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Clinical Short Communication

A nomogram to predict the probability of mortality after first-ever acute manifestations of cerebral small vessel disease

Manuel Cappellari[a,*], Cecilia Zivelonghi[a], Gianni Turcato[b], Stefano Forlivesi[a], Nicola Micheletti[a], Giampaolo Tomelleri[a], Paolo Bovi[a], Bruno Bonetti[a]

[a] Stroke Unit-Neurology, Department of Neuroscience, Azienda Ospedaliera Universitaria Integrata, Verona, Italy
[b] Emergency Department, Girolamo Fracastoro Hospital San Bonifacio (Verona), Italy

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ABSTRACT

Background and purpose: Symptomatic lacunar stroke (LS) and deep intracerebral hemorrhage (dICH) represent the acute manifestations of type 1 cerebral small vessel disease (cSVD). Recently, two studies showed that the risk factor profile of dICH differs from that associated with LS in subjects with biologically plausible cSVD; however, the prognostic predictors after acute manifestations are currently lacking.

We aimed to develop a nomogram for individualized prediction of the mortality probability in a cohort of patients with a first-ever acute manifestation of biologically plausible cSVD.

Methods: We conducted a retrospective analysis of data collected from consecutive patients with acute symptomatic non-embolic LS or primary dICH. The outcome measure was 3-month mortality. Based on multivariate logistic model, the nomogram was generated.

Results: Of the 288 patients who entered into the study for biologically plausible cSVD, 131 (45%) experienced a LS and 157 (55%) a dICH. After multivariate logistic regression, 5 variables remained predictors of mortality to compose the nomogram: dICH (OR:11.36; $p = 0.001$), severe presentation (OR:8.08; $p < 0.001$), age (OR:1.08; $p = 0.001$), glucose (OR:1.23; $p = 0.003$) and creatinine (OR:1.01; $p = 0.024$) at admission were predictors of mortality. The discriminative performance of nomogram assessed by using the area under the receiver operating characteristic curve (AUC-ROC) was 0.898. The model was internally validated by using bootstrap (1000 samples) with AUC-ROC of 0.895 and cross-validation (deleted-d method repeated 1000 times) with AUC-ROC of 0.895.

Conclusions: We developed the first nomogram for prediction of the mortality probability in a cohort of patients with a first-ever acute manifestation of biologically plausible cSVD.

1. Introduction

Type 1 cerebral small vessel disease (cSVD), also known as hypertensive microangiopathy, is an age-related and vascular risk-factor-related pathological process of small perforating arteries. It is mainly characterized by loss of smooth muscle cells from the tunica media, deposits of fibro-hyaline material, narrowing of the lumen, and thickening of the vessel wall [1]. Type 1 cSVD is a common and systemic disease that also affects the kidneys and retinas and is strongly associated with ageing, diabetes, and, in particular, hypertension. Symptomatic lacunar stroke (LS) and deep intracerebral hemorrhage (dICH) represent the acute manifestations of progressive type 1 cSVD. Because these two phenotypes share the same pathological substrate, two recent studies showed that the risk factor profile of dICH differs from that associated with LS in subjects with biologically plausible cSVD [2,3]; however, the prognostic predictors after acute symptomatic events of cSVD are currently lacking.

By using a continuous score, a nomogram is a graphical statistical instrument that calculates the continuous probability of a particular outcome for an individual patient; it is an important component of modern medical decision making and has been used in an extensive array of applications, including cancer, surgery and other specialties [4–6].

Therefore, the present study aimed to develop a nomogram for individualized prediction of probability of 3-month mortality in patients with a first-ever acute manifestation of biologically plausible cSVD.

* Corresponding author at: Stroke Unit-Neurology, Department of Neuroscience, Azienda Ospedaliera Universitaria Integrata, Piazzale A. Stefani 1, 37126 Verona, Italy.
E-mail address: manuel.cappellari@aovr.veneto.it (M. Cappellari).

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2. Methods

2.1. Study population

We reviewed data from the electronic medical records of all patients admitted within 12 h of symptoms onset to our Institution for ischemic stroke (IS) or intracerebral hemorrhage (ICH), between March 2011 and December 2014. We included only patients who experienced a first-ever symptomatic non-embolic LS or primary dICH.

The LS subgroup was composed of patients with a clinical subcortical lacunar stroke syndrome [7] in combination with a lacunar infarction (small deep infarct < 15 mm in perforator branch territory on computed tomography (CT) or magnetic resonance imaging (MRI) in an area corresponding to the symptoms).

The dICH subgroup was composed of patients with a deep hematoma. ICH location was assigned based on admission CT scan. Deep ICH involved the thalamus, basal ganglia, or brainstem.

When available, magnetic resonance imaging provided additional information on imaging markers, such as periventricular white matter hyperintensities, silent lacunes, and microbleeds.

In an attempt to detect in vivo only the subjects with LS or dICH related to biologically plausible cSVD, we used strict clinical exclusion criteria because LS and dICH may also be secondary to different causes. Exclusion criteria and risk factors definitions are provided in the online-only Data Supplement.

Acute manifestation was LS or dICH. Severe presentation was defined as Glasgow Coma Scale (GCS) ≤ 4 for patients with dICH and NIHSS score ≥ 14 for patients with LS [8,9].

