0.18–0.72)	0.004
Early seizures	–1.686	0.791	0.18 (0.04–0.87)	0.033
Smoking	–1.734	0.634	0.18 (0.05–0.61)	0.006

Model 1: Hosmer-Lemeshow goodness-of-fit test 0.999, subjects ≥ 85 years versus < 85 years were correctly classified in 58% of cases; Model 2: Hosmer-Lemeshow goodness-of-fit test 0.210, subjects ≥ 85 years versus < 85 years were correctly classified in 66% of cases; Model 3: Hosmer-Lemeshow goodness-of-fit test 0.064, subjects ≥ 85 years versus < 85 years were correctly classified in 66% of cases.

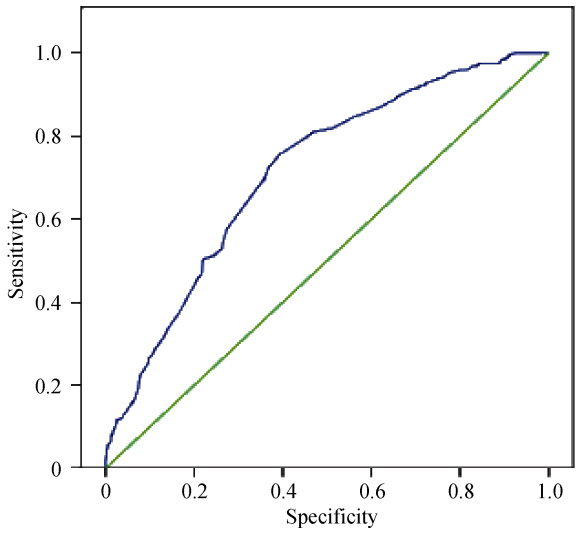

Figure 1. ROC curve for regression model 3 including demographics, cardiovascular risk factors, clinical features, vascular topography and complications (AUC: 0.715). AUC: area under the curve; ROC: receiver operating characteristics.

differences in mortality, lifestyles and impact of environmental and social factors.[22,23] Besides the female gender, congestive heart failure was also a significant predictor of cardioembolic infarction in very old patients. Most patients with heart failure are elderly, constituting up to 80% of patients suffering from this disease with both incidence and prevalence of the condition increasing with age. This is due to the progressive aging of the population as well as improved and better survival after cardiac insults, such as myocardial infarction, especially in developed countries; notably, acute heart failure is the leading cause of hospitalization in patients over 65 years.[24,25] Accordingly, early diagnosis and proper treatment are critical as they both influence prognosis in these patients, particularly taking into account a main the finding of our study, in which congestive heart failure was the most important predictor of cardioembolic stroke.

Other risk factors for cardiovascular disease such as hypertension, valve heart disease and smoking were more frequent among patients younger than 85 years of age. The low prevalence of heavy smokers among patients of 85 years or older is consistent with epidemiological data reported by Olindo, *et al*.[26] in very old patients in a black Caribbean population (Martinique, French West Indies). In the Uppsala Longitudinal Study of Adult Men study over 40 years, smoking was the risk factor showing the greatest decline in prevalence over time, changing from above 50% to 6% during the follow-up period.[27] This decline in smoking prevalence was paralleled with a decline in its impact as a risk factor for cardiovascular disease. The rapid decline in smoking is probably mainly attributed to an increased awareness in the general population on the hazard of smoking in the 1970s and 1980s, resulting in a voluntary smoking cessation in the majority of subjects. On the other hand, atrial fibrillation, which is a common emboligenous cause of cerebral infarction, was more frequent in the older age group than in younger patients but the difference was marginally significant. In the Framingham study,[28] the proportion of strokes associated with this arrhythmia increased steadily with age from 6.7% for ages 50 to 59 years to 36.2% for ages 80 to 89 years.

Altered consciousness was an independent predictor of cardioembolic infarction in the three regression models. Decreased level of consciousness at stroke onset is present in 19%–31% of cases of cardioembolic infarction.[21,29,30] In the study of Timsit *et al*.,[31] altered consciousness was a predictive factor of cardioembolic infarction, with an OR 3.2 as compared with atherothrombotic infarction. Decreased consciousness is explained by the large volume of the infarction. The relevance of this symptom in people over 85 years can be explained by the superior clinical fragility and greater involvement of the cerebral reserve of these patients and by the increase in cases of hemorrhagic transformation, either by delay in reperfusion or the prevalence of longer duration of anticoagulant treatment with a higher risk of iatrogenesis at these advanced ages.[32]

Patients aged 85 years or older showed a poor prognosis as shown by the higher mortality rate, longer hospital stay and higher rates of complications, particularly respiratory events as compared to younger patients. Very elderly patients are more prone to aspiration due to an increase in secretions related to immobility, predisposing to respiratory infection in this age subgroup. Therefore, intensive chest physiotherapy should be promptly instituted to facilitate cough and to keep the airways as clean as possible.

Limitations of the study include the retrospective analysis of data based on a single-center stroke registry, so that a hospital referral selection bias cannot be excluded. Laboratory and neuroimaging variables were not included in multivariate analysis, which would have provided a more robust regression model. Other possible confounding variables (e.g., concomitant medications) were not evaluated. Strengths of the study are the large number of patients analyzed, the systematic evaluation of predictors of cardioembolic infarction in very old patients based on risk factors, clinical features, vascular topography and complications, all of which are variables early to be collected at the bedside.

In summary, identification of a differential clinical profile of cardioembolic stroke between patients aged 85 years or more and those younger than 85 years helps clinicians to the optimal management of ischemic infarction in the oldest segment of the population.

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