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ORIGINAL RESEARCH

Two-Stage Clinical Model for Screening the Suspected Cases of Acute Ischemic Stroke in Need of Imaging in Emergency Department; a Cross-sectional Study

Somayeh Karimi[1], Lorraine Martins Dutra e Oliva[2], Hosein Rafiemanesh[3,4], Melissa Mendez Capitaine[5], Sarah Jabre[6], Alireza Baratloo[7,8]*

1. Prehospital and Hospital Emergency Research Center, Tehran University of Medical Sciences, Tehran, Iran.
2. School of Medicine, Nove de Julho University (UNINOVE), Sao Paulo, Brazil.
3. Non-communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran.
4. Department of Epidemiology and Biostatistics, School of Public Health, Alborz University of Medical Sciences, Karaj, Iran.
5. Department of Emergency Medicine, La Villa General Hospital, Health Secretary, Mexico City, Mexico.
6. Department of Emergency Medicine, Jackson Memorial Hospital, Miami, Florida, USA.
7. Research Center for Trauma in Police Operations, Directorate of Health, Rescue & Treatment, Police Headquarter, Tehran, Iran.
8. Department of Emergency Medicine, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran.

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Abstract: **Introduction:** Just as failure to diagnose an acute ischemic stroke (AIS) in a timely manner affects the patient's outcome; an inaccurate and misplaced impression of the AIS diagnosis is not without its drawbacks. Here, we introduce a two-stage clinical tool to aid in the screening of AIS cases in need of imaging in the emergency department (ED). **Methods:** This was a multicenter cross-sectional study, in which suspected AIS patients who underwent a brain magnetic resonance imaging (MRI) were included. The 18 variables from nine existing AIS screening tools were extracted and a two-stage screening tool was developed based on expert opinion (stage-one or rule in stage) and multivariate logistic regression analysis (stage-two or rule out stage). Then, the screening performance characteristics of the two-stage mode was evaluated. **Results:** Data from 803 patients with suspected AIS were analyzed. Among them, 57.4% were male, and their overall mean age was 66.9 ± 13.9 years. There were 561 (69.9%) cases with a final confirmed diagnosis of AIS. The total sensitivity and specificity of the two-stage screening model were 99.11% (95% CI: 98.33 to 99.89) and 35.95% (95% CI: 29.90 to 42.0), respectively. Also, the positive and negative predictive values of two-stage screening model were 78.20% (95% CI: 75.17 to 81.24) and 94.57% (95% CI: 89.93 to 81.24), respectively. The area under the receiver operating characteristic (ROC) curve of the two-stage screening model for AIS was 67.53% (95% CI: 64.48 to 70.58). Overall, using the two-stage screening model presented in this study, more than 11% of suspected AIS patients were not referred for MRI, and the error of this model is about 5%. **Conclusion:** Here, we proposed a 2-step model for approaching suspected AIS patients in ED for an attempt to safely exclude patients with the least probability of having an AIS as a diagnosis. However, further surveys are required to assess its accuracy and it may even need some modifications.

Keywords: Decision support techniques; Emergency service, Hospital; Stroke; Diagnosis, Differential

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1. Introduction

Acute ischemic stroke (AIS) is the most common neurological disorder with a disabling element in the world. It is considered a multifactorial disease, with incidence tending to increase with advancing age (1). World Health Organization (WHO) statistics indicate that all types of strokes are ranked

***Corresponding Author:** Alireza Baratloo; Department of Emergency Medicine, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran. Tel: +989122884364, Email: arbaratloo@sina.tums.ac.ir / alirezabaratloo@yahoo.com, ORCID: https://orcid.org/0000-0002-4383-7738.

as the third cause of death (13-15%) and were surpassed only by heart disease and cancer (2).

Since early diagnosis has a special value in terms of treatment efficacy and prognosis in modern emergency practices, several clinical tools are currently in use, which aim to establish AIS diagnosis, mostly in a prehospital setting (3-6). An ideal tool is one that combines the ability to screen positive cases with precise exclusion, in addition to the ease of applicability; while the evaluation of current tools demonstrates high sensitivity and median specificity (7), which implies a considerable amount of flawed diagnoses. It is noteworthy that such inaccurate diagnoses lead to increase in expenses for the patients and health systems with subsidiary tests, and may also delay the correct diagnosis and its required management (8-10).

