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Cerebrovascular Disease

R2CHA2DS2-VA Predictsthe Cardiovascular Risk after Carotid Endarterectomy

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Background: R2CHA2DS2-VA score has been used to predict short and long-term outcomes in many cardiovascular diseases. This study aims to validate the R2CHA2DS2-VA score as a long-term major adverse cardiovascular events (MACE) predictor after carotid endarterectomy (CEA). Secondary outcomes were also assessed regarding the incidence of all-cause mortality, acute myocardial infarction (AMI), major adverse limb events (MALE), and acute heart failure (AHF).

Methods: From January 2012 to December 2021, patients ($n = 205$) from a Portuguese tertiary care and referral center that underwent CEA with regional anesthesia (RA) for carotid stenosis (CS) were selected from a previously collected prospective database, and a *posthoc* analysis was performed. Demographics and comorbidities were registered. Clinical adverse events were assessed 30 days after the procedure and in the subsequent long-term surveillance period. Statistical analysis was performed by the Kaplan−Meier method and Cox proportional hazards regression.

Results: Of the patients enrolled, 78.5% were males with a mean age of 70.44 ± 8.9 years. Higher scores of R2CHA2DS2-VA were associated with long-term MACE (adjusted hazard ratio (aHR) 1.390; 95% confidence interval (CI) 1.173−1.647); and mortality (aHR 1.295; 95% CI 1.08−1.545).

Conclusions: This study demonstrated the potential of the R2CHA2DS2-VA score to predict long-term outcomes, such as AMI, AHF, MACE, and all-cause mortality, in a population of patients submitted to carotid endarterectomy.

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INTRODUCTION

Stroke remains 1 of the major causes of death and disability.[1] In the European Union, stroke affects 1.1 million inhabitants every year and is the second most common cause of death.[1] Approximately 80% of strokes are ischemic, and of these, 15−20% are due to atherosclerosis of the extracranial internal carotid artery.[2] Current guidelines recommend carotid endarterectomy (CEA) as the first-line treatment for stroke prevention in high-grade carotid stenosis (CS).[3,4] However, while being a risk factor for stroke, carotid atherosclerosis is also a marker of cardiovascular risk, and patients treated with CEA remain susceptible to major cardiovascular events.[5,6]

The CHA2DS2-VASc score was primarily developed to assess thromboembolic risk and guide anticoagulant therapy in patients with atrial fibrillation (AF).[7] In addition to AF, recent studies have also focused on the utility of this score as a risk stratification tool in a variety of clinical settings, and it has been useful in predicting all-cause mortality and major adverse cardiovascular events (MACE), such as stroke and acute myocardial infarction (AMI).[8] In the original CHA2DS2-VASc score, the female gender is included as an additional risk factor for stroke.[9] However, recent studies suggested that using this score without the gender criteria, known as CHA2DS2-VA, might be more useful in risk stratification for thromboembolic events.[9]

In this study, the R2CHA2DS2-VA, a previously validated adaptation from the CHAD2DS2-VAsc score, was used to predict the cardiovascular risk after CEA.[10,11] This score is intended to evaluate the addition of both renal dysfunction and age between 50 and 74 years, excluding the original female sex variable.[11] A previous large multicenter study suggested that the female sex was a risk modifier for stroke in patients with AF instead of an established risk factor, with an attributable absolute thromboembolic risk of 0.5%.[12] On the other hand, a 10-year retrospective analysis supported the utility of R2CHADS2 (including reduced creatinine clearance) as a clinical predictive score of stroke.[13,14] The R2CHA2DS2-VA score was comparable to the CHA2DS2-VA score, yet current evidence concerning its validity is minimal, leaving its usefulness unclear.[11]

This study aims to validate the R2CHA2DS2-VA score as a long-term MACE predictor after CEA. Secondary outcomes included assessing the role of this score in predicting all-cause mortality, AMI, major adverse limb events (MALE), and acute heart failure (AHF), as well as comparing it with other proposed scores - revised cardiac risk index (RCRI),[15] Carotid RCRI (CtRCRI) [15] and modified 5-item frailty index (mFI-5).[16]

MATERIALS AND METHODS

Study Sample and Data Source

Patients from a tertiary care and referral center that underwent CEA with regional anesthesia (RA) for CS were enrolled. The patients included in this study were admitted between January 2012 and December 2021 and were registered in a prospective database, selected, and *post-hoc* analysis was performed. Preoperatively, the patient's characteristics were assessed. All patients were on a daily statin and single antiplatelet therapy (100 mg acetylsalicylic acid per day) for at least 2 days before surgery.

