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Development of a risk of stroke score in the Lebanese population

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ABSTRACT

Background/Aims: As in all developing countries, there could be a large number of stroke cases that can be prevented provided that individuals at risk are recognized. We aim to develop a score for screening individuals at risk of stroke in the Lebanese population.

Methods: A hospital-based case-control study was conducted for the score generation. Data were collected through a designed data collection sheet at two Lebanese tertiary hospitals between January 1st, 2012 and December 31st, 2014. A logistic regression determined the association of stroke risk factors with stroke, and the rounded coefficients generated the Risk of Stroke Score (ROSS). Another case-control study was conducted for the score validation. Data were collected through a standardized questionnaire at five different Lebanese tertiary hospitals between January 1st, 2015 and December 31st, 2016. ROSS was validated by comparing it to hospitals final diagnosis.

Results: ROSS was constructed with good properties, comprising 10 items. The area under the curve was high at 0.869 (0.838–0.899; $p < 0.001$). A score < 2 points indicated a 94.4% high negative predictive value of stroke. A score > 10 points had more than 85.4% positive predictive value of stroke. In the validation study, ROSS had an area under the curve of 0.826 (0.790–0.863; $p < 0.05$), 88.7% negative prediction value and 96.2% positive prediction value.

Conclusion: It is highly recommended to use the ROSS, particularly in the primary care setting, as a good assessment tool to predict stroke among high-risk people and encourage them to get involved in intervention programs to prevent this disease.

1. Introduction

Stroke, or cerebrovascular accident (CVA), is a common cause of morbidity and mortality worldwide. Over the 1990–2013 period, there was a significant increase in stroke incident events, survivors, and deaths for both ischemic and hemorrhagic stroke and a substantial increase in the absolute number of DALYs (disability-adjusted life years) due to ischemic stroke.[1] Developing countries had the greatest share of global stroke burden and death compared to developed countries, comprising 75.2% of stroke mortality and 81.0% of stroke-related DALYs.[1]

Lebanon is a developing upper-middle-income country located in the Middle East. Although stroke is the second leading cause of death in Lebanon after cardiac diseases, there is still a scarcity of reliable information about stroke in this country. In general, the adjusted stroke prevalence in Lebanon was 0.50% (95% CI, 0.33–0.66) in 2012, and the rate of stroke mortality has reached 62.7/100,000 population in 2011, indicating that around 8 Lebanese people die every day because of stroke.[2,3] According to the Global Burden of Disease Study 2016 (GBD 2016) causes of premature death in Lebanon, stroke is striking at a younger age in this country. It took the fourth place in the top 10 causes of death in 2016.[4] The GBD 2016 assessed the years of life lost (YLLs) as well which quantifies premature mortality by weighing younger deaths more than older deaths. In 2016, stroke ranked 6th among the top 11 causes of YLLs in Lebanon.[4] Despite having stroke intervention rate in Lebanon higher than other reported rates in developing countries, Lebanon still struggles with limited intervention (administration rate of rt-PA is 10.3% for stroke cases at the largest tertiary care center in Lebanon) due to large time interval between arrival at the hospital and computerized tomography (CT) completion.[5]

Major stroke risk factors are common among populations and modifiable with effective interventions. It is well known that many unchangeable and treatable risk factors may increase the risk of having a stroke and speed up the process. In Lebanon, the prevalence of many stroke risk factors has reached high measures to a point where it is threatening the life of its population.[6] Modifying, treating and

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controlling major stroke risk factors through medications or lifestyle change in Lebanon is expected to result in reducing the risk of stroke in the Lebanese population. Many risk assessment tools have been developed to predict the risk of stroke (ie. Framingham Stroke Profile, California Score, ABCD [Age, BP (Blood pressure), Clinical features of the TIA, and Duration of symptoms], ABCD2 [Age, BP (Blood pressure), Clinical features of the TIA, Duration of symptoms, and History of Diabetes], ABCD3 [ABCD2 with dual TIA symptoms within 7 days], and ABCD3-I [ABCD3 with the presence of abnormal findings on neuroimaging], as well as $CHADS_2$ [Congestive heart failure, Hypertension, Age, Diabetes mellitus, and Stroke or TIA] and CHA2DS2-VASc among patients with atrial fibrillation [Age, Sex, Hypertension, Congestive heart failure, Stroke/TIA/Thromboembolism, Vascular disease, and Diabetes mellitus]) and numerous studies have been conducted to validate the use of these scores with great variation in accuracy concerning prediction for future stroke. [7–13] Although stroke risk-assessment are available, the complexity of the interactions existing between its different risk factors components and the effects of certain risk factors stratified by age, sex, race/ethnicity and geographic location is still incomplete and not entirely captured by existing risk-assessment tools. In any case, none of the existing prediction scales has ever been validated in the Lebanese population. Therefore, it is essential to determine a score for stroke risk in Lebanon to identify high risk people and encourage them to manage their controllable risk factors by appropriate interventions before developing a stroke. We aim to developing a tool for screening individuals at risk of having stroke in the Lebanese population.

2. Methods

2.1. Study design

This is a two steps study:

Score Generation Study: A retrospective hospital-based case-control study was conducted at two Lebanese tertiary hospitals located in the capital Beirut (one private and another governmental) between January 1st, 2012 and December 31st, 2014 to generate the score for stroke prediction. This study design has been explained in another article "Stroke Risk Factors: A Hospital-Based Case-Control Study in Lebanon" published at the Journal of Royal Society of Medicine (open).[6]

Score Validation Study: Another hospital-based case-control study with prospective data collection was conducted at five different tertiary hospitals in Lebanon (private and governmental) between January 1st, 2015 and December 31st, 2016 for the score validation. The Faculty of Pharmacy at the Lebanese University waived the approval of this study since it was observational with no traceability of patients. An oral consent was obtained from all included subjects before inclusion in the study.

