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ORIGINAL RESEARCH

Carotid endarterectomy (CEA) risk stratification for adverse events at one year follow-up: the role of preoperative functional capacity scores, age, BNP and hemoglobin

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Abstract

The aim of the study was to evaluate combination of functional status tools (American Society of Anesthesiologists Physical Status Classification System (ASA PS)) status, Metabolic Equivalent of Task (METs), Revised Cardiac Risk Index for Pre-Operative Risk (RCRI) largely used in preoperative risk assessment with humoral variables in building powerful predictive models of Major Adverse Cardiac Cerebrovascular Events (MACCE) in a one-year follow-up after carotid endoarterectomy (CEA). All consecutive patients undergoing CEA during a 12-month period, were enrolled in this prospective observational study. Demographic data, functional capacity (FC) measured by risk stratification scores RCRI, ASA physical status, METs and preoperative levels of hemoglobin and Brain Natriuretic Peptide (Pro-BNP), coexisting comorbidities, have been collected. 201 consecutive patients undergoing CEA under local anesthesia (men 137 (68.16%), women 64 (31.84%)) with a median age of 75 years (Interquartile range (IQR) 67–80 years), Body mass index (BMI) median of 26.23 (IQR 24.4–28.89) were enrolled. Combination of all variables studied leave at a good one-year prognostic tool with AUC of 0.93 (Sensitivity (SEN) 46.6, Specificity (SPEC) 95.7). Preoperative hemoglobin correlate with Major Adverse Cardiac Cerebrovascular Events (MACCE) at 3 months (p = 0.018), while the preoperative BNP at 12 months shows correlation with adverse events (p = 0.004). Age has a significant correlation with adverse events at 12 months between demographic and anthropometric factors (p = 0.002). MACCE may adversely affect short- and long-term outcomes after CEA. Evaluation of preoperative functional capacity by RCRI, ASA physical status and METs combined with age and biomarkers such as pro-BNP and hemoglobin, may improve risk stratification in patients undergoing carotid surgery.

Keywords

Carotid endoarterectomy (CEA); Major adverse cardiac cerebrovascular events (MACCE); BNP; RCRI; Hemoglobin; ASA PS; METs; Risk evaluation

1. Introduction

Carotid thromboendarterectomy (CEA) has been reported to reduce the risk of stroke in symptomatic patients with severe 79–90% carotid stenosis; more controversial are the benefits of the procedure in patients with stenosis of less severe degrees [1, 2]. The beneficial effects of CEA are maximal in patients with low perioperative risk, unfortunately a rare condition in vascular patients with typically high risk of cardiovascular and cerebral events [3]. CEA performed for asymptomatic stenosis showed a preoperative hospital mortality of 0.5%, while other complications such as cardiac were reported in 1.6%, perioperative stroke observed in less than 1% of patients; the rate of cardiovascular complications in symptomatic carotid surgery and in old patients is higher (1–5%) [4].

The search for models that estimate postoperative mortality and morbidity have found great development in recent decades. These predictive models can help patients and clinicians to understand, prevent and through the implementation of corrective interventions, reduce individual risk and adverse events and outcomes. Available indexes of perioperative risk of major adverse cardiac (MACE) and cerebral events (MACCE) can provide a reliable estimate of adverse complications in single patients and define appropriate therapeutic strategies

[5]. Several non-modifiable risk factors are associated with a poor postoperative prognosis including age, preoperative functional capacity, renal failure, diabetes, emergency surgery, ventricular dysfunction.

The Revised Cardiac Risk Index (RCRI) defined by Lee *et al*. [6] in 1999, is still applied in patients undergoing major non-cardiac surgical procedures [7]. This index was refined by Boersma [8]. RCRI showed limited predictive performance in noncardiac vascular surgery population, in any case the recently updated version of the RCRI seems more reliable than the original [9].

In recent years, identification of preoperative serum markers, has been independently associated with adverse outcomes and have therefore been added to MACCE risk prediction models. Among these markers, low preoperative hemoglobin values [10], preoperative dosing and postoperative monitoring of troponin [11–13], preoperative pro-BNP measurement has been found to be important prognostic indicators [14], identifying patients at high risk for heart failure, heart attack myocardial, progressive ventricular dilation, and death.