The present work follows the strengthening the reporting of cohort studies in surgery (STROCSS) criteria.[17] The study protocol was approved by the center's ethics committee (approval number 248−18) and is under European Union General Data Protection Regulation. Furthermore, this study protocol respects the Declaration of Helsinki.

Definitions

According to current guidelines of the European Society for Vascular Surgery,[18] symptomatic CS was defined and measured by duplex ultrasound or computed tomography angiogram.[19] Then, each component of the R2CHA2DS-VA was assigned a score according to the score instructions (Table I) and compared to other variants of it or other previously validated scores, such as CHA2DS2-VASc, CHA2DS2-VA, RCRI,[15] CtRCRI[15] , and mFI-5.[16]

MACE was considered as the composite of AHF, ischemic cardiovascular events, and all-cause mortality. Mortality etiology was determined by resorting to the electronic Death Certificates Information System (SICO™). Clavien−Dindo grading was used for classifying adverse events (i.e., surgical complications).[20]

Outcome Assessment

Patients were evaluated in the first and third months after surgical intervention and yearly since then, using clinical examination and duplex ultrasound. The primary outcome was the incidence of long-term (5 years) MACE. Secondary outcomes included all-cause mortality and the occurrence of AMI, MALE, and AHF.

Table I. Summary of the variables used in each risk model

Predictor variables	CHA2DS-VASc	CHA2DS2-VA	R2CHA2DS2-VA	MFI5	RCRI	CtRCRI
AGE >65	AGE ≥65 = 1 AGE≥75 = 2	AGE ≥65 = 1 AGE≥75 = 2	AGE ≥50 = 1 AGE≥75 = 2	-	-	-
Female sex	1	-	-	-	-	-
HTA	1	1	1	1	-	-
DM	1	1	1	1	1 (IDDM)	1 (IDDM)
CHF	1	1	1	1	1	2
CAD					1	1
Cerebrovascular disease	2	2	2	-	1	1
Vascular disease	1	1	1	-	-	-
COPD	-	-	-	1		
CKD			2		1 (Creat>2 mg/dl)	2 (Creat>2 mg/dl)
High-risk surgery					1	-
Dependence status						
Partial				1		
Total				2		

CAD, coronary artery disease; CHF, chronic heart failure; CKD, chronic kidney disease; COPD, chronic pulmonary obstructive disease; Creat>2 mg/dl, Serologic creatinine superior to 2 mg/dl; DM, diabetes mellitus; HTA, hypertension.

Statistical Analysis

Data were collected and analyzed using IBM SPSS Statistics (IBM Corp. release 2020. IBM SPSS Statistics for Windows, version 27.0, Armonk, NY).

Continuous and categorical data were subject to univariable analysis through Student's *t* and chi-squared tests, respectively. In addition, the Mann–Whitney *U* test was used to assess ordinal skewed variables, which are displayed as medians [interquartile range (IQR)]. Categorical variables are presented as percentages and continuous normally distributed variables as mean ± standard deviation (SD). For statistical significance, a *P*-value lower than 0.05 was assumed.

The Harrell's C-index was used to measure CHA2DS2-VASc and RCHA2DS2VA predictive discrimination.

Surgical Technique

Surgical technique, either patch angioplasty or eversion, was left to the surgeon's preference. RA was performed in all patients by cervical block with ropivacaine 0.5% w/v (in a total of 12–15 mL), followed by repeated neurologic examinations every 5 min.[21]

RESULTS

Demographic Data

From the studied population ($n = 205$ patients), 65 (31.7%) patients developed MACE following CEA. Demographic characteristics are displayed in Table II. The mean age was 70.4 ± 8.9 years, and 161 (78.5%) were male. Regarding cardiovascular risk factors, most patients had a history of hypertension (88.3%) and dyslipidemia (85.9%). Patients who developed MACE had a significant higher prevalence of kidney disease (23.1% vs. 7.1%, *P*-value = 0.001), peripheral artery disease (35.4% vs. 18.6%, *P*-value = 0.009), coronary disease (53.8% vs. 26.4, *P*-value<0.001), and chronic heart failure (CHF) (27.7% vs. 12.2%, *P*-value=<0.001) on univariable analysis. The mean R2CHA2DS2-VA score obtained in this population was 4.4 ± 1.5, and its distribution is shown in Figure 1.