2.2. Inclusion and exclusion criteria

Hospitalized stroke patients were included if they were Lebanese, 18 years or older, and diagnosed with stroke by CT scan, MRI, or both. Stroke patients were excluded if clinical information was unavailable or CT scan or MRI were not performed.

Control patients were included if they were Lebanese, 18 years or older, and admitted to the same hospitals of stroke patients but with disorders or procedures unrelated to stroke or TIA. Controls were chosen from the departments related to infectious diseases, cancer, endocrinology diseases, respiratory diseases, kidney diseases, and digestive diseases as well as injuries and orthopaedic surgeries.

For the score validation study, giving an oral consent was also a criterion for inclusion for both cases and controls.

2.3. Development of data collection sheet and questionnaire

The data collection sheet and questionnaire were based on different publications' findings, and included four parts. The first part included the socio-demographic characteristics of patients as well as questions about patients' body mass index, the reason of being admitted to the hospital and time of admission, imaging techniques and time, and drug exposure at home. The second part included patients' symptoms on admission and time of symptoms. The third part addressed all potential risk factors of stroke. The last part was related to patients' laboratory data upon admission to the hospital. The data collection sheet was written in English language and information collected were based on patients' medical records at the hospitals.[6] The questionnaire was written in English and translated into Arabic and was based on patients' answers and medical records at the hospitals.

2.4. Data collection and definition of stroke and certain diagnosis

All variables were collected based on information present in patients' files/physician's diagnosis/patient's answers.

In the score generation study, all data elements of the data collection sheet were collected retrospectively from patients' files at the hospitals.[6]

In the score validation study, all data elements of the questionnaire were collected concurrently after patients' diagnosis at the hospitals. The socioeconomic and demographic factors and stroke symptoms and risk factors were collected from patients' files at the hospitals and confirmed by patients' responses. Patients' diagnosis, laboratory tests, and time of arrival at the hospital and imaging were collected from patients' files at the hospitals.

Evidence of medical history was based on the definition of certain diagnostic categories including stroke, hypertension, diabetes, dyslipidemia, and obesity, the laboratory tests results stated, and the presence of a reported disease history or treatment history.

2.4.1. Stroke

Stroke is defined by the World Health Organization as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than vascular origin".[14]

Evidence of stroke and stroke types were collected from the final diagnosis stated in patient's file and from the brain Computed Tomography (CT), Magnetic Resonance Imaging (MRI) results or both.

2.4.2. Hypertension

The definition of hypertension and the classification of the three grades of blood pressure (BP) were adopted from the World Health Organization – International Society of Hypertension (WHO-ISH). [15]

In this study, a history of hypertension is defined based on different approaches, including: reported history of hypertension by the physician, reported antihypertensive treatment, or recorded blood pressure measurements at different time points (admission and mornings for every day after admission) where the mean of blood pressure for three consecutive days' measurements is considered.

2.4.3. Diabetes, dyslipidemia, overweight, and obesity

The definition of diabetes, dyslipidemia, overweight and obesity was based on the 2006 WHO – International Diabetes Federation (WHO-IDF), the National Cholesterol Education Program, and the World Health Organization, respectively.[16–18]

2.5. Statistical methods

Data were analyzed using SPSS version 24. P-value < 0.05 determined statistical significance. Continuous variables were presented as means with standard deviation and categorical variables as

percentages. The differences in baseline characteristics between stroke patients and stroke-free patients were analyzed using chi-square test for qualitative variables and sample t test for quantitative variables. Fisher's Exact test was used when the expected cell size was less than 5.

In order to develop the score from the score generation study, a stepwise ascending logistic regression was conducted by considering the potential of confounding. The details of this analysis has been explained in in another article "Stroke Risk Factors: A Hospital-Based Case-Control Study in Lebanon" published at the Journal of Royal Society of Medicine (open).[6]

The adjusted ORs obtained in the logistic regression conducted in the score generation study were rounded to the nearest units and used as coefficients to determine the score for stroke prediction. An index was constructed using the potential variables found to be associated with stroke in the logistic regression. Those that significantly predict the risk of stroke were selected and the index for stroke prediction was generated. Factor analysis evaluated the construct validity of this index and was conducted with a varimax rotation to determine the different dimensions of the distribution of the stroke risk factors with the different factors loading after ensuring adequate Kaiser-Meyer-Olkin (KMO) and sample adequacy by Bartlett Test. The reliability of the construct was assessed and Cronbach's alpha was calculated.

The score was calculated for each patient, case and control. The Receiver-Operating Characteristics (ROC) curve was sketched in order to determine the cut point of whether a stroke would be predicted or not with a great percentage. The sensitivity and specificity as well as the negative and positive predictive values for the new developed score were calculated to assess criterion validity.

For the validation of the generated score, the score was calculated for all patients included in the score validation study and results were compared with the hospital accurate diagnosis of stroke by CT scan, MRI, or both imaging techniques. Negative and positive predictive values were also calculated.

Moreover, the developed score was compared to the $CHADS_2$ and CHA2DS2-VASc scores to predict stroke among patients with a history of atrial fibrillation and who were not prescribed any anticoagulant medicament, clopidogrel, or aspirin.

