SPAN2 SCALE: A NEW PREDICTIVE SCALE OF DISABILITY IN MINOR STROKE WITHOUT LARGE-VESSEL OCCLUSION

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Abstract

Background: Currently there is no predictive model in acute minor stroke without large vessel occlusion.

Aims: Our objective was to evaluate the independent predictors that correlate with unfavourable outcome and to develop a predictive scale in acute setting.

Methods: Retrospective analysis of consecutive acute minor stroke (NIHSS $\leq$5) admitted within 4.5 hours to clinical onset who were previously not disabled and without large vessel occlusion on CT angiography (intracranial or extracranial occlusion or stenosis $\geq$50%). Unfavourable outcome was defined as modified Rankin Scale 3-6 at 90 days. Independent predictors of disability were included in the model.

Results: A total of 408 patients with acute minor stroke (NIHSS $\leq$5) were analyzed. Large vessel occlusion was detected in 83 (20%), who were excluded. The final analysis included 325 patients, with mean age of 68± 14 years, 59% were men and 14.5% had unfavourable outcome. On multivariate analysis, age $\geq$70 years, NIHSS $\geq$2, recurrent event, posterior circulation ischemia and previous stroke were associated with unfavourable outcome. Recurrent event was excluded to the model because this variable is not available in acute setting. With the variables detected in the logistic regression, a predictive model was made (SPAN$_2$ scale: previous Stroke, Posterior ischemia, Age $\geq$70 or NIHSS $\geq$2). The model correctly classified 84% of the patients with unfavourable outcome. A score $\geq$2 points on the SPAN$_2$ scale showed a sensitivity 95%, specificity 51%, PPV 25% and NPV 99% of unfavourable outcome at 90 days.

Conclusions: SPAN$_2$ scale could be useful to stratify the risk of unfavourable outcome in acute phase of minor stroke without large vessel occlusion. Future studies may validate its usefulness in the selection of patients for thrombolytic therapy.

Keywords: minor stroke, disability, recurrent event, outcome, LVO

Introduction

The pivotal National Institute of Neurological Disorders and Stroke (NINDS) recombinant tissue plasminogen activator (rtPA) Stroke Trials established intravenous rtPA as a therapy for acute ischemic strokes within 3 hours of initiation of the symptoms[1]. The NINDS trials required the exclusion of patients with ischemic stroke if they had specific minor or rapidly improving symptoms. This led to patients with minor neurological deficits being routinely excluded from thrombolytic treatment.

Currently, minor stroke symptoms defined as National Institutes of Health Stroke Scale (NIHSS) ≤ 5 points represent approximately two-third of patients with ischemic stroke[2] and a substantial proportion (20% to 46%) of patients are excluded from thrombolytic therapy due to uncertainly clinical benefit and the fear of symptomatic intracranial haemorrhage in a patient with "not disabling" deficit[3].

However, between 12%-31% of patients with minor stroke excluded from thrombolytic therapy will have poor outcome (Rankin scale 3-6) at 90 days [4-8].

Previous studies and meta-analyses[9-15] have yield conflicting results, demonstrating that the types of deficits in minor stroke or the total NIHSS score have a poor correlation with clinical outcome.

A consistent predictor of outcome in minor stroke is evidence of large vessel occlusion[16,17]. However, patients with persistent neurological deficit and no visible occlusion may have ongoing ischemia secondary to clot in penetrating arterioles or distal arteries, being able to benefit from thrombolytic therapy.

Therefore, it is necessary to better delineate the factors really identify acute minor stroke patients with poor outcome and develop more accurate predictive models, which take into account the presence of large vessel occlusion and other clinical factors.

This models may help to identify patients who are most likely to benefit from thrombolytic therapy and the design of clinical trials with thrombolytic therapy in this subtype of ischemic stroke.

Our objective was to analyze the independent predictors of outcome at 90 days in a prospective cohort of patients with acute minor stroke (NIHSS ≤ 5) without large vessel occlusion and to generate a predictive model.