Patients with vascular disease are a persistent challenge for anaesthetists; in particular, surgical risk should be accurately defined in patients undergoing vascular surgery to provide major long-term advantages from the procedure using ASA physical status score [15] and measurement of tolerance exercise before surgery (METs) [16] which appear to possess low power discrimination in preoperative risk assessment [15].

A new index, Vascular Study Group of New England Cardiac Risk Index (VSG-CRI), has been recently proposed by Bertges *et al*. [17] to refine RCRI and more accurately define the risk of cardiac complications of vascular procedures, including CEA [9].

Compared to RCRI and Erasmus model, VSG-CRI includes additional items, such as long-term treatment with beta blockers, smoking habits, chronic obstructive pulmonary disease (COPD), serum creatinine >1.8, previous surgical or endovascular coronary revascularization procedures (as protective condition) and eliminate other conditions, such as cerebral vascular disease, type of surgery in all vascular procedures.

The evaluation of MACE and MACCE risk of Vascular Study Group of New England (VSGNE) using the Vascular Quality Initiative (VQI) 1-Year Mortality Risk Index for CEA, Vascular Quality Initiative (VQI) 30-Day Stroke Risk Index for CEA and Vascular Quality Initiative (VQI) Cardiac Risk Index (CRI) Carotid Endarterectomy, is now possible after external validation studies conducted in recent year [18, 19].

Age, indeed, may adversely affect pre-existing multimorbidity, frailty, physical disabilities, cognitive impairment particularly and assisted living facilities in the perioperative phase, has been proposed as predictor of morbidity and mortality [20].

In patients with atherosclerotic carotid disease the presence of specific conditions may affect short- and long-term outcome. In addition to clinical parameters included in the abovementioned scores, risk stratification should include several humoral markers and procedures with variable impact on short- and long-term outcome. These parameters more objectively reflect pathologic process severity, the response to therapeutic interventions and more accurately define perioperative risk in patients undergoing CEA. In this perspective, combination of traditional preoperative risk factors and scores has recently tried to find the best predictive model for the recognition of MACE and MACCE in patients undergoing vascular surgery [21].

Literature concerning functional capacity scores risk stratification predictively in non-cardiac vascular surgery, generally, except for some of them [18, 19], considers all interventions without specifying surgery type (aneurysms and thromboendarterectomy, popliteal femoral bypass, *etc.*). We focused on evaluation of consolidated preoperative score, BNP, hemoglobin, and age taking into consideration a single intervention such as CEA performed under local anaesthesia, which has different peculiarities and complications. The integration of widely used, easy to perform and consolidated functional capacity measurements, associated with easily determinable markers such as BNP and pre-operative hemoglobin, can integrated a correct post-operative and medium-term complications risk stratification (follow-up to one year).

The aim of our study was to evaluate predictably of functional capacity scores (RCRI, ASA physical status, METs) biomarkers (BNP and hemoglobin) and age, on adverse events (MACCE) after CEA surgery performed under local anaesthesia (one year follow-up). Through their integration and combination, the model with the best predictive power in risk stratification was identified.

2. Material and methods

We enrolled all consecutive patients admitted to the participating centres ("SS. Filippo e Nicola "Hospital-Avezzano/L'Aquila and "San Salvatore "Hospital-Coppito/L'Aquila) undergoing CEA surgery in the 24 months of study duration. Exclusion criteria were denied consent, age <50 or >85 years, recent cardiac or cerebral events (unstable coronary artery disease, decompensate heart failure, myocardial infarction, and stroke in the previous 30 days), end-stage renal disease (GFR <15 mL/min) on replacement treatment and emergency CEA. During preoperative evaluation routine clinic examination was carried, demographic and anthropometric parameters (age, sex, body mass index) as well as clinical data were collected. Medical history and pharmacological treatment were investigated, including cardiac events within six months, previous percutaneous or surgical cardiac revascularization procedures, arterial hypertension, inadequate functional capacity (FC) defined as METs <4, diabetes mellitus (DM), COPD, renal function according to GFR calculated by Cockcroft-Gault formula. and simplified in 5 stages by Levey [22].

