A new stroke mimic prediction scale in a stroke center with a high thrombolysis rate

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ABSTRACT

Patients reaching the emergency department (ED) with symptoms of acute ischemic stroke (AIS) may be affected by a stroke mimics (SMs). A prompt clinical diagnosis could avoid unnecessary thrombolysis. We evaluated a new and rapid approach, the Santa Maria Nuova-Stroke Mimic (SMN-SM) scale, to improve a prompt clinical diagnosis. 340 consecutive patients admitted to the ED with suspected AIS were evaluated. The final diagnosis was: AIS in 267 (78,5%) and SMs in 73 (21,5%) patients. Multivariate logistical analysis showed that the following features – lack of facial paralysis, dizziness, migraine, seizure disorders, blood pressure <150, cognitive impairment, and female sex – were significantly more abundant in patients with SMs than in AIS. To each of these features we assigned a numerical score and we performed a receiver operating characteristic analysis. When the score of the scale was above 8 (cut-point), we obtained a specificity of 93% and a sensitivity of 56% for a SM diagnosis. Thus, the SMN-SM scale seems a rather useful tool to improve SMs diagnosis.

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Introduction

Acute ischemic stroke (AIS) diagnosis is based on brief history collection, clinical examination and head computed tomography (CT) scan, often combined with CT-angiography. The whole procedure cannot be time-consuming because the efficacy of the treatments (intravenous thrombolysis and/or other endovascular procedures) is strictly time-dependent. Stroke mimics (SMs) may have symptoms compatible with AIS including a negative head CT scan. In the emergency departments (ED), approximately 30% of suspected stroke patients are affected by a SMs and the potential risk of administering intravenous thrombolysis to SMs is substantial.[1,2]

Stroke mimic prediction scales that help with the differential diagnosis have been developed and validated.[3] These scales are based on clinical history and the presence or absence of signs and symptoms that are found with different probabilities either in AIS or in SMs. These procedures are considered helpful to identify SMs thus avoiding unnecessary fibrinolytic treatment.

The aim of our study was to identify variables that can predict SMs in a center with a high rate of fibrinolysis; moreover, we tested a new stroke mimic prediction scale in order to improve the differential diagnosis between AIS and SMs.

Materials and Methods

We conducted a retrospective study on patients admitted to our stroke unit with a diagnosis of suspected AIS. Inclusion criteria were age ≥18 years and a diagnosis of suspected ischemic stroke made in the ED. We excluded patients with findings in the head CT scan that could account for the clinical presentation: tumors, hemorrhagic strokes, and abscesses. Patients with a previous diagnosis of a severe neurologic disorder such as multiple sclerosis or amyotrophic lateral sclerosis were also excluded.

AIS was defined as evidence of brain infarction with CT or magnetic resonance imaging (MRI) during the hospitalization.

Diagnosis of SMs was made in absence of ischemic lesion at MRI or CT scan (when MRI was contraindicated) and presence of alternative clinical diagnosis. Every patient was reviewed by a senior physician with expertise in AIS management.

The diagnosis was made on clinical presentation, past medical history, resolution of symptoms during hospitalization, and post-thrombolysis MR with diffusion-weighted imaging (MR-DWI).

Datasets were based on age, sex and past medical history such as the presence of diabetes, systolic and diastolic blood pressure at presentation, atrial fibrillation, history of smoking, renal failure, chronic obstructive pulmonary disease, cirrhosis, obesity, history of cancer, heart failure, National Institutes of Health Stroke Scale (NIHSS) value at presentation. Other information such as history of seizures, history of migraine, cognitive impairment, absence of facial paralysis and isolated sensory symptoms that are included in most of the score scale predictions of SMs were registered. We also monitored if patients with suspected stroke had dizziness without neurologic deficits.

For each patient, we calculated four different SMs prediction scales: FAB (5), simplified FAB (6), Telestroke Mimic Score (7) and Khan score scale (8). We then elaborated a new simple stroke mimic prediction scale, named Santa Maria Nuova Stroke Mimic score (SMN-SM) and we compared its properties with the above-mentioned existing models. The study was conducted on the patients admitted to Santa Maria Nuova-Hospital in Florence, a center that achieved Diamond status in 2020 European Stroke Organization Angels Award Level, indicating that more than 75% of patients had a door-to-needle time <60 minutes and a door-to-groin <120 minutes.[4]

Statistical analysis

Descriptive statistics were recorded at admission at baseline with continuous data expressed as mean ± standard deviation and categorical data were expressed as count and percentage. Quantitative continuous variables were compared using the t-test. Categorical variables were compared using the $\chi^{2\ test}$. The quantitative logistic regression model was built considering as a candidate for inclusion in the SMs prediction scale all the factors associated with SMs at a 5% level. The shape of the effect of the continuous variable systolic blood pressure was linear and it was included in the final model as categorical for simplicity and for comparability with existing literature. The points in the score were assigned by reproducing the regression coefficients (rounded). We evaluated the performance of the score in terms of area under the curve (AUC) of the receiver operating characteristic curve (ROC). We also computed sensitivity and specificity as well as predicted values (using the observed prior probabilities for our scores at all cut points. The analysis was carried out using the statistical software programs SPSS25, Rstudio v. 1.4.1717, and Package pROC version 1.18.0.