Methods

We retrospectively evaluated consecutive acute minor stroke patients (NIHSS ≤ 5) admitted within 4.5 hours to clinical onset who were previously not disabled and without large vessel occlusion (LVO) on CT angiography between January 2012 to August 2019.

In our analysis, we excluded patients with transient ischemic attack, premorbid modified Rankin scale (mRS) >2 or serious co-morbidity illness that would likely result in death within 3 months.

Medical history, physical examination, severity of the neurological deficit by means of the National Institutes of Health Stroke Scale (NIHSS)[18], routine blood chemistry,

electrocardiogram (ECG), chest x-ray, echocardiography, cranial neuroimaging (CT scan) and arterial study (CT angiogram) was systematically performed in all patients at admission. Echocardiography and MRI were completed during the hospitalization.

CT angiography was assessed for the presence of any acute symptomatic intracranial or extracranial occlusion or stenosis ≥50% (LVO). The severity of extracranial stenosis was calculated using the standard North American Symptomatic Carotid Endarterectomy Trial (NASCET) method applied to reformatted axial CTA images[19].

The baseline vascular risk factors were defined as follows. Smoking was considered if the patient reported smoking cigarettes. Hypertension was defined as a systolic blood pressure ≥140 mmHg or diastolic ≥90 mmHg or current use of antihypertensive treatment. Diabetes mellitus was considered in patients with a history of fasting blood glucose ≥126 mg/dL or current use of antidiabetic drugs. Hypercholesterolemia was defined as a total cholesterol level ≥200 mg/dL or current use of lipid-lowering agents.

Stoke were classified aetiologically according to the TOAST criteria[20] as due to large -artery occlusive disease (LA), small-vessel disease (SV), cardioembolism (CE), other causes (OC) or undetermined cause (UND). Clinical subtypes of stroke were classified according the Oxfordshire Community Stroke Project[21] as TACI (total anterior circulation infarct), PACI (partial anterior circulation infarct), LACI (lacunar infarct), and POCI (posterior circulation infarct). Symptoms not captured by NIHSS as ataxia, diplopia or distal motor weakness were analyzed.

Symptomatic intracranial haemorrhage after thrombolysis (SICH) was defined as cerebral haemorrhage with clinical deterioration in NIHSS score of ≥4 points[22].

A recurrent event was defined as a functional deterioration in neurological status lasting >24 hours or a new sudden focal neurological deficit of vascular origin, occurring at any time between the initial assessment to 90 days follow-up.

Medical complications as dysphagia and bronchoaspitation[23] during the stay were evaluated. The follow up at 3 months was done by face-to-face interview. Unfavourable outcome was defined as dependency (modified Rankin Scale score of 3-5) or death.

Statistical analysis

Statistical analysis was performed using the statistics program SPSS, version 19.0 (IBM, Chicago, IL). Categorical variables were compared between favourable and unfavourable outcomes using chi-square test or by Fisher exact test. Continuous variables were analysed with the Mann-Whitney test in non-parametric variables or T-student test in parametric variables. To identify the cut-offs of variables that could be used for discriminating between favourable or unfavourable outcome, a ROC curve was used. The odds ratios (OR) for variables associated with unfavourable outcome were determined using multivariable logistic regression analysis, adjusted for variables with $p< 0.05$ on univariate analysis. With the

independent predictors detected at admission we generate a predictive model. It was considered statistically significant p< 0.05.

Results

A total of 408 patients with acute minor stroke (NIHSS ≤5) were analyzed. LVO was detected in 83 (20%) patients; 16.6% intracranial, 2.9% extracranial and 0.7 % extra and intracranial, who were excluded.

The final analysis included 325 patients, with mean age of 68± 14 years and 59% were men. The median NIHSS at admission was 3 points (range 0 to 5). According to Oxfordshire classification we detect the following distribution: total anterior circulation infarcts,

TACI (0%), partial anterior circulation infarcts, PACI (36%), lacunar infarcts, LACI (46%), and posterior circulation infarcts, POCI (18%).

