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Research Article

Recurrence after a First- ever Ischemic Stroke Development of a Clinical Prediction Rule

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Abstract

***Background*:** Cumulative risk of stroke recurrence is about 26% at five years, with overall mortality rate of 38%.

***Objective*:** to develop a user-friendly clinical prediction algorithm of ischemic stroke recurrence to help in the design of long-term strategies for secondary prevention.

***Design*:** Historical Cohort study.

***Setting*:** Tertiary urban hospital-based practice.

***Patients*:** Subjects admitted to the hospital for a first-ever ischemic stroke.

Measurements: Variables studied were clinical picture and management, previous vascular risk factors and comorbidity, Stroke subtype and severity. Predictors were determined by statistical models based on Cox regression and recursive partition analysis. The internal validity was calculated via bootstrapping and its performance (predictive ability) by the statistic C.

***Results*:** 303 patients were analyzed. They were classified as having: 1) "high or very high" risk of recurrence (probability > 51%) (those with left ventricular hypertrophy/hypertensive cardiomyopathy or chronic kidney disease) (21% of patients; 2) 'Intermediate' risk (probability 21-50%) (44% of patients); and 3) 'low' risk (those with age under 70 years without left ventricular hypertrophy/hypertensive cardiomyopathy nor

coronary heart disease or age over 70 years, but starting therapy with anticoagulants due to an underlying embolic condition) (probability <21%) (35% of patients). The C statistic was 0.7557 (95% CI: 0.697-0.813) demonstrating a good predictive ability.

***Conclusion*:** A few variables organized into a clinical prediction rule, could help physician's assessment of patients with a first stroke episode admitted to a health center to improve and facilitate the decision making and course of action.

Keywords: Stroke; Clinical prediction rules; Prognostic research.

Introduction

Stroke is the leading cause of adult disability in Western countries, and the second cause of cardiovascular mortality with high economic and social impact [1], [2]. One third of the strokes are recurrent attacks [3]. The total number of stroke deaths is currently estimated at 508,000 per year in Europe [4]. Ischemic stroke is the most frequent etiology (87%) [3].

The cumulative risk of stroke recurrence within five years after a first episode ranges between 15-40%[5,6]. The risk of recurrence is higher within the first year after the stroke (between 6-14%) than in subsequent years (4% annually), achieving its maximum incidence during the first month after the initial stroke.

The most relevant predictors of stroke recurrence identified in epidemiological trials include advancing age [9,10,12], arterial hypertension [12,14,15], a trial fibrillation [15,16], diabetes mellitus (DM) or impaired glucose tolerance [5,10,12,17], hyperlipidemia [15] and previous transient ischemic attack [5,16, 18].

There are still variability between studies that based in data drawn from point of care versus epidemiological settings, particularly in the role of long term medical treatment [19]. The ability to predict the risk of stroke recurrence through a clinical prediction algorithm would help to tailor future preventive and therapeutic measures according to the estimated risk of recurrence for each individual patient. We hypothesized that it will facilitate the decision-making process and long-term

strategies for stroke's secondary prevention. Thus, the main objective of this study was to develop a practical and user-friendly clinical prediction algorithm of ischemic stroke recurrence in patients admitted to the hospital after a first episode of ischemic stroke.

Materials and Methods

Study Design

This observational, historical cohort study was conducted at the University Hospital 12 de Octubre, Madrid (Spain). Study subjects were recruited throughout a three-year period, from October 1998 until October 2001, both years inclusive. The study was

approved by the Ethics Committee of the hospital and performed in accordance with Good Clinical Practices criteria.

The mean reference population for University Hospital 12 Octubre was numbered 550,000 by the year 2000. This hospital was the only one that attended acute strokes in their geographical area and most of the stroke patients were admitted to Internal Medicine and Neurology Departments (according beds availability).

Study Procedures

Patients older than 15 years old, admitted to the emergency room with the first episode of ischemic stroke (transient ischemic

attack included) were identified from the hospital's database and included in the study

Clinical information during hospitalization was obtained from inpatient medical records and follow-up information through outpatient medical records or by telephone contact with the patient or next of kin.