3. Results

3.1. Summary of primary results

In the score generation study, two hundred and fifty stroke cases were admitted to the interesting hospitals between January 1st, 2012 and December 31st, 2014. Among those, 48 stroke cases were not diagnosed with stroke by CT scan or MRI and therefore were excluded. Overall, 732 patients were included in the score generation study with 202 cases diagnosed with stroke and 530 stroke-free controls. The mean age of stroke was 68 ± 13 years. Males constituted 53.5% of stroke patients. Among stroke patients, 25.7% had TIA, 59.4% had ischemic stroke, and 14.9% had hemorrhagic stroke. The in-hospital stroke mortality rate was 7.4%, with hemorrhagic rate higher than ischemic rate, 20% vs 7.5% respectively.

Due to missing data in regards to patients' address (43.7% of the sample), this sample mainly represented Lebanese patients living in Beirut (46.6% of patients with available address in their hospital file) and Mount Lebanon (44.2%). Only 4.6% of patients with available address lived in Beqaa, 3.6% live in North Lebanon, and 1% live in South Lebanon.

Please refer to "Stroke Risk Factors: A Hospital-Based Case-Control Study in Lebanon" for additional results about this study.[6]

3.2. Construction of the Risk of stroke score (ROSS)

Based on the stepwise ascending logistic regression conducted in the score generation study, the adjusted odds ratio showed that age (≥65 years old) is a major risk factor for total stroke as well as a history of hypertension, cardiac arrhythmia, coronary heart disease/myocardial infarction, deep venous thrombosis/pulmonary embolism, migraine, and cigarette smoking. Having a grade 3 BP had the highest OR (44.11; 95% CI, 16.14–120.53). Antihypertensive and anticoagulant treatments were significantly associated with reduced risk of total stroke (Table 1).

Table 1
Factors predicting stroke risk in the Lebanese population.

Variable	OR adjusted	95% CI	P value
Age ≥ 65 years	1.81	1.07–3.08	0.028*
History of Cardiac Arrhythmia/Atrial Fibrillation	2.67	1.16–6.11	0.020*
History of Coronary Heart Disease/ Myocardial Infarction	6.50	2.69–15.72	< 0.001*
History of Deep Venous Thrombosis/ Pulmonary Embolism	5.62	1.97–16.01	0.001*
History of Migraine	6.26	2.34–16.74	< 0.001*
History of Hypertension	7.09	2.78–18.14	< 0.001*
Current Grade 1 BP	4.31	2.35–7.89	< 0.001*
Current Grade 2 BP	9.04	4.30–18.99	< 0.001*
Current Grade 3 BP	44.11	16.14–120.53	< 0.001*
Taking Antihypertensive Treatment	0.15	0.06–0.41	< 0.001*
Taking Anticoagulant Medication	0.17	0.05–0.60	0.006*
Current Cigarette Smoking	2.02	1.19–3.44	0.009*

OR, odds ratio; CI, confidence interval; BP, blood pressure; *, statistically significant ($p < 0.05$).
Note: Table 1 is taken from "Stroke Risk Factors: A Hospital-Based Case-Control Study in Lebanon" published in the Journal of Royal Society of Medicine (open).[6].

The Risk of Stroke Score (ROSS) was computed by taking into account the adjusted ORs from Table 1 and rounding to the nearest unit. A simplified version of the ROSS is presented in Table 2.

The ROSS could have a minimum of −7 and a maximum of 39. In the sample, the ROSS minimum was −7 and maximum 38. In individuals with stroke, the mean of ROSS was 10.31 and the standard deviation 9.274, while in stroke-free patients, the mean was 1.79 and the standard deviation 3.448.

Table 2
Risk of Stroke Score (ROSS).

Variables	Clinical features	Risk of Stroke Score
Age ≥ 65 years	No	+ 0 × 1
	Yes	+ 1 × 1
History of cardiac arrhythmia/atrial fibrillation	No	+ 0 × 2
	Yes	+ 1 × 2
History of coronary heart disease/ myocardial infarction	No	+ 0 × 3
	Yes	+ 1 × 3
History of deep venous thrombosis/ pulmonary embolism	No	+ 0 × 3
	Yes	+ 1 × 3
History of migraine	No	+ 0 × 3
	Yes	+ 1 × 3
History of hypertension	No	+ 0 × 4
	Yes	+ 1 × 4
Current blood pressure	Grade 0	+ 0
	Grade 1	+ 1 × 2
	Grade 2	+ 1 × 5
	Grade 3	+ 1 × 22
Taking antihypertensive treatment	No	- 0 × 4
	Yes	- 1 × 4
Taking anticoagulant treatment	No	- 0 × 3
	Yes	- 1 × 3
Current cigarette smoker	No	+ 0 × 1
	Yes	+ 1 × 1

Table 3
Construct validity and reliability of stroke risk factors index.

Items	Loading on factor 1	Loading on factor 2	Loading on factor 3
Age (≥65 years)	0.497		
Antihypertensive	0.849		
Hypertension history	0.872		
Coronary heart disease/ myocardial infarction history	0.560		
Anticoagulant		0.868	
Cardiac arrhythmia/atrial fibrillation history		0.755	
Migraine history			0.965

KMO = 0.678; Bartlett's test of sphericity $p < 0.001$; $\alpha = 0{\cdot}657$.

3.3. Construct validity and reliability of stroke risk index

A factorial analysis was conducted and the ten variables identified from the multivariate analysis were entered. Seven items were retained and found to be distributed on three factors, explaining 65% of the total variance: four items loaded on one factor, two items loaded on a second factor and one last item loaded on a third factor. This index had a good reliability with Cronbach alpha = 0.657 (Table 3).

3.4. ROSS properties and thresholds

The ROC curve for stroke prediction is shown in Fig. 1. The area under the curve was high at 0.869 (0.838–0.899; $p < 0.001$). We could identify two important cutoff values, one at 2.5 with a sensitivity of 0.864 and a specificity of 0.723, and another at 3.5 with a sensitivity of 0.744 and a specificity of 0.822 (Supplementary material Table I).