2.2. Outcome measures

The outcome measure was mortality at 3 months.

2.3. Statistical analysis

The statistical analysis was performed with STATA 13.0.1 (StataCorp, College Station, Texas, USA). Categorical variables are reported as proportion and continuous variables as mean and standard deviation (SD). Descriptive differences between groups were examined with the $\chi 2$ test and 1-way ANOVA F test, when appropriate.

To generate the nomogram, multivariate logistic regression analysis was performed for predicting the probability of 3-month mortality using a forward stepwise method that included all variables with a probability value < 0.10 in the univariate analysis. Regression coefficients and odds ratios (OR) with two-sided 95% confidence intervals (CI) for each of the variable included in the model were finally calculated. The predictive accuracy of the nomogram model using the original sample was assessed by calculation of the area under the receiver operating characteristic curve (AUC-ROC). The model was internally validated by using bootstrap (1000 samples) and cross-validation (deleted-d method repeated 1000 times).

3. Results

Two hundred eighty eight patients with biologically plausible cSVD entered into the study. LS was the acute manifestation in 131 (45%) patients and dICH in 157 (55%); their clinical features are provided in the Table 1. Atrial fibrillation, chronic kidney disease, use of vitamin K antagonist and statin, and severe presentation were more frequent in patients with dICH, while vascular disease was more frequent in patients with vascular disease. Values of blood glucose, systolic and diastolic blood pressure were higher in patients with dICH.

Mortality at 3 month occurred in 38 (13%) patients. Of the seven variables (dICH, chronic kidney disease, severe presentation, brainstem lesion, age, glucose and creatinine levels at admission) that entered the

Table 1
Clinical characteristics of the patients. Categorical variables were reported as proportion and continuous variables as mean (standard deviation).

	All patients (n = 288)	LS (n = 131)	dICH (n = 157)	P value
Demographic				
Age (years), mean (SD)	68.3 (13)	69 (12.7)	67.8 (13.2)	0.405
Female sex, n (%)	122 (42.4)	52 (39.7)	70 (44.6)	0.473
Medical history				
Hypertension, n (%)	226 (78.5)	102 (77.9)	124 (79)	0.886
Diabetes mellitus, n (%)	57 (19.8)	27 (20.6)	30 (19.1)	0.768
Hypercholesterolemia, n (%)	54 (18.8)	18 (13.7)	36 (22.9)	0.051
Current smoking, n (%)	67 (23.3)	29 (22.1)	38 (24.2)	0.780
Atrial fibrillation, n (%)	12 (4.2)	0	12 (7.6)	0.001
Congestive heart failure/LF dysfunction, n (%)	13 (4.5)	9 (6.9)	4 (2.5)	0.093
Vascular disease, n (%)	38 (13.2)	25 (19.1)	13 (8.3)	0.008
Chronic kidney disease, n (%)	49 (17)	11 (8.4)	38 (24.2)	< 0.001
Alcohol consumption, n (%)	9 (3.1)	3 (2.3)	6 (3.8)	0.517
Vitamin K antagonist treatment, n (%)	10 (3.5)	0	10 (6.4)	0.002
Antiplatelet treatment, n (%)	78 (27.1)	42 (32.1)	36 (22.9)	0.086
Statin treatment, n (%)	29 (10.1)	3 (2.3)	26 (16.6)	< 0.001
Admission data				
Severe presentation, n (%)	49 (17)	5 (3.8)	44 (28)	< 0.001
Hemoglobin (g/L), mean (SD)	138.5 (19.1)	139.7 (19.8)	137.5 (18.5)	0.328
Thrombocytes (10^9/L), mean (SD)	226.2 (65.0)	226.7 (63.6)	225.7 (66.3)	0.903
INR, mean (SD)	1.05 (0.08)	1.04 (0.07)	1.06 (0.09)	0.052
Glucose (mmol/L), mean (SD)	7.6 (3)	6.9 (2.6)	8.2 (3.2)	< 0.001
Creatinine (μmol/L), mean (SD)	93 (48.9)	92.2 (42.7)	93.7 (53.6)	0.792
Alanine transaminase (U/L), mean (SD)	26.8 (18)	25 (12.4)	28 (21)	0.285
Systolic blood pressure (mm Hg), mean (SD)	176.4 (30.9)	171 (30.1)	181.7 (30.8)	0.008
Diastolic blood pressure (mm Hg), mean (SD)	91.9 (17.6)	88.2 (15.8)	95.6 (18.6)	0.001
Other data				
Total cholesterol (mmol/L) < 24 h, mean (SD)	4.7 (1.1)	4.7 (1.2)	4.8 (1.1)	0.518
High-density lipoprotein (mmol/L) < 24 h, mean (SD)	1.3 (0.5)	1.2 (0.5)	1.3 (0.5)	0.332
Low-density lipoprotein (mmol/L) < 24 h, mean (SD)	2.9 (1)	2.9 (1)	2.8 (0.9)	0.903
Brainstem lesion, n (%)	20 (6.9)	13 (9.9)	7 (4.5)	0.101

Abbreviations: LS = lacunar stroke; dICH = deep intracerebral hemorrhage; SD = standard deviation; LF = left ventricular; INR = International Normalized Ratio.