Ischemic stroke was defined as a cerebrovascular event that rapidly led to the development of clinical signs of acute neurological focal disturbance, or leading to death with no apparent cause other than vascular origin. Recurrent stroke was defined as a cerebrovascular event subsequent to the initial stroke and occurring in an anatomic site or vascular territory different from that of the initial stroke. Diagnosis of ischemic

stroke (initial or recurrent) was done based on inpatient and outpatient medical records and computed tomography or magnetic resonance imaging scan reports. Cranial CT scan was performed in all patients included in the study. Doppler sonography of cervical (vertebral and carotid) arteries was performed in 72%, echocardiography in 41% and cerebral MRI in 39%. We defined Hypertensive Cardiomyopathy as the presence of conventional electrocardiographic and/or ultrasonographic criteria for left ventricular hypertrophy and/or for diastolic dysfunction.

Protocol study included the following patient's related information: demographic and clinical data, previous vascular risk factors (VRF) such as HTA, smoker status, diabetes, atrial fibrillation, cardiovascular events or antecedents of ischemic

heart disease, hypertensive cardiomyopathy, left ventricular hypertrophy based on conventional electrocardiographic or ultrasonographic criteria. Ischemic stroke subtype was classified based on TOAST classification criteria [20] and severity of stroke at discharge based on RANKIN INDEX [21], (scale that assesses the degree of physical disability after stroke). Also degree of control of cardiovascular risk factors after first ever ischemic stroke. We considered non-optimal control -uncontrolled arterial hypertension- if there were in the patient clinical record more than 2 documented BP measures above 140/90 mmHg or more than 2 references of inadequate BP control, non-optimalglycemic control if A1c hemoglobin > 7%, non-optimal lipid profile control if LDL cholesterol above 100 mg/dl; new cardiovascular events during follow-up (stroke, acute coronary heart disease), and therapy: anticoagulant and antiplatelet drugs among others.

Statistical Analysis

Qualitative variables were expressed as absolute frequencies and percentages. Continuous variables were described using mean and standard deviation.

Significant risk factors for ischemic stroke recurrence were identified using a univariate analysis. Then, a multivariate analysis of significant risk factors of ischemic stroke identified in the univariate analysis, as well as other risk factors that we considered clinically relevant, was performed using the Cox proportional hazards model.

If death and a possible recurrent ischemic stroke were recorded as occurring simultaneously, only the death was considered as a

censoring event because of the difficulty of documenting the ischemic stroke recurrence at that precise moment. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated for each risk factor. Lastly, clinically relevant risk factors of ischemic stroke recurrence were subjected to a classification and regression tree analysis. Only patients who had all the necessary information to assign the best documented and validated score were included in this analysis.This recursive partitioning method was used for the multivariate analysis due to its ability to identify groups with similar prognosis, place the different prognostic factors in a hierarchy, and demonstrate the relationships between them. The recursive partitioning method may reutilize the same variable in different segments of the tree. In each segment, the most convenient cut off-point that optimizes the partition criterion is chosen. Continuous variables were

dichotomized to create two groups with different probability of event.

The prediction models were estimated regarding recurrence during the first two years given that is the time spam with more information and sample size. The area under the receiver operating characteristic (ROC) curve was calculated to evaluate the performance (predictive ability) of the Cox regression and classification and regression model. Finally, the areas under the ROC curves obtained in each model were compared to identify any differences regarding the discrimination power between the models.

The internal validity of the model's estimations was calculated via bootstrapping. 200 bootstrap samples were needed for accurate assessment of outer confidence limits.

All statistical analyses were carried out using STATA V 11 software. Significance was set at $p<0.05$.

Ethical approval: The proposal for the project was approved as observational study by the Institutional Review Board (ref. 149/05) in compliance with the Helsinki Declaration and BPC (CPMP/ICH/135/95).