Results

A total of 340 patients were admitted to the stroke area in the period between January 1st, 2019, and December 31st, 2020. They were retrospectively evaluated and assigned to either "True stroke" 267 (78,5%) or to "Stroke mimics" group 73 (21,5%). The final diagnosis of the last group of patients was: seizures (31%), dizziness (23%), migraine (10%), functional (conversion) disturbances (10%), peripheral neuropathy (7%), syncope (4%), other (15%). We underscore the high rate of thrombolysis in both groups (40.1% in AIS, 39.7% in SMs).

Table 1 shows the main demographics and clinical characteristics of the studied population. We found that the percentage of females in the SMs group was higher than that of males. We also found that patients in the AIS group were slightly older and had a mean systolic blood pressure higher than that of the SMs group. NIHSS was higher in the AIS than SMs group. A statistically significant association with SMs was also present in patients with: i) cognitive impairment; ii) presence of seizures; iii) migraine in the anamnesis; iv) presence of an isolated sensory deficit; v) lack of facial nervous paresis. Finally, we noted that vi) the presence of dizziness (a situation not previously considered) was significantly associated with SMs.

At the multivariate logistic regression analysis, the absence of facial nerve paralysis (OR 44; 95% CI 6-333), history of vertigo/dizziness (OR 12.5; 95% CI 4-37), migraine (OR 9.1; 95% CI 1.1-72), seizures (OR 6.3; 95% CI 2-22); low blood pressure (OR 4.9; 95% CI 1.3-19), cognitive impairment (OR 3.5; 95% CI 1.6-7.6) 7) and female sex (OR 2.4; 95% CI 1.1-5.1) were significantly associated with SMs group (Table 2). On the basis of these data, we calculated the SMN-SM by assigning 4 points to each patient of the group without facial paralysis, 3 points to the presence of vertigo/dizziness, 2 points to seizure or migraine history, and to systolic blood pressure <150 mmHg; 1 point to cognitive impairment, female sex, and systolic blood pressure >150 and <180mmHg (Table 2).

Then, using ROC analysis, we noticed that, when the score cut-off was set at 8, our model had a specificity of 94%, and a sensitivity of 56%, with a positive predictive value of 70.7%, a negative predictive value of 88.5% and an AUC of 0,89. Basically, when the scores were above 8 we had a very high probability of being in the presence of SMs (Tables 3-4). By comparing the results of the SMN-SM ROC curve with other predictors present in literature such as FAB,[5] simplified FAB,[6] Telestroke Mimic Score scale,[7] or Khan score scale, our results showed that SMN-SM scale AUC had the highest discrimination power (Figure 1; Tables 3 and 5).

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Discussion

In our study, SMs were 21.5% of the total number of patients admitted to the ED with stroke-like symptoms. Females, with low blood pressure were particularly abundant in the SMs group. Furthermore, patients with the presence of epilepsy, migraine, or psychiatric diseases in their anamnesis were particularly abundant in the SMs group and, in accord with previous reports,[7] the absence of facial nerve palsy was a strong predictor of SMs (OR: 44).

We started from these results to elaborate a new stroke mimic score scale (SMN-SM) which appeared useful for the differential diagnosis of patients with stroke-like symptoms. In this new scale, we included dizziness/vertigo among the parameters to be evaluated and we found that the new scale had a very high discrimination for SMs (Table 3 and Figure 1).

Table 1. Demographics and clinical features of the patients admitted to the stroke area.