Another factor that may necessitate designing a new clinical tool with desirable sensitivity and specificity for diagnosis of AIS is the latest pandemic of COVID-19. Among well-established post-COVID comorbidities, the state of hypercoagulability after infection is a consolidated issue. This clinical condition has been reported as an aggravation of COVID-19, which could enhance the pathological mechanism of AIS, and consequently, further increase the incidence of AIS. This emphasizes the importance of accurate care in emergency departments (EDs) to achieve satisfactory outcomes (11-14). Importantly, inaccurate raising of AIS diagnosis leads to unnecessary tests, imaging, and consults that may prolong the ED length of stay, which are recommended to be avoided, especially during the pandemic. This could be considered as an additional reason for need of an accurate clinical tool for ruling out AIS in EDs.

We believe that, just as failure to diagnose an AIS in a timely manner affects the patient's outcome, an inaccurate and misplaced impression of AIS diagnosis is not without drawbacks and may even be associated with significant problems. Therefore, we decided to introduce a novel clinical tool to aid in terms of screening AIS patients, in need of further evaluation in the ED. This tool may help identify the patients who do not need emergency imaging and neurological consultation.

2. Methods

2.1. Study design and setting

This was a diagnostic accuracy study, in which we decided to introduce a new scoring system for screening of AIS patients in need of imaging in the ED. This study was approved by the ethical committee of Tehran University of Medical Sciences (IR.TUMS.CHMC.REC.1401.128). Informed consent was obtained from all the subjects and/or their legal guardian(s) of the patients, and it was explained that all methods were performed in accordance with the relevant guidelines. It should be mentioned that we did not interfere with the patients' management process, and just used the recorded data, so no additional costs were imposed neither on the patients, nor on the system.

2.2. Study population

This study was a multicenter survey in which, all patients who were referred to the ED of four educational hospitals in Tehran, Isfahan, and Ahvaz, in Iran during the year 2020 and for whom a brain magnetic resonance imaging (MRI) was performed with suspicion of AIS, after the evaluation of an in-charge physician, were included. Patients with a history of any known neurological disease, head trauma, previous neurological surgery, and those who had left the ED against medical advice before undergoing brain MRI were excluded.

Assuming a prevalence of at least 50% of AIS in suspected patients referring to the hospitals' ED, as well as examining a maximum of 25 variables for the new stroke screening tool and considering at least 10 patients for each variable, we needed at least 500 patients to design a model. Also, considering two-thirds of the samples for model design and one-third of the samples for testing, we needed another 250 patients. Therefore, to meet the objective of this study, in total, the minimum required sample size was determined to be 750 patients.

2.3. Data collection

All data were gathered by an emergency medicine resident under the supervision of an emergency medicine specialist. Data were collected using a pre-prepared checklist consisting of three sections.

The first section of the checklist included baseline characteristics and demographics of the patients including age, gender, past medical history, drug history, and the time of symptom onset.

The second part included physical examination findings of 18 variables from nine existing AIS screening tools [Cincinnati Pre-hospital Stroke Scale (CPSS), Face-Arm-Speech-Time (FAST), Los Angeles Pre-Hospital Stroke Screening (LAPSS), Medic Prehospital Assessment for Code Stroke (Med PACS), Melbourne Ambulance Stroke Screen (MASS), Ontario Pre-Hospital Stroke Screening (OPSS), Pre-Hospital Ambulance Stroke Test (PreHAST), Rapid Arterial Obstruction Evaluation (RACE), Recognition Of Stroke In The Emergency Room (ROSIER)]. These nine tools are validated stroke scales used to diagnose AIS in pre-hospital and hospital settings.

The third part included the final diagnosis of the patients, all of which were made based on the interpretation of their brain MRI, which was considered the gold standard for the diagnosis of AIS in this study. The brain MRI scans were interpreted by a radiologist and/or a neurologist.

2.4. Modeling and statistical analysis

Modeling for the new criterion was done in two stages. In the first stage, based on the experts' opinion, the clinical criteria that the person should be referred for further investigation of the imaging were determined. At this stage, the best model was selected among the two models obtained based on the percentage of correct classification of patients. The patients who were not positive for these clinical criteria met the criteria for entering the second part of the screening or rule-out model, which is a statistical model. In the statistical model, based on the available variables (except for the variables of the first stage), a multivariable model was designed for the rule-out of patients.