Results

During the 3-year inclusion period (1998-2001), 449 patients with a first-ever ischemic stroke were identified. Of these, 35 were excluded due to insufficient clinical data, 37 because they died of the initial stroke and 52 because they could not be followed up after hospital discharge. Thus, 325 patients were finally included and followed up according to the study protocol.

Mean age of study subjects was 70±12 years, and 56% were males. Those patients included had an averaged historical follow up of 41±34 months until closing the data set for this study. Baseline patient characteristics are shown in table 1.

Table 1: Baseline Patient Characteristics (N=325).

Please See Table 1 in Full PDF Version

During follow-up, 56 patients died (17%) (21 of them died of stroke recurrence, 19 of other cardiovascular events, and 16 of non-vascular disease). Ischemic stroke recurrence during follow-up, including stroke deaths were of 33%.

In patients with stroke recurrence, only 3% were younger than 50 years while 43% were older than 75 years old.
Of the 106 patients who suffered from an ischemic stroke recurrence, 45 patients (43%) suffering in the first year, 29 (27%) during the second year, 19 (18%) during the third year, and 13 patients (12%) during the following years.

Table 2 shows the characteristics of patients with stroke-recurrence.

Table 2: Characteristics of Patients with Stroke Recurrence

Please See Table 2 in Full PDF Version

Significant risk factors of ischemic stroke recurrence after a first episode identified with univariate analysis were: age (Hazard ratio –HR-: 1.038; p<0.001), chronic kidney disease (HR: 2.47 p=0.01), coronary heart disease (HR: 1.841; p=0.004), hypertensive cardiomyopathy/left ventricular hypertrophy (HR: 2.127;p=0.01), uncontrolled arterial hypertension (HR: 2.160;p=0.025) and stroke despite previous antiplatelet therapy (HR: 2.037; p=0.002). However, starting oral anticoagulants (HR:

0.483; p=0.007) was identified as factor associated with lesser risk of ischemic stroke recurrence.

The variables identified in the multivariate analysis were: age (HR: 1.046; p<0.0001), chronic kidney disease (HR: 3.537; p=0.0004), ischemic heart disease (HR: 1.998; p=0.0013), hypertensive cardiomyopathy/LVH (HR: 2.387; p=0.0056) and previous antiplatelet therapy (HR: 2.177; p=0.0001) (Table 3). Starting therapy with oral anticoagulants (HR: 0.390; p=0.003) and clopidogrel use (HR: 0.318; p=0.01) were associated with a lower recurrence.

Table 3: Cox Multivariate Analysis of Predictive Risk Factors of Ischemic Stroke Recurrence (N=325)

Variable	HR	95% CI	p
Age	1.046	1.023-1.065	<0.0001
Chronic kidney disease	3.537	1.760-7.108	0.0004
Coronary heart disease	1.998	1.309-3.050	0.001
Left Ventricular Hypertrophy	2.387	1.290-4.416	0.005
Previous Antiplatelet Therapy	2.177	1.458-3.250	0.0001
Starting therapy with Clopidogrel	0.318	0.127-0.794	0.01
Starting Oral anticoagulants	0.390	0.207-0.734	0.003

CI: Confidence interval. HR: Hazard ratio.

The area under the ROC curve for the multivariate Cox analysis was 0.7495 (95% CI: 0.675-0.803), bootstrap validation confirm

the size of the area under the curve again (bias-corrected 95% CI: 0.671-0.800), indicating a good predictive power (Figure 1).