3.5. ROSS and prediction of stroke

ROSS was recorded into 5-point categories (based on the median of patients scores = 2 and the cut points from the ROC curve) and increased predictive values for stroke were found with increased ROSS (Fig. 2). A score < 2 points indicated a high negative predictive value of stroke of 94.4%. A score > 10 points had a good positive predictive value of stroke of more than 85.4%. A score between 2 and 10 points indicated a grey zone (Fig. 2).

3.6. Validation of ROSS

Around 650 hospitalized patients were included in the score validation study for ROSS validation. Data were collected through a standardized questionnaire for 205 stroke patients and 445 stroke-free patients admitted to five Lebanese tertiary hospitals between January 1st, 2015 and December 31st, 2016. Among included participants, 1.3% of controls had a history of stroke compared to 34.6% of cases. Among stroke cases, ischemic stroke constituted the majority of cases (69.8%) followed by hemorrhagic stroke (15.1%) and transient ischemic attack (15.1%).

Twelve stroke patients were excluded from the study due to lack of imaging or clinical information. Moreover, 75.1% of included stroke cases had a CT scan, 16.1% had an MRI, and 8.8% had both, CI and MRI. None of the controls patients had undergone a CT scan or MRI.

Stroke patients statistically differed from stroke-free patients in respect to antihypertensive medication, lipid-lowering medication, antidiabetes medicine, anticoagulant treatment, aspirin, clopidogrel treatment, and antidepressants. There was also a statistically significant difference concerning patients' body mass index and medical history including hypertension, cardiac arrhythmia, coronary heart disease/ myocardial infarction, peripheral artery disease, heart failure, deep venous thrombosis/pulmonary embolism, diabetes, dyslipidemia, previous TIA/CVA, angina pectoris, and family history of CVA and heart diseases as well as physical activity, cigarette and waterpipe smoking. Those patients also showed significantly higher values of systolic and diastolic blood pressure than stroke-free patients (Table 4).

In the score validation study, ROSS had an area under the curve of 0.826 (95% CI, 0.790–0.863; $p < 0.05$) (Fig. 3). Around 353 (54.3%) patients had a ROSS score < 2; among those patients, 313 patients (88.7%) were stroke-free and 40 (11.3%) were stroke patients. Almost 244 (37.5%) patients had a ROSS score between 2 and 10; among those patients, 130 (53.3%) were stroke-free and 114 (46.7%) were stroke patients. Finally, 53 (8.2%) patients had a score > 10; among those 2 (3.8%) were stroke-free and 51 (96.2%) were stroke patients ($p < 0.001$).

A ROSS score < 2 points indicated a negative prediction value of stroke by 88.7% and a ROSS score > 10 points indicated a positive prediction value of stroke by 96.2%.

3.7. Comparison between ROSS, $CHADS_2$, and CHA_2DS_2-VASc

The CHADS2 score was calculated as follows: 1 point for Congestive heart failure, 1 point for Hypertension, 1 point for Age ≥75 years, 1 point for Diabetes mellitus, and 2 points for a history of Stroke or TIA. The CHA2DS2-VASc was calculated as follows: 1 point for Congestive heart failure, 1 point for Hypertension, Age: 2 points for ≥75 years/1 point for 65-74 years/0 point for < 65 years, 1 point for female sex, 1 point for Diabetes mellitus, 1 point for vascular disease, and 2 points for a history of Stroke/TIA/thromboembolism.

In both studies, the score generation study and the score validation study, 59 patients were found to have a history of atrial fibrillation and without any treatment of anticoagulant medicament, clopidogrel, or aspirin. The 59 patients were included in the comparison between ROSS, $CHADS_2$, and CHA_2DS_2-VASc. The three scores were computed for every patient of these 59 patients and then we sketched the ROC curve. ROSS significantly had the greater AUC 0.854 (95% CI, 0.761–0.948) compared to CHADS2 and CHA_2DS_2-VASc (Fig. 4).

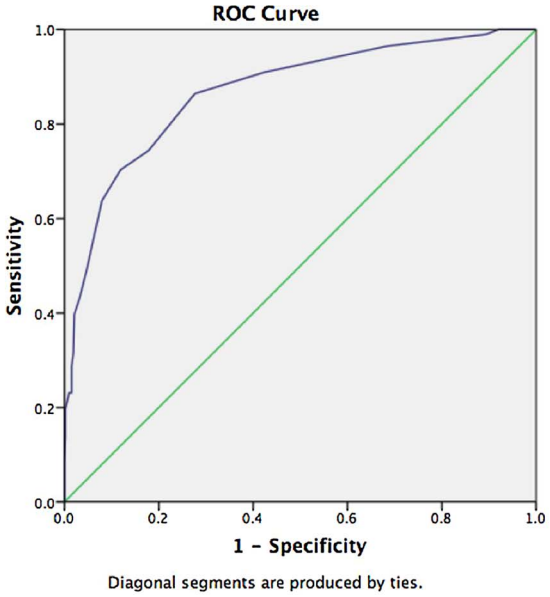
Since ROSS included the 2 factors, cardiac arrhythmia and anticoagulant medication, in the assessment of the risk, with (+2) points given for the presence of cardiac arrhythmia/atrial fibrillation and (−3) points given for the presence of anticoagulant medication and our patients compared for ROSS, $CHADS_2$, and CHA_2DS_2-VASc were already atrial fibrillation patients with no antithrombotic treatment, we tried to repeat this comparison by adding a constant (−2) to the ROSS in order to eliminate the effect of these two factors in our score. However, this gave significantly the same AUC for ROSS in our comparison.