The data were described as frequency and percentage or mean and standard deviation (SD), as appropriate. The frequency distribution of variables in each criterion was compared between patients with and without stroke using a Chi-square test. In addition, an univariable logistic regression analysis was conducted for all variables presented in all nine stroke screening tools and other independent variables. The new screening tool was developed based on multivariable logistic regression analysis. Results were presented as odds ratios (OR) with 95% confidence intervals (CI) and p-values. A p-value <0.05 was considered statistically significant. Also, we calculated sensitivity, specificity, positive (PPV) and negative predictive value (NPV) as well as area under the receiver operating characteristic (ROC) curve with 95%CI for the two-stage screening model. All analyses were performed using STATA software version 14, College Station, TX: StataCorp LLC.

3. Results

3.1. Baseline characteristics of participants

In this study, data from 803 patients with suspected AIS were analyzed (57.4% male). The mean age of the studied participants was 66.9 ± 13.9 years. The diagnosis of AIS was finally confirmed for 561 (69.9%) cases. Table 1 compares the baseline characteristics as well as 18 extracted variables from 9 studied tools between cases with and without confirmed AIS.

3.2. Developing the two-stage clinical screening model

- Stage one (Rule-in stage)

Among the nine tools examined in this study, some variables are examined in most tools, like "Speech or aphasia", which is present in all tools except LAPSS, while some were examined in only one or two tools, such as "Terminally Ill or Palliative Care Patient" only in OPSS or "Commands (one or non-correct)" and "Sensory (pain)" only in pre-HAST tool (table 2).

Based-on expert opinion, among the 18 assessed variables from 9 tools, 5 variables from 4 different tools were selected such that if a patient met any, they would need further evaluation with emergent brain imaging. The criteria "Arm drift or weakness/Hand grip" from CPSS and "Leg weakness/drift" from Med PACS overlapped with "Unilateral arm/leg weakness or drift" from OPSS; thus, two models were conceived for the initial screening (rule-in), one with 3 variables and the other with 4 variables. Combination of 3 variables included "Facial droop or palsy", "Speech disturbance or aphasia", and "Unilateral arm/leg weakness or drift"; Combination of four variables included "Facial droop or palsy", "Speech disturbance or aphasia", "Arm drift or weakness/Hand grip", and "Leg weakness/drift". The percentage of correct classification of AIS (83.06% vs 82.69%) as well as OR (25.30 (95%CI: 15.75 – 40.65) vs 24.71 (95%CI: 15.28 – 39.95)) of the three-variable model were higher than the four-variable model. Therefore, the three-variable model was selected for the first stage of patient screening.

Based on the three-variable model, 647 patients (80.6%) were considered positive for AIS, of which 111 (17.16%) were false positives. Figure 1 shows the Venn diagram of variables for screening positive cases, in need of imaging. Out of 647 patients, 250 (38.64%) cases were positive for all 3 criteria. Also, 46 (41.44%) cases out of the 111 false positive patients, had two or three positive variables.

-Stage two (Rule-out stage)

Based on the remaining variables of the 9 studied tools (14 variables), a model for screening negative patients was designed. Based on the univariate logistic regression analysis, male gender (OR=2.76), history of cerebral vascular accident (CVA) (OR=3.93), and being a smoker (OR=3.30), were the strongest predictors of AIS in negative patients remaining from the first stage of screening. Also, "symptoms of the stroke have resolved" (OR=2.64, p=0.076), and "Visual field defect" (OR=11.30, p=0.052) were marginally significant (Table 1).

A multivariable model was performed to design a screening criterion (table 3). The model obtained in the Backward Wald approach showed the best performance based on 4 variables: "CVA history", "Smoking", "Symptoms of the stroke have resolved" and "Visual field defect". "CVA history", "smoking, "symptoms of the stroke have resolved" were attributed scores of 1 while "Visual field defect" a score of 2. Based on this scale and a cut-off point score less than 1 (Figure 2), 92 patients were diagnosed as negative (11.46% of the total patients), only 5 (0.62% of the total patients) of which had a false negative result. In other words, the probability of AIS among patients who were negative in all four variables in the second stage of screening was equal to 5.43%.