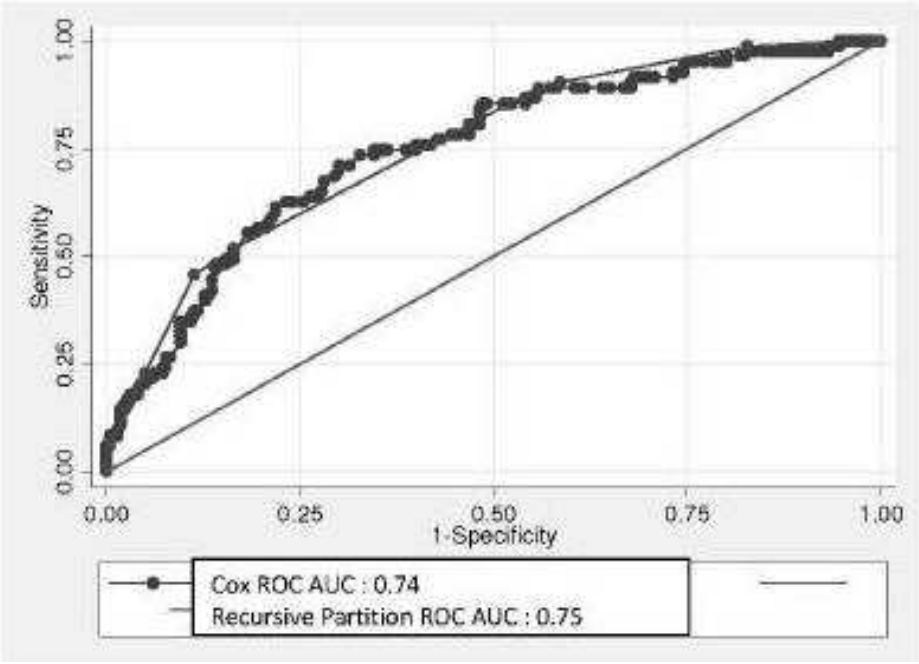

Figure 1: Comparison of Areas under the ROC Curve Obtained in the Cox and Recursive Partition Algorithm Analyses

Recursive partition and regression classification algorithm analysis for clinical prediction rule, by this method, only 303 patients fulfilled all requirements. The best single predictor of stroke recurrence in the first 2 years was being older 70 years old.

The major independent predictor of stroke recurrence in patients elder than 70 years old was the presence of hypertensive cardiomiopathy or left ventricular hypertrophy. However, anticoagulant therapy was clearly protective factor.

Table 4 shows the final recursive partition algorithm analysis together with the probability of stroke recurrence, the number of patients, and the clinical characteristics for the four risk groups were identified by the model.

Table 4: Clinical Prediction Rule. Clinical Predictors of 2-Year Stroke Recurrence after Recursive Partition Algorithm Analysis

Predictors of stroke recurrence				Probability of suffering a stroke recurrence (%)	Patients (n=303)
Age ≤ 70	LVH/HC = 1			0.58	12
"	LVH/HC = 0	CHD=1		0.31	16
"	"	CHD=0		0.12	99
Age > 70	OA=1			0.14	7
"	OA=0	LVH/HC = 1		0.58	45
"	"	CKD=1		0.83	6
"	"	CKD=0	LVH/HC =0	0.26	118

1=patient has the risk factor

0=patient does not have the risk factor.

LVH/HC: Left ventricular hypertrophy/ hypertensive cardiomyopathy; CHD: Coronary heart disease; OA: start oral anticoagulants; CKD: chronic kidney disease.

Color code	Risk stratification	Probability of ischemic stroke recurrence (%)
	Very high	≥61
	High	51-60
	Intermediate	21-50
	Low	≤20

From the 303 patients studied, 6 of them (2%) were classified as having a 'very high' risk, 57 (19%) as 'high' risk, 134 (44%) as

‘intermediate’ risk, and 106 (35%) as ‘low’ risk of ischemic stroke recurrence.

According to the recursive partition algorithm analysis (table 3), patients with left ventricular hypertrophy/hypertensive cardiomyopathy or chronic kidney disease were classified as a “high” or “very high” risk of ischemic stroke recurrence. In other hand, the patients elder than 70 years old whose starting anticoagulants therapy, and younger than 70 years old without any pathology were considered low risk.