3.8. Inclusion of antihypertensive and anticoagulant medications in the ROSS

ROSS included the two factors, antihypertensive and anticoagulant medications, in the assessment of the risk of stroke. Their presence reduces the ROSS and thereby reduces the risk of stroke. However, during the prospective data collection, we noticed that not all patients prescribed those two treatment were adhering to their medications.

We tried to repeat the ROSS in the score validation study. Patients who were prescribed those two treatments and who were taking their medications on time and not forgetting to take them were truly considered as taking the medications, and therefore, we deducted 4 from their ROSS for antihypertensive treatment score and/or 3 for anticoagulant treatment. Patients who were not taking their medications on time and who were forgetting to take their medications every day were considered as not taking the medications and nothing was deducted from their ROSS.

We called this score ROSSadherence. We repeated the analysis and sketched the ROC curve. The AUC for ROSSadherence was higher than the one for ROSS with AUC 0.845 (0.810–0.880; $p < 0.001$) (Fig. 5).



Area Under the Curve

Test Result Variable(s): ROSS

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.869	.016	.000	.838	.899

The test result variable(s): ROSS has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Fig. 1. ROC curve and area under the curve for the prediction of the risk of stroke score.

3.9. Inclusion of waterpipe smoking in the ROSS

In the score validation study, we found that waterpipe smoking is also a risk factor for stroke. We repeated the calculation of the ROSS in the score validation study by substituting the cigarette smoking factor by tobacco smoking factor with tobacco including cigarette, waterpipe or both. We called this score ROSSsmoking. The AUC for ROSSsmoking was very close but slightly higher than the AUC for ROSS, 0.831 (0.795–0.866; $p < 0.001$) and 0.826 (95% CI, 0.790–0.863; $p < 0.001$), respectively (Fig. 6).

4. Discussion

The identification of patients at highest risk of stroke may allow immediate evaluation, targeted interventions and even hospital admission in order to minimize their risk of future stroke and maximize

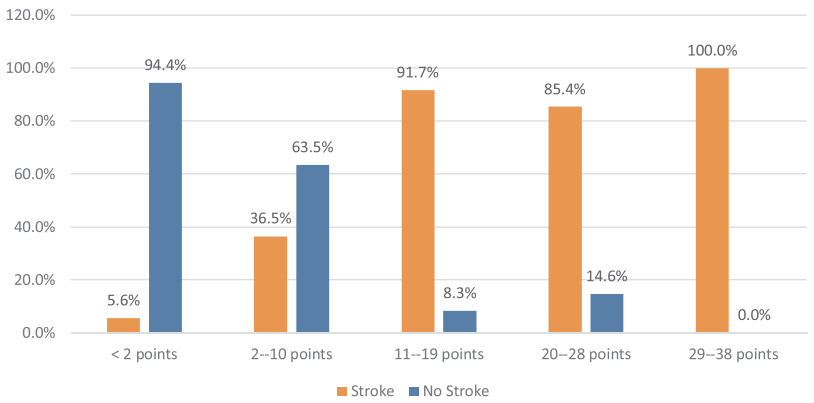


Fig. 2. Percentages of stroke and stroke free (no stroke) by category of ROSS in the Lebanese population.

Table 4
Medical and health characteristics of the prospective data.