	True stroke (267)	Stroke mimic (73)	P
Age (years±SD)	77±14	72±19	0.027
Females n (%)	147 (55)	51 (70)	0.024
SBP mmHg means±SD	150±28	139±22	0.002
DBP mmHg means±SD	80±16	78±11	0.458
Arterial hypertension n (%)	162 (60,7)	34 (46.3)	0.033
Diabetes mellitus	50 (18.7)	11 (15.1	0.606
Previous stroke/TIA	58 (21.8)	21 (29.2)	0.21
Smoking	21 (7.9)	12 (16.4)	0.042
Renal damage (GFR <50 ml/min)	16 (6)	2 (2.7)	0.382
Coronary a. diseases	33 (12.4)	6 (8.2)	0.233
Peripheral vascular diseases	74 (27.7)	22 (30.1)	0.663
COPD	15 (5.6)	3 (4.1)	0.773
HFrEF	10 (3.7)	3 (4.1)	1
Cirrhosis	1 (0.4)	0 (0)	1
PE/DVT	2 (0.7)	1 (1.4)	0.513
Active neoplasms	11 (4.1)	1 (1.4)	0.473
Obesity	13 (4,9)	4 (5.5)	0.344
Seizures in the anamnesis	5 (1.9)	10 (13.7)	<0.001
Migraine in the anamnesis	3 (1.2)	5 (6.8)	0.013
Dyslipidemia	44 (16.5)	15 (20.8)	0.385
Cognitive impairment	41 (16.2)	23 (32.8)	0.003
Ischemic lesions	79 (31.3)	24 (33.3)	0.775
NIHSS (±SD)	5 (±5)	3 (±4)	<0.001
Dizziness/Isolated vertigo	7 (2.7)	21 (28.8)	<0.001
Isolated sensory problems	4 (1.6)	8 (11.1)	< 0.001
Lack of facial nerve paralysis	133 (51)	71 (98.6)	< 0.001
Systemic thrombolysis	107 (40.1)	29 (39.7)	1

SD, standard deviation; TIA, transient ischemic attack; GFR, glomerular filtration rate; COPD, chronic obstructive pulmonary disease; HFrEF, heart failure with reduced ejection fraction; PE, pulmonary embolism; DVT, deep vein thrombosis.

Table 2. Multivariate logistic regression analysis of the clinical features positively associated with stroke mimics. The score assigned for the evaluation of the Santa Maria Nuova-stroke mimic scale is also indicated in the last column.

	Odd ratio	Confidence limits	P-value	Score assigned
Absence of facial nerve paralysis	44.0	5.8-333	<0.001	4
Isolated vertigo/dizziness	12.5	4.2-37	<0.001	3
History of migraine	9.1	1.14-72	0.037	2
History of seizure disorder	6.3	1.8-22	0.004	2
Systolic blood pressure <150 mmHg *vs.* >180 mmHg	4.86	1.3-19	0.02	2
Cognitive impairment	3.46	1.6-7.6	0.002	1
Systolic blood pressure Blood >150<180 mmHg *vs.* >180 mmHg	3.35	0.8-15	0.11	1
Female sex	2.38	1.1-5.1	0.025	1

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Patients with dizziness without neurological deficits are considered particularly challenging for a correct stroke diagnosis in the ED. In our experience, dizziness was present in 23% of all SMs diagnosis and its association with SMs had an OR of 12.5 (Table 2); similar findings were reported in a recent comprehensive review where vertigo/dizziness accounted for 23.2% of SMs,[9] thus resulting the leading symptom in this group. Clinical differentiation between peripheral and central causes of vertigo is frequently difficult. In most previous studies on acute stroke treatment, patients with vertigo/dizziness were not included. However, since it is now well accepted that vertigo without neurological symptoms can be the only clinical symptom of a posterior stroke,[10] it is correct to include vertigo/dizziness patients in the differential diagnosis between AIS and SMs. Head impulse-nystagmus-test-of skew (HINTS) has been proposed as a three-step oculomotor examination with a sensitivity higher than early MR-DWI for the detection of posterior stroke.[11] However, in the above-mentioned study, HINTS was evaluated in a population with relatively high stroke risk (76%) since all the patients with acute positional nystagmus were excluded and the clinical examination was performed by oto-neurologists;[11] in our centre, as in most EDs, oto-neurologist are not available and stroke patients are evaluated by emergency physicians. Despite these clinical tools, it is widely accepted that dizziness is a symptom often linked to a missed diagnosis of stroke.[12]

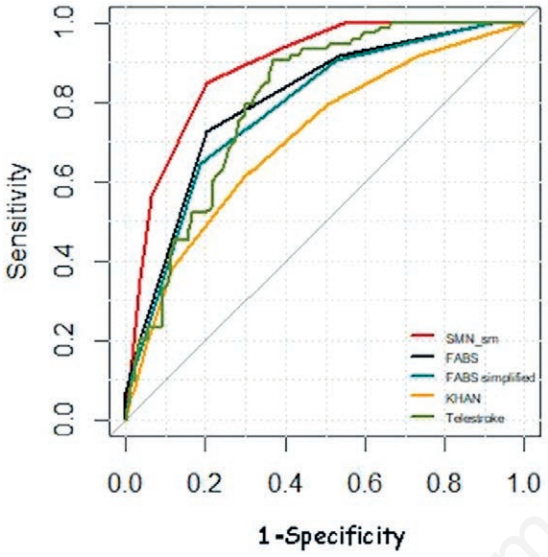

Figure 1. Comparison of different receiver operating curves for strake mimic prediction scale. The graphic shows that the Santa Maria stroke mimic score scale has the maximal area under the curve: the y axis reports the sensitivity and x axis the decremental specificity (1-specificity).