Table 1: Comparing the baseline characteristics as well as extracted variables from 9 studied tools between cases with and without confirmed acute ischemic stroke (AIS)

Variable	Total	Final diagnosis of AIS		OR (95%CI)	P
		Yes (n=562)	No (n=244)		
Baseline characteristics					
Age>45 years 1	143 (91.7)	118 (90.1)	25 (100)	>100 (NA)	0.999
Sex, male	74(47.4)	57(43.5)	17(68.0)	2.76 (1.11-6.84)	0.029
History of CVA	22(14.1)	14(10.7)	8 (32.0)	3.93 (1.44-10.76)	0.008
History of HTN	108 (69.2)	90(68.7)	18(72.0)	1.17 (0.45-3.02)	0.744
History of IHD	46(29.7)	39(30.0)	7 (28.0)	0.91 (0.35-2.35)	0.841
Smoker	32(20.5)	22(16.8)	10(40.0)	3.30 (1.31-8.31)	0.011
Stage one variables					
Facial droop or palsy	342 (42.5)	311 (55.3)	31 (12.8)	8.43 (5.58-12.73)	<0.001
Speech disturbance or aphasia	512 (63.6)	440 (78.3)	72 (29.6)	8.57 (6.09-12.04)	<0.001
Unilateral arm/leg weakness or drift	537 (66.8)	469 (83.6)	68 (28.0)	13.12 (9.17-18.77)	<0.001
Arm drift or weakness/ Hand grip	511 (63.5)	449 (79.9)	62 (25.5)	11.60 (8.14-16.54)	<0.001
Leg weakness/drift	501 (62.2)	441 (78.5)	60 (24.7)	11.11 (7.80-15.84)	<0.001
Stage two variables					
Seizure or epilepsy absent	147 (94.2)	123 (93.9)	24(96.0)	1.56 (0.19-13.06)	0.681
Symptoms of the stroke have resolved	20(12.8)	14(10.7)	6 (24.0)	2.64 (0.90-7.71)	0.076
Blood glucose between 50 and 400 mg/dl	131 (94.2)	109 (94.0)	22(95.7)	1.41 (0.17-12.07)	0.752
Blood sugar < 4mmol/l	1(0.7)	1(0.9)	0(0.0)	0.0 (NA)	1.0
Loss of consciousness or syncope	11 (7.1)	8(6.1)	3 (12.0)	2.01 (0.52-8.52)	0.301
Glasgow Coma Scale <10	0(0.0)	0(0.0)	0(0.0)	NA	-
Patient is not wheelchair bound or bedridden	151 (96.8)	127 (96.9)	24(96.0)	0.76 (0.08-7.06)	0.806
Head and Gaze Deviation	1(0.6)	1(0.8)	0(0.0)	0.0 (NA)	1.0
Symptom duration less than 24-25 hours	107 (69.0)	88(67.7)	19(76.0)	1.51 (0.56-4.06)	0.413
Terminally ill or palliative care patient	1(0.6)	1(0.8)	0(0.0)	NA	1.0
Visual field defect	3(1.9)	1(0.8)	2(8.0)	11.30 (0.98-129.83)	0.052
Commands (none or non-correct)	1(0.6)	1(0.8)	0(0.0)	0.0 (NA)	1.0
Sensory (pain)					
0: Normal	137 (87.8)	117 (89.3)	20 (80.0)	1.0	0.161
1: Apprehends less or different on one side	18(11.5)	13 (9.9)	5 (20.0)	2.25 (0.72-7.0)	0.306
2: Apprehends only on one side	1(0.6)	1(0.8)	0(0.0)	0.0 (NA)	1.0

CI: confidence interval. CVA: Cerebral vascular accident, HTN: Hypertension, IHD: Ischemic heart disease, OR: Odds ratio;
CI: confidence interval.

3.3. Screening performance characteristics of the two-stage model

The sensitivity and specificity of stage-one were 95.54% (95% CI: 93.84 to 97.25) and 54.13% (95% CI: 47.85 to 60.41), and for stage-two they were 80.0% (95% CI: 64.32 to 95.68) and 66.41% (95% CI: 58.32 to 74.50), respectively. The total sensitivity and specificity of two-stage screening model were 99.11% (95% CI: 98.33 to 99.89) and 35.95% (95% CI: 29.90 to 42.0), respectively. Also, the positive and negative predictive values of the two-stage screening model were 78.20% (95% CI: 75.17 to 81.24) and 94.57% (95% CI: 89.93 to 81.24), respectively. The area under the ROC curve of the two-stage screening model for AIS was 67.53% (95% CI: 64.48 to 70.58). Overall, using the two-stage screening model presented in this study, more than 11% of suspected AIS patients were not referred for MRI, and the error of this model is about 5%.