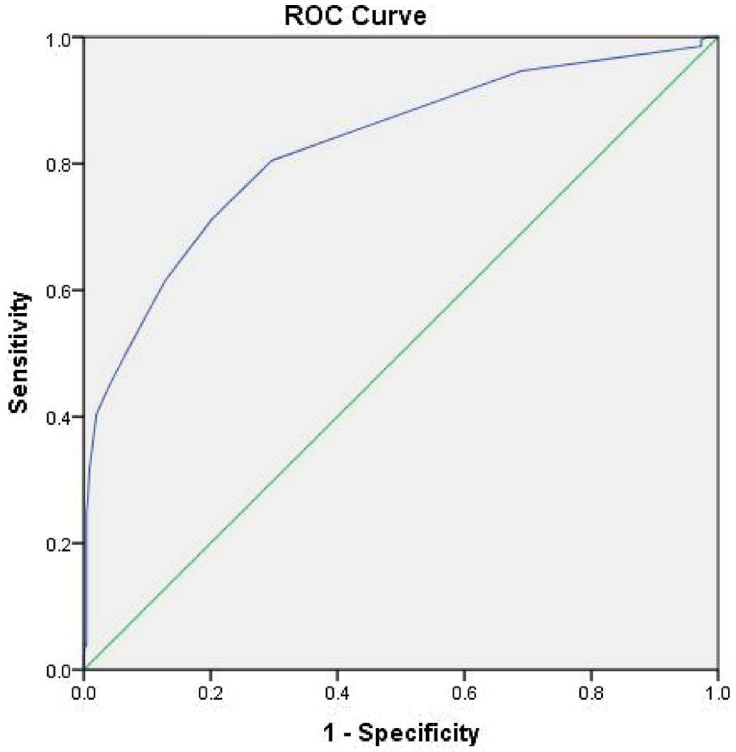
Variables	Total (n = 650)	Stroke Patients (n = 205)	Stroke-free Patients (n = 445)	P value
Body mass index (Kg/m^2; mean ± SD)	26.5 ± 5.1	27.2 ± 5.4	26.2 ± 4.9	0.016*
Medication History N(%)				
Antihypertensive	274 (42.2)	140 (68.3)	134 (30.1)	< 0.001*
Lipid lowering medication	153 (23.5)	70 (34.1)	83 (18.7)	< 0.001*
Anti-diabetes	174 (26.8)	72 (35.1)	102 (22.9)	0.002*
Antidepressant	86 (13.2)	36 (17.6)	50 (11.2)	0.034*
Anticoagulant	47 (7.2)	29 (14.1)	18 (4.0)	< 0.001*
Aspirin	210 (32.3)	99 (48.3)	111 (24.9)	< 0.001*
Clopidogrel	60 (9.2)	29 (14.1)	31 (7.0)	0.005*
Medical History N(%)				
Hypertension	278 (42.8)	152 (74.1)	126 (28.3)	< 0.001*
Diabetes Mellitus	172 (26.5)	75 (36.6)	97 (21.8)	< 0.001*
Dyslipidemia	137 (21.1)	62 (30.2)	75 (16.9)	< 0.001*
Cardiac Arrhythmia/Atrial Fibrillation	93 (14.3)	57 (27.8)	36 (8.1)	< 0.001*
Coronary Heart Disease/Myocardial Infarction	128 (16.2)	87 (42.4)	41 (9.2)	< 0.001*
Peripheral Artery Disease	24 (3.7)	17 (8.3)	7 (1.6)	< 0.001*
Heart Failure	65 (10.0)	35 (17.1)	30 (6.7)	< 0.001*
Deep Venous Thrombosis/Pulmonary Embolism	41 (6.3)	25 (12.2)	16 (3.6)	< 0.001*
Chronic Kidney Disease	22 (3.4)	10 (4.9)	12 (2.7)	0.165
Migraine	12 (2.3)	4 (2.0)	8 (1.8)	1.000
Obesity	144 (22.2)	53 (25.9)	91 (20.4)	0.128
Inflammation	18 (2.8)	7 (3.4)	11 (2.5)	0.607
Epilepsy	18 (2.8)	9 (4.4)	9 (2.0)	0.120
Hypothyroidism	27 (6.9)	12 (5.9)	15 (3.4)	0.144
Sleep apnea	52 (8.0)	17 (8.3)	35 (7.9)	0.877
Previous TIA/CVA	77 (11.8)	71 (34.6)	6 (1.3)	< 0.001*
Herpes zoster	17 (2.6)	7 (3.4)	10 (2.2)	0.430
Angina pectoris	76 (11.7)	34 (16.6)	42 (9.4)	0.012*
Intermittent claudication	45 (6.9)	20 (9.8)	25 (5.6)	0.067
Oral contraceptive (among female)	20 (5.2)	1 (0.9)	19 (7.0)	0.011*
Physically active	251 (38.6)	58 (28.3)	193 (43.4)	< 0.001*
Cigarette smoking status N(%)				< 0.001*
Non-smokers	410 (63.1)	106 (51.7)	304 (68.3)	
Current smokers	194 (29.8)	83 (40.5)	111 (24.9)	
Previous smokers	46 (7.1)	16 (7.8)	30 (6.7)	
Waterpipe smoking status N(%)				0.001*
Non-smokers	584 (89.8)	172 (83.9)	412 (92.6)	
Current smokers	47 (7.2)	21 (10.2)	26 (5.8)	
Previous smokers	19 (2.9)	12 (5.9)	7 (1.6)	
Family history of CVA N(%)	108 (16.6)	72 (35.1)	36 (8.1)	< 0.001*
Family history of cardiac disease N(%)	214 (32.9)	90 (43.9)	124 (27.9)	< 0.001*
Systolic blood pressure on admission (mm Hg; mean ± SD)	127.7 ± 21.4	143.7 ± 23.2	119.7 ± 15.5	< 0.001*
Systolic blood pressure classification on admission N(%)				< 0.001*
Grade 1	95 (14.6)	63 (30.7)	32 (7.2)	
Grade 2	39 (6.0)	34 (16.6)	5 (1.1)	
Grade 3	20 (3.1)	19 (9.3)	1 (0.2)	
Diastolic blood pressure on admission (mm Hg; mean ± SD)	74.6 ± 10.3	80.3 ± 11.6	71.9 ± 8.4	< 0.001*
Diastolic blood pressure classification on admission N(%)				< 0.001*
Grade 1	34 (5.2)	31 (15.1)	3 (0.7)	
Grade 2	11 (1.7)	11 (5.4)	0 (0.0)	
Grade 3	6 (0.9)	5 (2.4)	1 (0.2)	
Blood pressure classification on admission N(%)				< 0.001*
Grade 1	95 (14.6)	62 (30.2)	33 (7.4)	
Grade 2	39 (6.0)	34 (16.6)	5 (1.1)	
Grade 3	24 (3.7)	22 (10.7)	2 (0.4)	

SD, standard deviation; TIA/CVA, transient ischemic attack/cerebrovascular accident; *, statistically significant.

their chances of access to thrombolysis or thrombectomy and thereby improve handicap-free survivals. The designed tool constructed in the score generation study, ROSS, had good properties and included 10 characteristics, including age, smoking, and a history of hypertension, cardiac arrhythmia, coronary heart disease/myocardial infarction, deep venous thrombosis/pulmonary embolism, migraine, antihypertensive and anticoagulant treatment, as well as the exact measurements of patient's BP.