Outcome and Survival Analysis

The median follow-up time was 63 (30–87) months. In Kaplan–Meyer analysis, MACE (log-rank = 0.003) and all-cause mortality (log-

Table II. General patient's characteristics and preoperative comorbidities

Demographics	*N* = 205 *n* (%)	MACE *n* 65 (%)	Control *n* 140 (%)	*P*
Age (years) (mean ± SD)	70.4 ± 8.9	71.6 ± 9.6	69.9 ± 8.6	0.214
Side (Right)	98 (50.5)	36 (56.3)	62 (47.7)	0.262
Sex (Male)	161 (78.5)	50 (79.6)	111 (79.3)	0.701
HTA	181 (88.3)	58 (89.2)	123 (87.9)	0.776
Smoking history	104 (50.7)	32 (49.2)	72 (51.4)	0.770
Diabetes	86 (42.0)	27 (41.5)	59 (42.1)	0.935
Dyslipidemia	176 (85.9)	52 (80.0)	124 (88.6)	0.101
CKD	25 (12.2)	15 (23.1)	10 (7.1)	0.001
BMI >30 kg/m2	38 (18.5)	9 (13.8)	29 (20.7)	0.239
PAD	49 (23.9)	23 (35.4)	26 (18.6)	0.009
CAD	72 (35.1)	35 (53.8)	37 (26.4)	<0.001
Vascular disease	93 (45.4)	43 (66.2)	50 (35.7)	<0.001
COPD	22 (15.7)	5 (7.7)	27 (13.2)	0.114
CHF	7 (5.0)	18 (27.7)	25 (12.2)	<0.001
AF	15 (7.4)	7 (10.8)	8 (5.8)	0.201
ASA				0.148
II	32 (16.9)	6 (9.8)	26 (20.3)	
III	145 (76.7)	52 (85.2)	93 (72.7)	
IV	12 (6.3)	2 (4.9)	9 (7.0)	
Cerebrovascular disease	92 (44.9)	23 (35.4)	69 (49.3)	0.063
Stenosis degree (mean ± SD)	73.7 ± 10.4	75.7 ± 9.4	72.8 ± 10.8	0.061
Contralateral stenosis degree (mean ± SD)	52.9 ± 18.5	55.6 ± 20.5	51.7 ± 17.5	0.159

Vascular disease (prior MI, peripheral artery disease, or aortic plaque).
AF, atrial fibrillation; ASA, American Society of Anesthesiologists Physical Status Classification System; CAD, coronary artery disease; CHF, cardiac heart failure; CKD, chronic kidney disease (creatinine = 1.5 mg/dl); COPD, chronic obstructive pulmonary disease; Obesity, body mass index >30 kg/m2; PAD, peripheral artery disease; SD, standard deviation; HTA, hypertension.

rank = 0.035) were significantly increased in patients with R2CHA2DS2-VA score ≥6 (Fig. 2).

On univariate Cox regression analysis, there was a significant association between MACE and higher values of red cell distribution width - coefficient of variation (RDW-CV) (hazard ratio (HR) 1.306; 95% confidence interval (CI) 1.124−1.516, *P*-value<0.001); and R2CHA2DS2-VA (HR 1.352; 95% CI 1.154−1.583, *P*-value=<0.001). The association was maintained when the confounders were adjusted, with aHR for RDW-CV 1.286; 95% CI 1.107−1.494, *P*-value <0.001); and R2CHA2DS2-VA aHR 1.390; 95% CI 1.173−1.647, *P*-value <0.001) (Table III).

R2CHA2DS2-VA also was associated with occurrence of AMI (HR 1.394; 95% CI: 1.0−1,943, *P*-value = 0.050), AHF (HR) = 1.351; CI: 1.010−1,806, *P*-value = 0.043), MACE (HR) = 1.352; CI: 1.154−1.583, *P*-value = 0.000); and all-cause mortality (HR) = 1.295; CI: 1.084−1.546, *P*-value = 0.004). There was not a statistically significant difference regarding the occurrence of stroke and MALE (Table IV).

RCRI (C = 0.616), mFI5 (C = 0.588), CtRCRI (C = 0.660), and R2CHA2DS2-VA (C = 0.626) were statistically significantly associated with the ability to predict MACE (Fig. 3). The cerebrovascular disease did not significantly impact the outcome-adjusted odds ratio of 0.92 (CI: (0.54−1.57), *P* = 0.75). Specifically, the carotid symptomatic status did not significantly impact long-term MACE (log rank = 0.135).