Anaesthesiologic risk from anamnestic data according to ASA physical Status criteria the Revised Cardiac Risk Index score (RCRI) for development of cardiovascular complication was calculated using online software calculators. Patients were classified according to RCRI at low, intermediate, and high risk, depending on predictive factors included in each classification. Two blinded anaesthesiologists gave the value of each score; in case of disagreement were solved by a senior anaesthesiologist. In pre-operative phase and 24 hours before procedure, hemoglobin (Hb), creatinine and pro-BNP were measured. All patients received local anaesthesia according to the Moore median cervical plexus block or the Costagliola superficial cervical plexus block with levobupivacaine 0.25%, 20 mL and mepivacaine 2%, 10 mL. In all patients, radial artery was cannulated, and blood pressure invasively monitored. Moreover, an electrocardiogram (lead II and V), pulse oximetry, capnography via nasal cannula were monitored throughout the procedure. Stump pressure (SP) during a two-minute clamping test was assessed in all patients for clinical purposes.

Cerebral perfusion throughout surgical procedure, during clamping test and thromboendoarterectomy, was assessed by clinical monitoring (squeeze contralateral hand at request, or play special devices with the contralateral hand). Intraoperative contralateral internal carotid flow and tolerance to two-minutes clamping test were monitored when a temporary shunt placement was required.

During 48 hours from surgery presence of major cardiac (severe arrhythmias, acute coronary syndromes ST-elevated myocardial infarction (STEMI), non-ST elevated myocardial infarction (NSTEMI) cardiac insufficiency, death) and cerebral (major and minor strokes in terms of focal or hemispheric defects) complications (MACCE) and minor adverse events (local hematomas, incision site infections) was assessed by clinical and instrumental examination. Neurologic conditions were evaluated by the "National Institute of Health (NIH) Stroke Scale".

Phone calls and/or office visits follow-up were performed at discharge at 3 and 12 months after surgery.

Shapiro-Wilk test was performed to verify normality of continuous variables Continuous variables have been reported as median and interquartile range, categorical variables as frequency and percent values. Clinical and humoral parameters were analysed by χ^2 test or fisher exact or Kruskal-Wallis test for categorical variables and Wilcoxon' rank-test for continuous ones.

We divided the entire sample into two groups based on adverse effects development at three month and at one month of follow-up. A logistic regression model was used to determine the odds ratio (OR) for each risk factors statistically significant in the descriptive analysis. A post-hoc analysis was also performed with goodness of fit and receiver operating characteristic curve (ROC) curve. Software Stata 17, StataCorp, 4905 Lakeway Driv College Station, Texas 77845, USA was used.

3. Results

We included 201 patients (men 137 (68.16%), women 64 (31.84%)) with a median age of 75 years (IQR 67–80 years), BMI median of 26.23 (IQR 24.4–28.89) (Table 1).

No significant differences were found in drugs assumed, adverse events and comorbidities detected with anamnestic data as showed in Table 1. At 12 months of follow-up global MACCE adverse events were recorded in 17.9% (n = 36) of these 3% (n = 6) deaths, neurological complications (TIA and stroke) were recorded in 10% (n = 20) and cardiovascular complications (heart failure myocardial infarction, arrhythmias, pulmonary oedema) in 5% (n = 10).

Age has a significant correlation with adverse events at 12 months between demographic and anthropometric factors (p = 0.002).

As regards the preoperative evaluation performed through ASA physical status, RCRI index and MET, statistical significance was found at three months of follow-up for ASA 4 (p = 0.005); MET >4 at both 3 and 12 months ($p < 0.001$); and for RCRI index >3 to 3 months (p = 0.006) (Table 1).

Among biochemical parameters taken into consideration, preoperative hemoglobin levels correlate significantly with MACCE at 3 months (p = 0.018), while preoperative BNP at 12 months shows a significant correlation with adverse events (p = 0.004). The analysis of the ROC curves for single biochemical markers and for preoperative functional scores does not show statistically significant values in the discriminatory ability at 3- and 12-months (**Supplementary Table 1**, Table 2).