ROSS is developed from minimal information present in patients' files. This risk of stroke tool is designed to assess stroke risk among all Lebanese patients and does not concentrate on a specific group of patients. It considers patients 65 years and older at higher risk of stroke as well as those presenting a history of specific vascular diseases. ROSS also includes the different BP grades of patients by taking the mean of three BP measurements for three consecutive days at the hospitals since not all hypertensive patients are aware of their disease in Lebanon.[19] Moreover, since the risk of stroke increases based on BP pressure grades, including this factor in our stroke optimized the prediction of stroke in our population.[20,21] Adding to this, all factors included in our score are also supported by other well-conducted international studies that identify them as risk factors to increase the risk of stroke.[22–25]

ROSS is a significant step forward in the prediction of stroke among the Lebanese population to identify high-risk people and encourage them to manage their risk through appropriate intervention or provide rapid evaluation and treatment to prevent the incidence of stroke. As seen on the ROC analysis in the score generation study, the area under the curve was high for our sample, AUC 0.869 (0.838–0.899), with significant specificity (0.822) and sensitivity (0.864) which may



Area Under the Curve

Test Result Variable(s): ROSS

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.826	.019	.000	.790	.863

The test result variable(s): ROSS has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

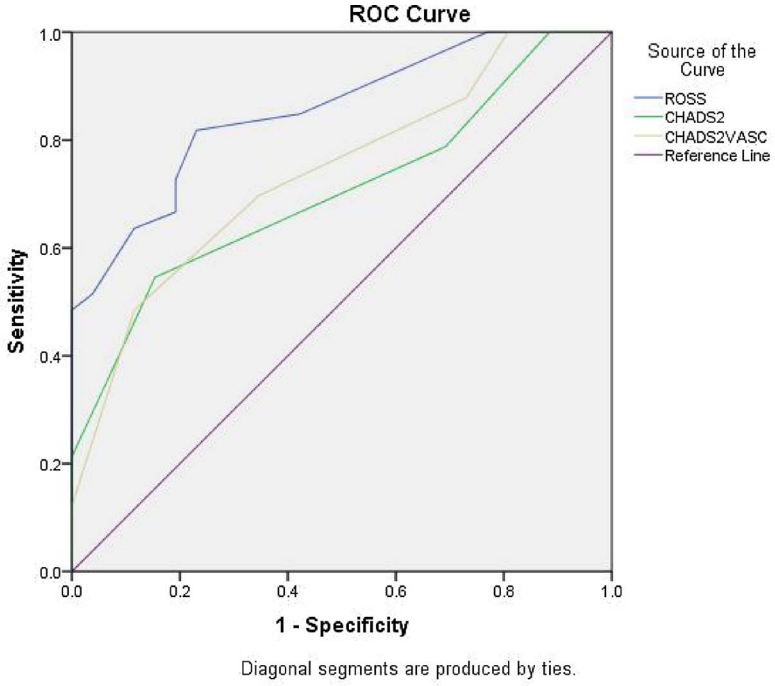
b. Null hypothesis: true area = 0.5

Fig. 3. Roc curve and area under the curve for ROSS in the score validation study.

encourage the use of ROSS in the primary care setting. Our scale had a good probability to predict the risk of stroke among the Lebanese population. A score < 2 points indicated a 94.4% negative prediction of stroke risk. A score > 10 points had more than 85.4% positive prediction of stroke risk. The probability of stroke in an individual depends highly on the presence and level of the risk factors included in the score. However, the presence of a grade 3 BP is considered associated with the highest risk of stroke.

ROSS has also been validated for predicting stroke risk in a score validation study conducted among the same Lebanese population during 2015–2016. ROSS is a predictive tool that does not have dichotomous outcome (positive/negative test results) in order to use the sensitivity and specificity as measures of accuracy of this test in comparison with the accurate diagnosis at the hospital by CT scan or MRI. In fact, ROSS results are recorded in ordinal scale (low-risk, intermediate risk, and high-risk), therefore the sensitivity and specificity are computed across all possible threshold values and they vary across the different threshold values.[26] Hence, the area under the ROC curve (AUC) is considered as an effective measure of accuracy with meaningful interpretations, where combined measure of sensitivity and specificity describe the validity of the ROSS.[26] Around 650 patients were included in the prospective data, ROSS had good area under the curve for the prediction of stroke, AUC 0.826 (95% CI, 0.790–0.863; p = 0.000). A ROSS score < 2 points indicated a negative prediction value of stroke by 88.7% and a ROSS score > 10 points indicated a positive prediction value of stroke by 96.2%.

In comparison with the Framingham Stroke Profile, ROSS included the majority of variables suggested by the Framingham Stroke Profile such as age, hypertension, antihypertensive treatment, cigarette smoking, and cardiovascular disease.[7] However, the Framingham



Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
ROSS	.854	.048	.000	.761	.948
CHADS2	.705	.067	.007	.573	.836
CHADS2VASC	.739	.064	.002	.613	.864

The test result variable(s): ROSS, CHADS2, CHADS2VASC has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Fig. 4. Roc curve and area under the curve for ROSS, $CHADS_2$, and CHA_2DS_2-VASc in both studies for atrial fibrillation patients.

Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
ROSS	.826	.019	.000	.790	.863
ROSSadherence	.845	.018	.000	.810	.880

The test result variable(s): ROSS, ROSSadherence has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Fig. 5. Area under the curve for ROSS and ROSSadherence in the score validation study.

Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
ROSS	.826	.019	.000	.790	.863
ROSSsmoking	.831	.018	.000	.795	.866

The test result variable(s): ROSS, ROSSsmoking has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Fig. 6. Area under the curve for ROSS and ROSSsmokiong in the score validation study.