4. Discussion

In light of the importance of clinical applicability and cost efficiency for the worldwide healthcare systems, this study was conducted to create a helpful AIS screening tool for the ED physicians. The objective of our study was not to help achieve a final diagnosis as we already have the tools to diagnose an AIS; as there are multiple stroke scales that are validated, and further guidance is needed in terms of which items to look for when deciding which patients need to undergo immediate imaging and neurological consult (15, 16). In this study, we suggested a two-stage model for approaching suspected AIS patients in ED to attempt to safely exclude patients with the least probability of having an AIS as a diagnosis. First, patients who satisfy none of the criteria including “Facial droop or palsy”, “Speech disturbance or aphasia” or “Unilateral arm/leg weakness or drift criteria” were selected for the second stage of the study, while those who

Table 2: The variables of nine studied tools

Variable	LAPSS	CPSS	FAST	OPSS	Med PACS	MASS	RACE	Pre-HAST	ROSIER
Facial droop or palsy	X[a]		X	X	X	X	X		X
Arm drift or weakness/Hand grip		X	X[b]		X	X[c]	X		X
Speech or aphasia		X	X	X	X	X	X	X	X
Seizure	X			X	X	X			X
Symptoms of the stroke have resolved				X[d]					
Blood glucose between 50 (or 60) and 400 mg/dl	X				X	X			
Leg weakness/drift					X		X		X
Blood Sugar < 4mmol/l				X[d]					
Consciousness or syncope				X					X
Patient is not wheelchair bound or bedridden	X					X			
Head & Gaze Deviation					X		X	X	
Age>45 years	X					X			
Symptom duration less than 24-25 hours	X				X				
Unilateral arm/leg weakness or drift	X[e]			X				X	
Terminally Ill or Palliative Care Patient				X					
Visual field defect								X	X
Commands (one or non-correct)								X	
Sensory (pain)								X	

Cincinnati Pre-Hospital Stroke Scale (CPSS), Face-Arm-Speech-Time (FAST), Los Angeles Pre-Hospital Stroke Screening (LAPSS), Medic Prehospital Assessment for Code Stroke (Med PACS), Melbourne Ambulance Stroke Screen (MASS), Ontario Pre-Hospital Stroke Screening (OPSS), Pre-Hospital Ambulance Stroke Test (Pre-HAST), Rapid Arterial Obstruction Evaluation (RACE), Recognition of Stroke in The Emergency Room (ROSIER).

a. Facial paralysis or arm strength weakness;
b. Arm weakness (Left/ Right);
c. Have two items, arm drift and hand grip;
d. Exclusion criterion;
e. Facial paralysis or arm strength weakness.

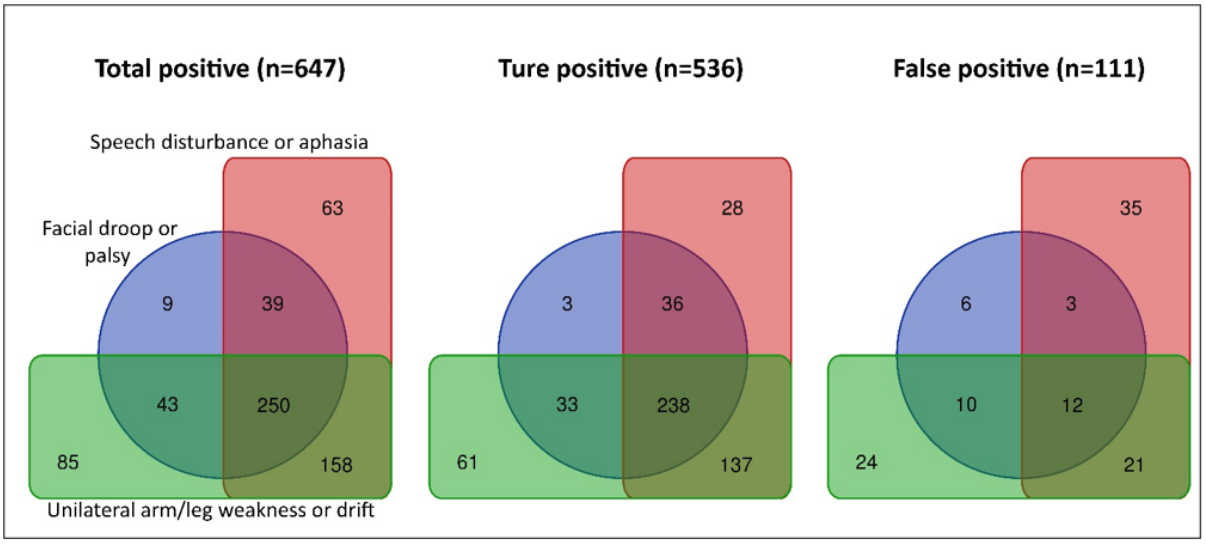

Figure 1: The Venn diagram of the three-variable model (stage one of the two-stage screening model) for screening of suspicious acute ischemic stroke cases in need of imaging in emergency department.