According to TOAST criteria the strokes were classified as follows: LA (0%), SV (30%), CE (25.4%), OC (10%), and UND (34.6%). Thrombolysis with intravenous recombinant plasminogen activator was administered in 53 patients (16%), and none patients suffered symptomatic intracranial haemorrhage.

Most of the patients had a favourable functional outcome, being discharged at home (95%), mRS 0-1 (75%) and mRS 0-2 (85.5%) at 90 days of follow up. (Table1).

Table 1. Clinical characteristics and functional outcome of patients with or without recurrence at 3 months after minor stroke.

	Overall (n=325)	Recurrence (n=46)	No recurrence (n=278)	P value
Demographics				
Age, years, mean (SD)	68 ±14	70±12	65±13	0.02
Male (%)	59	63	59	0.6
Risk factors (%)				
Atrial fibrillation	15	26.1	12.9	0.02
Hypertension	69	82.6	66.9	0.03
Diabetes Mellitus	30	32.6	25.6	0.7
Ischemic heart disease	13	23.9	11.5	0.03
Previous Stroke/TIA	25	34.8	23.7	0.1
Smoker	26	21.7	27.3	0.4
Hypercholesterolemia	50	45.7	51.4	0.5
Stroke etiologic subtype (%)				0.10
Cardio-embolic	25.4	41.4	23.6	
Large vessel	0	0	0	
Small vessel	30	13.8	32	
Other causes	10	10.3	10	
Undetermined	34.6	34.5	34.4	

	Overall (n=325)	Recurrence (n=46)	No recurrence (n=278)	P value
Clinical stroke subtypes (%)				0.1
TACI	0	0	0	
PACI	35.7	32.6	36.3	
LACI	45.8	39.1	46.8	
POCI	18.5	28.3	16.9	
NIHSS, median (IQR)	3(0-5)	4 (0-5)	3 (0-5)	0.005
Thrombolysis (%)	16.3	17.4	16.2	0.8
Symptomatic ICH (%)	0	0	0	-
Symptoms not captured by NIHSS				0.8
Ataxia (%)	19.4	17.4	19.4	
Diplopia (%)	3.1	2.2	3.2	
Distal motor weakness (%)	12.9	2.2	14.7	
Medical complications				
Dysphagia (%)	8.6	19.6	6.8	0.01
Bronchoaspiration (%)	1.2	8.7	0	0.000
Length of stay, mean (SD)	5.7±4.5	10±7.5	5±3.4	0.000
Outcome (%)				
mRS 0-1 at 90 days	75	39	80.9	0.000
mRS 0-2 at 90 days	85.5	50	91.4	0.000
Mortality at 90 days	2.2	10.9	0.7	0.001
Vascular mortality	0.9	6.5	0	0.003

Forty- six of 325 patients (14%) experienced recurrent stroke. Of these patients 50% had an unfavourable outcome, while patients without recurrence 8.6% had a poor prognosis (p=0.0001).

Patients with recurrence at 3 months were more likely to be older, with a higher rate of hypertension, atrial fibrillation, coronary heart disease, dysphagia and a higher median of NIHSS score than those without recurrence. We did not detected any variable as independent predictor of vascular recurrence. Regarding the functional prognosis, the univariate analysis detected as predictors of poor prognosis (mRS 3-6 at 90 days): Age, HTA, NIHSS, previous stroke, POCI, dysphagia and recurrent events.

The multivariate logistic regression detected as independent predictors : Age, NIHSS, POCI, previous stroke and recurrent events (Table 2). Although vascular recurrence was the most important predictor of disability (OR 13.92 95% IC 5.29-36.59, p=0.0001) was not included in the model because this variable is not known in acute setting.

The optimal cut-off for an unfavourable outcome in age and NIHSS were: ≥70 years,

with a sensitivity of 81% , a specificity of 52% (area under the receiver operating characteristic curve of 0.70) and NIHSS $\geq$2 , with a sensitivity of 82%, a specificity of 39% (area under curve of 0.628).