Note that some logical clinical profiles expected were absent due to the lack of enough subjects in the data set with these characteristics. The area under the ROC curve of the recursive partition algorithm analysis was 0.7557 (95% CI: 0.697-0.813),

(bootstrap bias-corrected 95% CI: 0.688-0.804) demonstrating a good predictive ability. When the areas under the ROC curve obtained in the Cox regression analysis and the recursive partition algorithm analysis were compared, no significant differences were observed regarding the ability to predict a stroke recurrence after a first episode (p=0.827) (Figure 2).

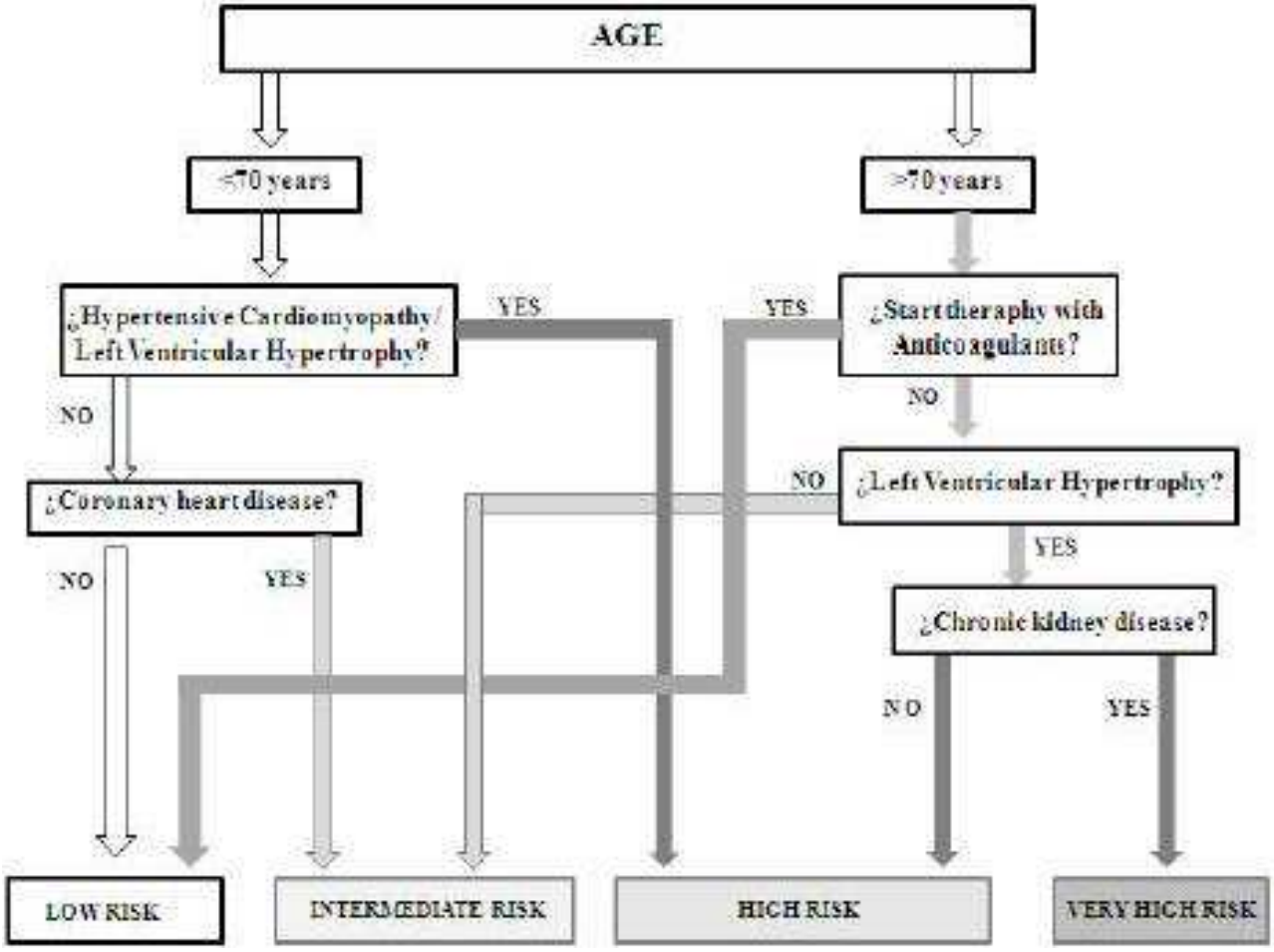

Figure 2: Algorithm for Easily Stratification Stroke Recurrence Risk

Discussion

Stroke is a major public health problem, and in particular ischemic stroke is the subtype that generates the greatest burden of disease [22] Thus, the development of practical and user-friendly clinical prediction algorithms to rapidly and accurately estimate the patient's short and long-term risk of suffering a stroke recurrence is both timely and necessary.

Our results showed that after a mean follow-up period of 41 months, the third part (33%) of the patients had suffered from an ischemic stroke recurrence; moreover, 6% of patients died as a consequence of the recurrence.

These results underscore the fact that, although the incidence of stroke recurrence varies depending on stroke subtypes, study design and other controlled and uncontrolled factors, it is high and must be addressed in time to avoid recurrence-related morbidity and mortality.

The predictive factors used in our study to develop clinical prediction rule for recurrent ischemic stroke, have already been described in previous studies. [10, 14, 15, 25-27].According to our results, age ($p<0.0001$), chronic kidney disease ($p=0.01$), coronary heart disease ($p=0.004$), hypertensive cardiomyopathy/ left ventricular hypertrophy ($p=0.01$) and uncontrolled arterial hypertension ($p=0.025$) were significant predictors of ischemic stroke recurrence after a first episode. Starting therapy with oral anticoagulants (in patients with demonstration of underlying

disease with indication for it) (p=0.007) and the use of clopidogrel (p=0.01) were significant predictors of lower risk of recurrence.

There is enough scientific evidence to support the finding that advancing age is associated with an increased risk of stroke recurrence [10,14,24,25].