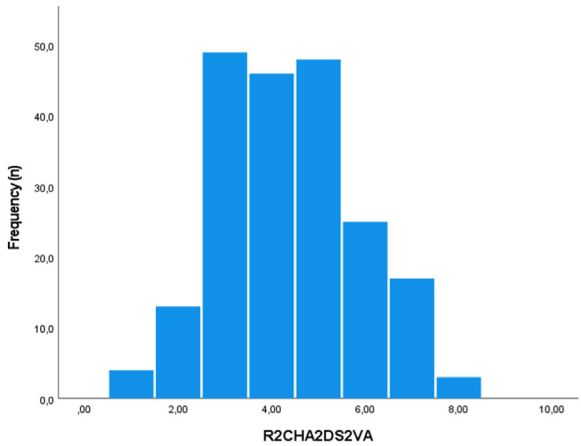
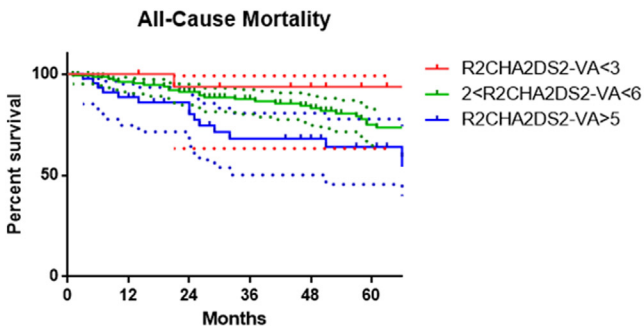
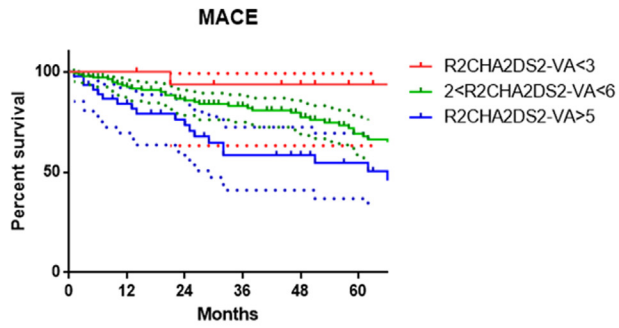


Fig. 1. Histogram of R2CHA2DS2-VA score (Mean = 4.361 ± 1.50, *n* = 205).

Furthermore, in the studied scores, chronic kidney disease (CKD) (aHR 2.73, CI 1.46−5.11,



All-cause Death Log rank=0.035		30d	12	24	36	48	60
R2CHA2DS2-VA<3	%	100	100	93.8	93.8	93.8	93.8
	SE (%)	-	-	6.1	6.1	6.1	6.1
	Cases	0	0	1	1	1	1
	N° at risk	16	16	15	15	9	9
R2CHA2DS2-VA 3-5	%	99.3	95.5	90.6	86.9	82.5	74.4
	SE (%)	0.7	1.8	2.6	3.1	3.6	4.5
	Cases	1	6	12	16	20	26
	N° at risk	141	124	103	83	69	53
R2CHA2DS2-VA>5	%	97.8	88.6	80.3	68.1	68.1	64.1
	SE (%)	2.2	4.8	6.3	7.8	7.8	8.3
	Cases	1	5	8	12	12	13
	N° at risk	44	36	28	21	18	15



MACE Log rank=0.003		30d	12	24	36	48	60
R2CHA2DS2-VA<3	%	100	100	93.8	93.8	93.8	93.8
	SE (%)	-	-	6.1	6.1	6.1	6.1
	Cases	0	0	1	1	1	1
	N° at risk	16	16	15	15	12	9
R2CHA2DS2-VA 3-5	%	99.3	91.8	85.1	82.4	76.8	68.7
	SE (%)	0.7	2.4	3.2	3.4	4.0	4.8
	Cases	1	11	19	22	27	33
	N° at risk	141	119	97	79	65	49
R2CHA2DS2-VA>5	%	97.8	84.1	73.4	58.5	58.5	54.6
	SE (%)	2.2.	5.5	6.9	8.1	8.1	8.5
	Cases	1	7	11	16	16	17
	N° at risk	44	34	26	19	16	14

Fig. 2. Survival curves R2CHA2DS2-VA score models for long-term results.

P-value = 0.002) and vascular diseases - prior MI, peripheral artery disease, or aortic plaque (aHR 2.58 (1.46—4.55, *P*-value <0.001), were the most impacting categories in the score (Fig. 3).