met any of these three criteria required emergent brain imaging. The second stage of the study consisted of using a scoring system based on 4 criteria: "history of CVA" (score=1), "smoking" (score=1), "symptoms of the stroke have resolved" (score=1), and "visual field defect" (score=2). Using this scale and considering a cut-off point score of less than 1, the diagnosis of AIS would be very unlikely based on the results of our study.

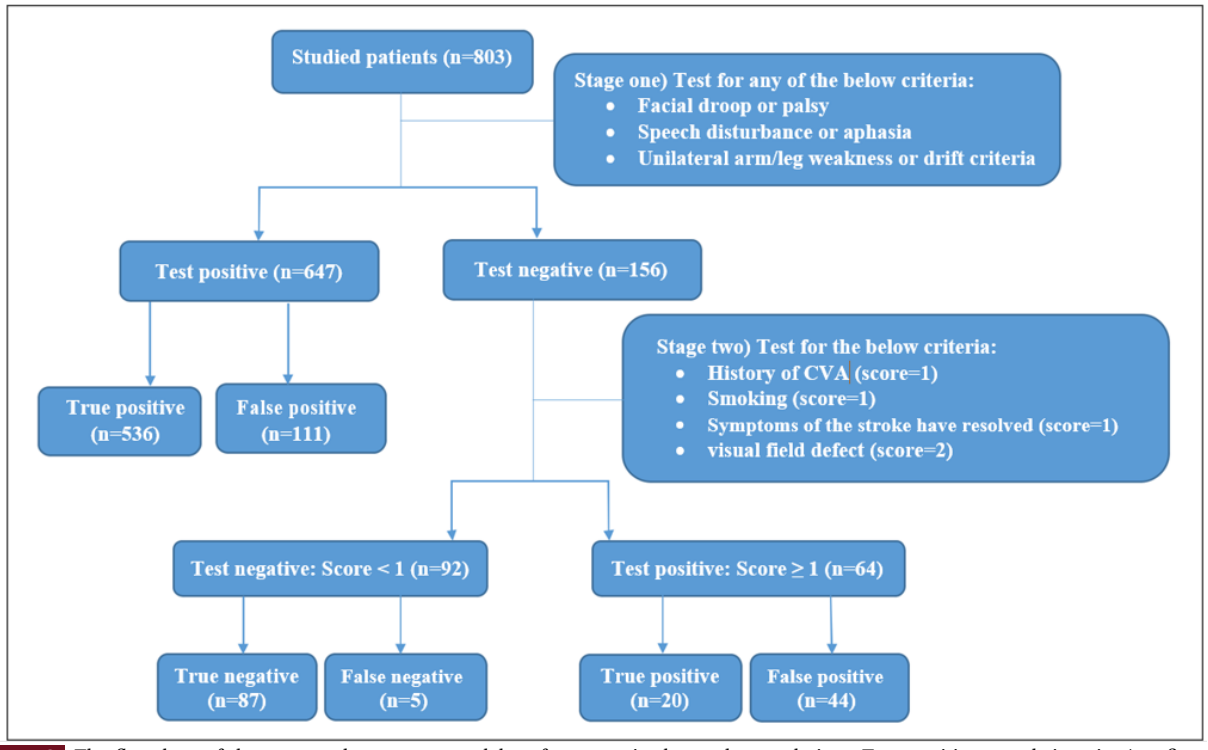

Figure 2: The flowchart of the proposed two-stage model performance in the study population. True positive: needs imaging/confirmed acute ischemic stroke (AIS); False positive: needs imaging/not AIS (waste imaging); True negative: does not need imaging/not AIS (AIS ruled out correctly); False positive: does not need imaging/confirmed AIS (missed cases). CVA: Cerebral vascular accident.