Low predictive power was also recorded in evaluation of ROC analysis at 3 (**Supplementary Table 2**) and 12 months, creating binary combinations of scores and markers as shown in Table 3. RCRI combined with METs evaluation have better detective powers than the other combinations studied at 3 (p = 0.001, AUC 0.76) and 12 ($p < 0.001$, AUC 0.81) months of follow-up respectively.

Finally, sum of the score routinely used for perioperative risk stratification (ASA, METs and RCRI) to BNP, hemoglobin and age show predictive models at 12 months with a better capacity and statistically significant predictive ability (Table 4, Fig. 1).

4. Discussion

After adequate identification of high-risk patients, a modification of therapy or lifestyle should be immediately implemented to reduce possible adverse postoperative events [23].

The undisputed benefits of carotid endarterectomy in preventing stroke have been widely demonstrated in several trials over the past decades. a recent survey conducted on a large national database in the United States identified more than 130.000 cases of carotid revascularization in asymptomatic patients [24].

Sazgary *et al*. [25] recently showed that one in five high-risk patients undergoing non-cardiac surgery will develop one or more MACE within 365 days; the risk of MACE appears to remain high for approximately 5 months after non-cardiac surgery.

The aim of this study was to compare different preoperative risk scores usually used perioperatively (ASA physical status, METs and RCRI) in vascular elective surgery and the role of age, preoperative hemoglobin, and BNP values, in a large two-institute patient population, underwent carotid endarterectomy.

4.1 Perioperative risk score stratification for AEs

International guidelines recommend the use of clinical risk scores for predict postoperative cardiac events, as they are associated with severe morbidity and mortality, as well as health care costs [26].

Revised Cardiac Risk Index (RCRI) was created to predict major cardiac complications after non-cardiac surgery [23].

TABLE 1. Demographics anthropometrics data (age, sex, BMI), perioperative functional capacity score (ASA physical status, METs, RCRI), laboratory data (eGFR, Hb, BNP), Co-morbidities and home therapy. Adverse Events (MACCE) at 3-month and 12-month follow-up.

	N = 201	Major Adverse Cardiac Cerebrovascular Events (MACCE)					
		3 mouth			12 mouth		
	Median, Interquartile range (IQR) (%)	Yes	No	*p*	Yes	No	*p*
Age (years)							
	75.0 (67.0–80.0)	78.5 (66.5–85.0)	74.5 (66.5–80.0)	0.175	79.5 (70.0–83.5)	74.0 (65.0–80.0)	0.002
Sex							
male	137 (68.16)	18 (13.24)	118 (86.76)	0.493	26 (18.98)	111 (81.02)	0.564
female	64 (31.84)	58 (90.62)	6 (9.38)		10 (15.62)	54 (84.38)	
Body mass index (BMI)							
	26.23 (24.07–28.89)	25.71 (24.33–27.78)	26.24 (24.05–28.9)	0.691	26.45 (24.26–29.39)	25.71 (22.81–27.34)	0.060
ASA Preoperative scores							
Physical Status Classification System (PS)							
2	64 (31.84)	3 (4.76)	60 (95.24)	0.005	11 (17.19)	53 (82.81)	0.877
3	114 (56.72)	14 (12.28)	100 (87.72)		20 (17.54)	94 (82.46)	
4	23 (11.44)	7 (30.43)	16 (69.57)		5 (21.74)	18 (78.26)	
Metabolic Equivalent of Task (METs)							
4	144 (71.64)	8 (5.56)	136 (94.44)	<0.001	9 (6.25)	135 (93.75)	<0.001
>4	57 (28.36)	16 (28.57)	40 (71.43)		27 (43.37)	30 (52.63)	
Revised Cardiac Risk Index for Pre-Operative Risk (RCRI)							
1	80 (39.80)	5 (6.33)	74 (93.67)	0.006	13 (16.25)	67 (83.75)	0.869
2	77 (38.31)	10 (13.00)	67 (87.00)		15 (19.48)	62 (80.52)	
≥3	44 (21.89)	9 (20.45)	35 (79.55)		8 (18.18)	36 (81.82)	
Biochemical parameters							
Estimated Glomerular Filtration Rate (eGFR)	61.7 (49.5–81.0)	58.0 (44.0–74.0)	62.0 (50.0–81.0)	0.701	58.5 (43.5–73.5)	63.0 (50.0–82.0)	0.193
Hemoglobin (Hb)	12.8 (11.5–13.7)	11.5 (10.7–13.1)	12.9 (12–13.7)	0.018	12.9 (11.9–13.7)	12.2 (10.8–13.3)	0.058
Brain Natriuretic Peptide (BNP)	237.63 (104.25–495.81)	113.64 (58.21–270.09)	104.56 (55.0–256.0)	0.096	248.53 (121.21–435.45	100.76 (52.1–238.29)	0.004
Comorbidities							
Diabetes							
Yes	55 (27.36)	8 (14.55)	129 (88.97)	0.495	11 (20.00)	44 (80.00)	0.635
No	146 (72.64)	16 (11.03)	47 (85.45)		25 (17.12)	121 (82.88)	
Arterial Hypertension							
Yes	160 (79.60)	19 (11.88)	141 (88.12)	0.913	27 (16.88)	9 (21.95)	0.449
No	41 (20.40)	5 (12.50)	35 (87.50)		9 (21.95)	32 (78.05)	
Coronary artery disease (CAD)							
Yes	37 (18.41)	6 (16.22)	31 (83.78)	0.403	4 (10.81)	33 (89.19)	0.246
No	164 (81.59)	18 (11.04)	145 (88.96)		32 (19.51)	132 (80.49)	