DISCUSSION

Although there is evidence that the R2CHA2DS2-VASc score is a predictor of all-cause mortality in the short- and long-term in other populations,[22] the predictive ability of the R2CHA2DS2-VA has not been studied regarding outcomes after CEA. In this study, MACE and all-cause mortality were significantly associated with higher scores of the R2CHA2DS2-VA in patients who underwent CEA surgery, especially in scores over 6 points. After CEA surgery, this score also showed an association with AMI and AHF but not with stroke. Also, it was found that RDW-CV is an independent predictor of MACE in patients submitted to CEA. This may be due to the confounding factor of CEA in stroke after surgery, which differs among patients not submitted to CEA.[23]

Compared to other variants or previously validated scores (CHA2DS2-VASc, CHA2DS2-VA, RCRI, CtRCRI, and mFI-5), the R2CHA2DS2-VA demonstrated a good predictive ability for MACE after CEA (Fig. 4). In addition, CHA2DS2-VASc has been demonstrated as an independent prognostic factor for long-time survival and MACE after internal carotid artery interventions.[24] It improves stroke risk prediction in patients with AF when carotid intima-media thickness or the presence of carotid plaque is included in the score.[25]

Impaired renal function has been independently associated with stroke in AF patients and is addictive to CHADS2 score.[26] CKD was also associated with MACE after CEA surgery, as has been previously reported.[27,28] Although CKD is a risk factor for cardiovascular disease,[29] both contribute independently to increasing the risk of cardiovascular events.[30]

As renal function is a powerful predictor of stroke and systemic embolism, the inclusion in the score increases its predictive value. The precursors of this score were the R2CHADS2 and the R2CHA2DS2-VAsc scores.[11] The R2CHADS2 score can estimate postoperative events after cardiovascular surgery with acceptable accuracy and be used as a simple preoperative risk tool.[31] R2CHA2DS2-VASc, adding vascular disease, age between 65—74 years, and female sex, is a significant predictor of both short- and long-term all-cause mortality after acute coronary syndrome and transcatheter aortic valve replacement.[32,33]

Therefore, R2CHAD2DS2-VA might be an indicator of the progression of atherosclerosis, with higher

Table III. Multivariable analysis of major adverse cardiovascular events

Risk variables	HR	(5−95% CI)	*P*	aHR	(5−95% CI)	*P*
Sex (male)	1.001	0.559−1.792	0.997	-	-	-
Smoking history	1.057	0.649−1.721	0.825	-	-	-
Dyslipidemia	0.630	0.342−1.161	0.138	-	-	-
Obesity	0.801	0.396−1.621	0.537	-	-	-
AF	1.916	0.870−4.218	0.106	-	-	-
COPD	0.776	0.311−1.941	0.558	-	-	-
Stenosis degree	1.243	0.964−1.602	0.094	-	-	-
Contralateral stenosis degree	1.080	0.958−1.216	0.208	-	-	-
RDW-CV	1.306	1.124−1.516	<0.001	1.286	1.107−1.494	<0.001
R2CHA2DS2-VA	1.352	1.154−1.583	<0.001	1.390	1.173−1.647	<0.001

AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; CI, confidence interval; OR, odds ratio; aOR, adjusted odds ratio.

Table IV. R2CHADS2-VA−Multivariate analysis

Risk outcomes	HR	CI	*P*
AMI	1.394	1.0−1.943	0.050
AHF	1.351	1.010−1.806	0.043
Stroke	1.162	0.930−1.452	0.186
MALE	0.889	0.708−1.115	0.308
MACE	1.352	1.154−1.583	<0.001
All-causemMortality	1.295	1.084−1.546	0.004

AMI, acute myocardial infarction; AHF, acute heart failure; MALE, major adverse limb events; MACE, major adverse cardiovascular events.