The American Heart Association report described that, patients who have a first-ever stroke of any type, in those aged 40 to 69 years 13% of men and 22% of women will have a stroke recurrence within the first five years after the first episode.

This incidence increases to 23% in men and 28% in women aged 70 years or more.

In a Mediterranean country as Spain, Modrego et al, showed that age, arterial hypertension, Diabetes mellitus and cardiovascular diseases, were significant predictors of stroke recurrence in 425 patients with a first episode of stroke. [9]

Arterial hypertension is a recognized risk factor for cardiovascular and cerebrovascular disease[28]related with atherosclerosis [29-32]. It is known that optimal control of blood pressure reduces the risk [33]as well as the recurrence of ischemic stroke[34,35].

We showed that hypertensive cardiomyopathy/ left ventricular hypertrophy and un-controlled arterial hypertension were strong predictive factors for stroke recurrence.

Although cardioembolic and atherothrombotic stroke have been linked to increased risk of recurrence in some studies[36,37] in our study, as in others [38],there was no difference in recurrence between different etiological subtypes of ischemic stroke.

We also observed that patients in treatment with antiplatelet therapy before first episode of stroke had more likelihood of recurrence. It could be explained by the presence of some illness (for instance a trial fibrillation, coronary heart disease, peripheral artery disease…), with potential added risk in these patients.

As it is well known, clopidogrel is an effective antiplatelet used for primary and secondary prevention of cardiovascular and cerebrovascular disease [39-43]. We noted that starting therapy

with clopidogrel after a first-ever ischemic stroke was identified as a protective factor for stroke recurrence.
We observed the same results with anticoagulants therapy.

Thus, we proposed a useful algorithm based on the combination of 5 clinical parameters (figure 2), that facilitates the physician to classify the stroke recurrence risk of the patient into one of the four risk subgroups (very high, high, intermediate and low risk).

With this simple algorithm, the physician's assessment of patients with a first stroke episode admitted to the hospital may be substantially enhanced, improving and facilitating the decision making process and course of action at the point of care, [44] and thereby with potential to slow down the morbidity and mortality of this prevalent entity.

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