MR-DWI has a better sensitivity than the CT scan in the early ischemic phases of stroke, but it has limited availability, especially in the acute setting, where "time is brain" and MR-DWI can potentially delay reperfusion therapies. For this reason, the most recent American Heart Association guidelines suggest to perform a CT scan and then promptly start intravenous administration of a thrombolytic agent thus avoiding additional time-consuming diagnostic tests when AIS is strongly suspected.[13] Accordingly, the increased awareness of stroke as a medical emergency resulted in a lower threshold worldwide for admission to a stroke area.[14] For these reasons, in our Diamond Angels Center, with a high rate of thrombolysis, the threshold to give thrombolysis in patients with acute vertigo in the absence of obvious evidence of peripheral origin is relatively low; this accounts for a significant proportion of patients with vertigo admitted in our stroke area.

Nevertheless, stroke represents 3-5% of all patients with dizziness presenting to the ED, and our and other results show that vertigo/dizziness should be considered strong predictors of SMs and should be included in the stroke mimic score scales.[9,15]

The strength of our study is to consider brain posterior circulation in our scoring system. In other scales such as FABS, posterior strokes were not included, thus increasing their sensibility and specificity.[5]

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Table 3. Receiver operating characteristic analysis of Santa Maria Nuova stroke mimic score scale. Positive predictive value; negative predictive value.

Scores	Sensitivity	1-Specificity	PPV%	NPV%
0	1.000	1.000	21	N.A.
1	1.000	0.98	21.7	100
2	1.000	0.88	23.5	100
3	1.000	0.68	28	100
4	1.000	0.54	33.3	100
5	0.97	0.48	35.5	98.6
6	0.93	0.38	40.0	97.1
7	0.84	0.20	53.4	95.7
8	0.56	0.06	70.7	88.5
9	0.35	0.03	72.2	84.5
10	0.15	0.01	73.3	80.0
11	0.05	0.04	80.0	79.4
12	0.00	0.00	N.A.	78.5

PPV, positive predictive value; NPV, negative predictive value.

Table 4. Distribution of the 340 patients admitted to the emergency department with suspected acute ischemic stroke on the basis of the score values calculated as indicated in Table 2. The prediction for a true acute ischemic stroke was calculated using the receiver operating characteristic curve of the Santa Maria Nuova stroke mimic and considering a cut point >8 (see Figure 1).

Patient score value	N° of patients (total 340)	% of total	Prediction for a true AIS
0	4	1.2	100.0%
1	26	7.6	98.8%
2	54	15.9	91.2%
3	37	10.9	75.3%
4	19	5.6	64.4%
5	30	8.8	58.8%
6	54	15.9	50.0%
7	58	17.1	34.1%
8	22	6.5	17.1%
9	21	6.2	10.6%
10	10	2.9	4.4%
11	5	1.5	1.5%

AIS, acute ischemic stroke.

Table 5. Area under the curve of the stroke prediction scale we propose and the scales present in literature.

Score scale	AUC	Confidence limits
SMN-MS	0.88	0.85-0.93
FABS	0.80	0.75-0.85
Telestroke mimic score	0.80	0.75-0.85
FABS semplified	0.78	0.72-0.83
Khan score	0.71	0.64-0.77

AUC, area under the curve; SMN-MS, Santa Maria Nuova stroke mimic.

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Limitations

The main limits of our proposal are: i) we performed a retrospective analysis of data; ii) we analyzed data collected in a single center.

Obviously, the stroke mimic score scale we proposed requires to be tested in different centers, in a larger number of patients, and possibly in prospective studies. The percentage of stroke mimic cases in our study was 21,5% (73 out of a total of 340 diagnoses). We consider this percentage rather high. However, recent literature data suggest that the group of stroke mimics may reach values of 1/3 of the total stroke diagnosis.[16,17]

For our SMN-SM score model, we deliberately chose a cut-off at 8 points thus favoring specificity over sensitivity. This could help to accurately select patients with a high probability of being SMs and eventually select them for further investigations (MR-DWI) in order to reduce the frequency of inappropriate thrombolysis.

Conclusions

In conclusion, we propose the use of a simple score scale (SMN-SM) which includes vertigo/dizziness among the SMs predictors. This scale may improve the prompt differentiation of AIS from SMs thus allowing a more accurate selection of the patients requiring further diagnostic tests (MR-DWI).

Our study doesn't want to question the fundamental principle of early thrombolysis in acute ischemic stroke suspicion. However, better knowledge and awareness of conditions associated with SMs may improve patients' safety, decrease the number of inappropriate thrombolysis, and select the best therapeutic approach for these patients.

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