Table 3: The multivariate logistic regression analysis of independent predictors of acute ischemic stroke in patients without symptoms of stage one variables

Variable	Model 1		Model 2		Model 3	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Male gender	2.49 (0.83-7.48)	0.105	3.14 (1.14-8.66)	0.027	-	-
CVA history	3.08 (1.02-9.25)	0.045	3.67 (1.28-10.51)	0.015	3.43 (1.16-10.11)	0.025
Smoker	3.04 (0.98-9.39)	0.053	-	-	4.20 (1.43-12.32)	0.009
Symptoms resolved	4.62 (1.32-16.22)	0.017	-	-	4.67 (1.37-15.95)	0.014
Visual field defect	32.25 (2.30-452.65)	0.010	29.32 (2.28-376.54)	0.010	19.61 (1.48-259.37)	0.024
Possible score	0 to 4		0 to 4		0 to 5	

Model 1: Enter, Model 2: Forward Wald, Model 3: Backward Wald.
CVA: Cerebral vascular accident, OR: Odds ratio, CI: Confidence interval.

It is well known that, in dealing with an AIS patient, "time is brain" (2, 17). Indeed, any patient suspected of having AIS should be transported to the nearest hospital with staff experienced in AIS management and emergency brain imaging as quickly and safely as possible (17-19). But before that, how do we quickly rule out AIS? This is where the importance of exclusion criteria and this new tool described is reflected. We intended to eliminate unnecessary imaging, tests, and consults, which lead to high expenses and increase ED length of stay in those for whom AIS can be easily and safely eliminated from the list of differential diagnoses (20-22). However, it is always mandatory to perform a complete neurological examination, once the patient presents with symptoms such as dizziness, paresthesia, deviation of the labial commissure, dysphagia, weakness of any limb, difficulty in or loss of vision; among many others, to alert the clinician to look for various neurological causes (2, 19, 23).

Some patients with stroke who receive tPA may re-canalize and have a negative MRI. This may happen spontaneously as well. These patients would be predicted to have a stroke using the derived model on the basis of "symptoms of stroke have resolved" (e.g. score > 1 on step 2) but would be considered as stroke "negative" using the criteria for presence or absence of stroke used in this study (positive MRI). Thus, they

would show up as false positives. It is just as important to accurately identify these patients as for complete strokes since they need the same evaluation and institution of appropriate secondary prevention strategies.
The use of MRI as the sole criterion of diagnostic accuracy, ignores the reality of false negative MRI for acute stroke, which may particularly occur with small, early, brainstem lesions, especially if there is artifact or the DWI sequence is not optimized for contrast-to-noise. Again, biasing the model against small or brainstem strokes.

5. Limitations

This work is not the end, but the beginning and the gateway for future analysis, patients from other continents can be integrated, and the classification and clinical criteria can be adjusted according to the population studied. Since each stroke scale used in this study has been elaborated by a different country or city, the risk factors may thus vary epidemiologically. Another limitation is the consensus made to identify a clinical tool, without modifying the absolute reliability of the new scale and therefore, improving its specificity.

6. Conclusions

In this study, we suggested a two-stage model for approaching suspected AIS patients in ED to attempt to safely exclude patients with the least probability of having AIS as the diagnosis. First, patients who satisfy none of the criteria including "Facial droop or palsy", "Speech disturbance or aphasia" or "Unilateral arm/leg weakness or drift criteria" were selected for the second step of the study, while those who met any of these three criteria required emergent brain imaging. The second stage of the study consisted of using a scoring system based on 4 criteria: "history of CVA" (score=1), "smoking" (score=1), "symptoms of the stroke have resolved" (score=1), and "visual field defect" (score=2). A patient with a true stroke would be missed in only 0.6% (5/803) of cases if applying the two-stage screening tool on a suspected AIS patients presenting to the ED, at the expense of 19.3% (155/803) false positive stroke identifications. However, further surveys are required to assess its accuracy and it may even need some modifications.

7. Declarations

7.1. Acknowledgments

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7.2. Conflict of interest

The authors declare that there is no conflict of interest.

7.3. Fundings and supports

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7.4. Authors' contribution

The conception and design of the work by All the authors; Data acquisition by SK and AB; Analysis and interpretation of data by HR and AB; Drafting the work by SK, LMDO and MMC; Revising it critically for important intellectual content by HR, SJ and AB; All the authors approved the final version to be published; AND agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work.

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