With the variables detected in the logistic regression, a predictive model was made (Table 2). The model showed an area under the curve value of 73%.

This model was used to generate the SPAN$_2$ scale (previous Stroke, Posterior ischemia, Age $\geq$70, NIHSS $\geq$2) where each item can have a value 0-1. The relationship between SPAN$_2$ score and functional prognosis at 90 days is showed in figure 1.

Table 2. The variables detected in the multivariable analysis for unfavourable outcome at 90 days (mRS 3-6). The model correctly classified 84% of the patients with unfavourable outcome.

Variable	Model		
	OR	95% IC	P
POCI	4.02	1.99-8.33	0.000
Age $\geq$70	6.23	2.91-14.70	0.000
NIHSS $\geq$2	7.53	2.45-33.39	0.002
Previous stroke	2.25	1.08-4.69	0.029
Classification with to the model (%) Unfavourable / favourable outcome (global)	83.8/61.7(80.6%)		

Figure 1. Relationship between SPAN$_2$ score and functional outcome at 90 days in acute minor stroke without large vessel occlusion.
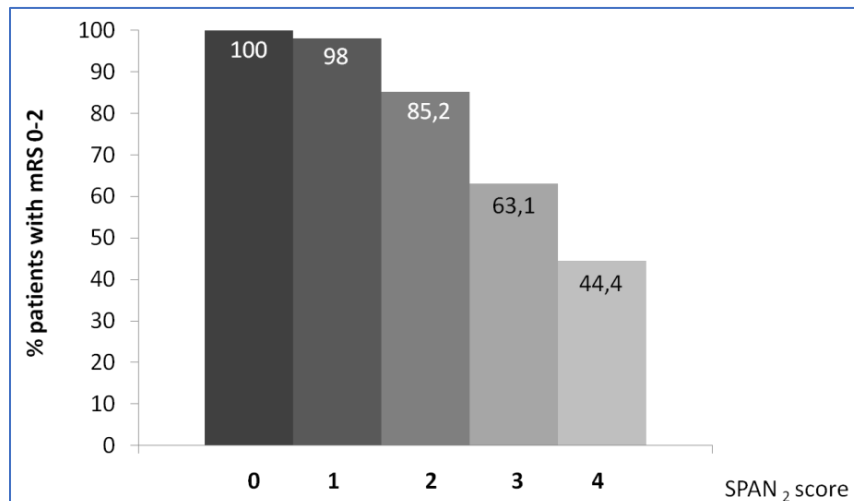
Scores ≥ 2 points on the SPAN$_2$ scale showed a sensitivity of 95%, specificity of 51%, a positive predictive value of 25% and a negative predictive value 99% for a unfavourable outcome at 90 days.

Discussion

In the present study we found that a minority of patients with acute minor stroke without extra/intracranial large vessel occlusion suffered disability (14%) or vascular death (0.9%). The recurrence rate at 3-months was 14%, similar to previous studies [24,25], being the most important predictor of unfavourable outcome (OR 13.92).

The multivariate analysis revealed that the age $\geq$ 70 years, NIHSS $\geq$ 2, posterior territory ischemia, and previous stroke were independent predictors of disability outcome, while other symptoms not captured by NIHSS as diplopia, ataxia or distal motor weakness did not show relationship.

With the independent predictors detected, we generate the SPAN$_2$ scale, where a score ≥ 2 points was highly predictive of poor prognosis (negative predictive value of 99%). Even though, the vascular recurrence was the most important predictor of unfavourable outcome, was not included in the predictive model, because this variable is not known in acute phase.

Although previous studies have identified multiple prognostic predictors as leg weakness, extinction/inattention[26], older age, female gender, black race ethnicity, diabetes mellitus, atrial fibrillation, coronary heart disease, hypertension, previous stroke [8,27], our

scale is the first predictive model applicable to acute minor stroke without LVO.