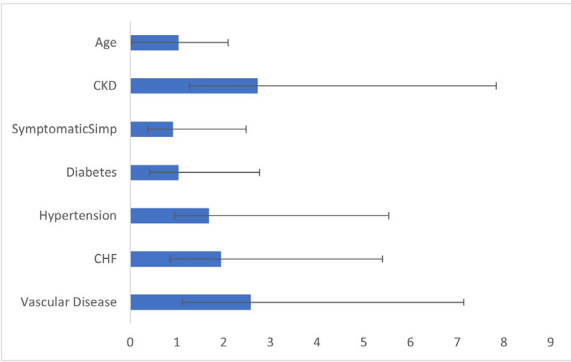


Fig. 3. Importance of each variable to the R2CHA2DS2-VA as measured by logistic beta coefficient squared.

scores meaning a higher load of atherosclerosis and polyvascular disease, which increase the risk of MACE and mortality.[34−36]

RDW-CV, after adjustment for other covariates, also predicted long-term MACE in accordance with a previous study.[28] This association has been related to higher plasma levels of inflammatory biomarkers and consequent elevation of the risk of cardiovascular events.[37]

R2CHAD2DS2-VA, similarl to RCRI and CtRCRI, includes renal dysfunction and excludes the female sex, differing from the original CHA2DS2-VASc. Renal dysfunction seems to be independently associated with MACE in our population, highlighting its importance in a score that aims to predict such risk. The importance of including the renal item in the score correlates with the fact that CKD is a predictor of premature cardiovascular death, defined as the occurrence of myocardial infarction or stroke before 55 years in males and 65 years in females.[33] Note that the female sex was not associated with MACE in our population. The underrepresentation of women may explain this finding.

Unlike R2CHAD2DS2-VA, RCRI, and CtRCRI do not include hypertension, age, and vascular disease. Vascular disease was a significant variable associated with MACE in our population, again highlighting its association with MACE. MFI5 differs in the inclusion of dependency in the score. However, due to the surgical nature of our cohort, dependent patients are hardly candidates for invasive procedures. Therefore, this score might not add much to the other scores besides the comorbidities included. All in all, R2CHAD2DS2-VA might be clinically useful in identifying patients that will benefit the most from intensive treatment against the progression and evolution of atherosclerosis. Patients with a

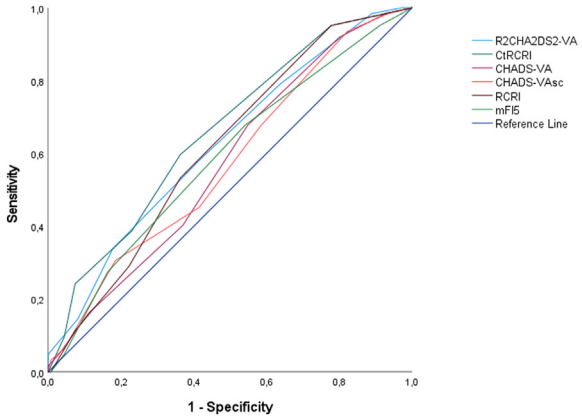


Fig. 4. Comparison between scores; CtRCRI-Carotid Revised Cardiac Risk Index; mFI5-Modified Fragility Index − 5 item; RCRI- Risk Cardiac Risk index.

	C Statistic	95% CI	*P* value
CHA2DS2-VA	0.573	0.490−0.656	0.100
CHA2DS2VASc	0.575	0.491−0.660	0.091
RCRI	0.616	0.536−0.697	0.009
mFI5	0.588	0.503−0.673	0.044
R2CHADS2-VA	0.626	0.544−0.709	0.007
CtRCRI	0.660	0.580−0.740	<0.001

high R2CHA2DS2-VA score and CS might need more careful monitoring and follow-up to optimize risk factor control and best medical treatment due to their higher incidence rate of cardiovascular events and all-cause mortality.

STRENGTHS AND LIMITATIONS

The main strength of this study was its prospective nature and extended follow-up of the included patients. However, this study has some limitations that should be mentioned. First, the patients enrolled in this study are from a single tertiary care center, whose characteristics may be different from those in othwhoer health care settings. Second, although the study design includes a prospective database, the *posthoc* analysis may overestimate the results, demanding a careful interpretation. Finally, as this is a surgical cohort, only patients who were candidates and also submitted to surgery were included, which limits conclusion for other groups of patients.

CONCLUSIONS

This study demonstrated the ability of R2CHA2DS2-VA to predict long-term outcomes, such as MACE and other cardiovascular outcomes, including AMI, AHF, MACE, and all-cause mortality after CEA surgery. R2CHA2DS2-VA has the main advantages of being inexpensive and less time consuming. Thus, it can help predict adverse outcomes and practice tailored decision-making regarding preoperative measures preceding CEA. Moreover, this score might be clinically useful to identify patients who will benefit most from the intensive treatment of cardiovascular risk factors and pathologies. However, larger prospective studies are needed to validate these results in patients undergoing CEA and in other surgical settings.

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