Stroke Profile included the systolic blood pressure as one component in the score compared to ROSS which emphasizes the role of all blood pressure grades in assessing the risk of stroke, since diastolic blood pressure alone was found to also increase the risk of stroke by many well developed studies.[27] Nevertheless, the Framingham risk score is a good risk assessment tool but it seems to be varying across different ethnic groups, and therefore we suggest that the ROSS would be a good tool for stroke prediction in the Lebanese population.[28,29]

Compared to $CHADS_2$ and CHA_2DS_2-VASc which are both accurate assessment tools for stroke risk prediction during the first year after atrial fibrillation, ROSS included the majority of components of CHA_2DS_2-VASc and similarly considered age ≥ 65 years and hypertension as risks of stroke.[12,13] ROSS did not limit the assessment of the risk of stroke to a specific group of patients, indeed, it considered all Lebanese people and showed high accuracy in predicting the risk of stroke among this population. However, ROSS was compared to $CHADS_2$ and CHA_2DS_2-VASc in both studies by only including patients with a history of atrial fibrillation and without any filled prescription of

anticoagulant, aspirin, and clopidogrel. ROSS showed a greater area under the curve with good accuracy in all comparison data with $CHADS_2$ and CHA_2DS_2-VASc with AUC 0.854 (95% CI, 0.761–0.948). Therefore, ROSS is highly recommended for use among atrial fibrillation patients in the Lebanese population compared to the other two scores. Antithrombotic therapy has been associated with severe bleeding if not monitored intensively and one reason why patients have been classified as low-, intermediate-, and high-risk of stroke is to consider wisely the advantages and disadvantages of anticoagulation therapy.[30] However, ROSS showed better stroke-risk classification of atrial fibrillation patients and better area under the curve suggesting that this score is helpful in term of clinical decision-making where it might help clinicians direct the most effective antithrombotic treatment towards atrial fibrillation patients at high-risk of stroke. Patients identified by ROSS at high-risk of stroke would be recommended to start antithrombotic treatment, and patients at moderate-risk would be assessed for either antiplatelet or anticoagulant therapy.

It is important to emphasize that although ROSS included cardiac arrhythmia and anticoagulant treatment as factors in its risk of stroke prediction, those two factors did not affect the score results. When another analysis was conducted by eliminating the effect of these two factors, ROSS still proved that it is a good indicator of stroke risk and its predictive ability is independent of anticoagulant treatment.

Moreover, since medication was included in the assessment of the risk of stroke, the AUC for ROSSadherence indicates that if patients were prescribed the treatment but were not taking their medication properly, we cannot deduct 4 or 3 in the calculation of their ROSS. This analysis increased the accuracy of ROSS even more in the Lebanese population.

Additionally, since waterpipe smoking was found to be a significant risk factor for stroke in the Lebanese population with a stronger association with stroke compared to cigarette smoking, we tried to replace the cigarette smoking factor in the ROSS with cigarette, waterpipe, or both. The results found suggest that ROSSsmoking has a very close AUC compared to ROSS suggesting that both, cigarette smoking and waterpipe smoking, play a critical role in the prediction of stroke in this population.

This study has many strengths, including: (1) This is the first research to develop and validate a score for stroke prediction in the Lebanese population; (2) This study included patients from seven different hospitals private and governmental) in Lebanon from different governorates; (3) TIA and stroke were diagnosed based on the hospital CT scan, MRI, or both and on examination by an experienced neurologist, so no misclassification has occurred between ischemic or hemorrhagic stroke; (4) All common types of potential biases in case-control studies were limited. To reduce verification bias, the majority of both studies' participants were selected from public and private hospitals located in the same area. To reduce the selection bias, control patients were selected from the same hospitals as case patients; community-based controls were unfeasible. Moreover, since controls did not have a brain CT scan and/or MRI, stroke-free diagnosis depended on the final diagnosis of patients documented in patients' file at the hospitals based on physicians' final diagnosis. To minimize recall bias, patients were blinded for the study hypothesis. To minimize observer and inter-observer's bias, standardized collection sheet and questionnaire were used to collect data and a protocol was developed for collecting, measuring, and interpreting information; (5) Adjusted odds ratios were used for the development of ROSS which limited the role of confounders in over or underestimating in ROC diagnosis; (6) The factor analyses used in the score generation analysis showed the strength of the items constituting our developed score; (7) ROSS was compared to international stroke-related scores.

However, this study has some limitations, including; (1) ROSS excluded diabetes as one component in risk assessment as seen in many worldwide scores. Diabetes did not show significant association with the risk of stroke among the Lebanese population in the score generation and score validation multivariate analysis. This is in occurrence with Farah et al. study that also did not show any association between diabetes and stroke symptoms among stroke-free Lebanese population despite its high prevalence rate;[31] (2) This research is a hospital-based study which might not be representative of the whole population. However, the inclusion of different tertiary hospitals from different governorates in the validation study has improved the representability of the population; (3) ROSS was developed from a retrospective study which might have limited certain data value and affected the results including specific diets, alcohol consumption, and physical activity. A population cohort might have augmented the predictive accuracy of ROSS. However, the validation study proved that ROSS had high negative and positive predictive values and AUC which encourage its use in the Lebanese population; (4) Although ROSS showed a greater area under the curve compared to CHADS2 and CHA2DS2-VASc, the large 95% CI indicates the necessity of a larger sample size for an accurate comparison between ROSS, CHADS2 and CHA2DS2-VASc; (5) ROSS system does not predict the type of stroke. In the score generation study, TIA patients had a ROSS between −1 and 27 points, ischemic patients had a ROSS between −1 and 38 points and hemorrhagic patients had a ROSS between 1 and 34 points. Therefore, we were not able to identify a specific scale range for each type of stroke. However, a larger population-based study would be of interest in order to tackle this concern.

5. Conclusion

In conclusion, ROSS proved to be a good assessment tool to indicate stroke risk among the Lebanese population. It is highly recommended to use the ROSS, particularly in the primary care setting, as a good assessment tool to predict stroke among high-risk people and encourage them to get involved in intervention programs to prevent this disease. However, more studies are required to validate the ROSS worldwide.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgment

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.cegh.2018.02.003.

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