The presence of LVO is associated with deterioration when thrombolysis is withheld[16,28]. In previous studies, 10% of minor stroke and transient ischemic attack patients had an identifiable LVO[29], and the probability of neurological deterioration was greater both intracranial arterial occlusion (19% vs 2%)[29] as extracranial occlusion (OR 8.3)[30]. In our study, 16% of patients presented intracranial occlusion, a percentage higher possibly because we excluding TIA patients.

Large cerebral artery occlusions typically lead to more severe stroke and some patients can suffer significant clinical deterioration as the initial hours pass[31]. However, in the presence of a complete circle of Willis and a well collateral circulation, patients with proximal arterial occlusions may at times present with only relatively mild symptoms. Early neurological deterioration is reported in 30% of patients with terminal internal carotid artery or tandem occlusions (internal carotid artery and middle cerebral artery) and 17% in extracranial carotid occlusions versus 3.1% in those with no occlusion. Among patients with any occlusion and early neurological deterioration, 77% will die or have a poor functional outcome at three months[32]. Therefore, symptomatic arterial occlusion is an important predictor of neurological deterioration in patients with acute minor stroke and may not represent mild stroke in acute period, for this reason, in our study patients with LVO were excluded of the model.

One third of all acute ischemic stroke patients presenting within the acute window are not given intravenous rt-PA solely based on clinical judgment of mild or rapidly improving symptoms[28,33]. Many clinical trials use a NIHSS ≥ 5 cut-off in an effort to identify mild stroke patients, assuming they will go on to have a non-disabling functional outcome.

Recent observational studies have proposed different definitions of minor strokes with the aim of identifying definitions associated with a more benign outcome. Varying definitions included a low total NIHSS score ≤ 1[34] or ≤ 3[35], isolated symptom on the level of consciousness, gaze, facial palsy, sensory, or dysarthria items[34]. However, the association between the NIHSS scores and outcomes is not linear and not all deficits are captured by the NIHSS. Therefore, it is necessary to use different predictive parameters that help us to better delineate the prognosis in these patients. Identifying cases with a higher likelihood of an unfavourable prognosis could help consider acute thrombolytic treatment.

The biggest reason to withhold thrombolytic treatment is the risk of cerebral haemorrhage. However, the overall risk of spontaneous haemorrhagic transformation in minor strokes is low and does not significantly contribute to disability[29].

In our study none patients suffered symptomatic intracranial haemorrhage, similar to previous studies (1% to 5%)[1,36-38], where intravenous rt-PA had a good safety profile.

The benefits of thrombolytic treatment in minor patient population are still unclear.

Meta-analysis of acute stroke trials [39] and post hoc analysis of the original NINDS rt-PA study have shown benefit of intravenous rt-PA across the spectrum of stroke severity [15], while the PRISMS trial did not shown benefit [40].

In these studies, minor stroke was defined only under a single clinical criteria, NIHSS 0-5, without including acute arterial study, when large arterial occlusion is the greatest predictor of neurological deterioration. Therefore, when defining a minor stroke, arterial status should be evaluated in order to assess the benefit of thrombolysis in patients with and without arterial occlusion separately. The new radiological techniques of perfusion (perfusion CT or perfusion-diffusion MRI) can show potentially viable brain tissue after the onset of a stroke, being a potentially very useful tool in the selection of patients who are candidates for thrombolysis and salvageable brain tissue [41].

Our study had some limitations, 1) It is a retrospective analysis of consecutive data in one center, 2) Perfusion images in cranial CT could have been helpful to identify better the subtype of acute stroke and the prognostic predictors. However we do not have this information in all cases and therefore it was not included in the analysis, 3) our scale has not been validated in other populations.

Conclusions

Acute minor stroke without large vessel occlusion and SPAN $_2$ score ≥ 2 had a higher risk of disability at 3- months. Future studies will validate the scale and its usefulness in the decision of thrombolytic treatment.

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