TABLE 1. Continued.

	N = 201	Major Adverse Cardiac Cerebrovascular Events (MACCE)					
		3 mouth			12 mouth		
	Median, Interquartile range (IQR) (%)	Yes	No	p	Yes	No	p
Chronic obstructive pulmonary disease (COPD)							
Yes	24 (11.94)	5 (20.83)	19 (79.17)	0.178	5 (20.83)	19 (79.17)	0.776
No	177 (88.06)	19 (10.80)	157 (89.20)		31 (17.51)	149 (82.49)	
Drugs							
Oral hypoglicemizant							
Yes	55 (27.36)	4 (10.26)	35 (89.74)	1.000	8 (20.51)	31 (79.49)	0.645
No	162 (80.60)	20 (12.42)	141 (87.58)		28 (17.28)	134 (82.72)	
Insuline							
Yes	22 (10.95)	5 (22.73)	17 (77.27)	0.153	4 (18.18)	18 (81.82)	1.000
No	179 (89.05)	19 (10.67)	159 (89.33)		32 (17.88)	147 (82.12)	
Angiotensin-converting-enzyme inhibitors							
Yes	66 (32.84)	8 (12.12)	58 (87.88)	1.000	11 (16.67)	55 (83.33)	0.846
No	135 (67.16)	16 (11.94)	118 (88.06)		25 (18.52)	110 (81.48)	
Sartanics							
Yes	81 (40.30)	8 (9.88)	73 (90.12)	0.512	10 (12.35)	71 (87.65)	0.096
No	120 (59.70)	16 (13.45)	103 (86.55)		26 (21.67)	94 (78.33)	
Diuretics							
Yes	80 (39.80)	10 (12.50)	70 (87.50)	0.859	12 (15.00)	68 (85.00)	0.382
No	121 (60.20)	14 (11.67)	106 (88.33)		24 (19.83)	97 (80.17)	
Ca-antagonist							
Yes	56 (27.86)	5 (8.93)	51 (91.07)	0.405	12 (21.43)	44 (78.57)	0.419
No	145 (72.14)	19 (13.19)	125 (86.81)		24 (16.55)	121 (83.45)	
Beta-blokers							
Yes	49 (24.38)	8 (16.33)	41 (83.67)	0.283	8 (16.33)	41 (83.67)	0.740
No	152 (75.62)	16 (10.60)	135 (89.40)		28 (18.42)	124 (81.58)	

RCRI considers the following of high-risk surgical procedures, history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, DM requiring insulin treatment, and preoperative serum creatinine >2.0 mg/dL (177 mol/L).

Major cardiac complication rates occur in 11% of patients with a score $\geq$3. In fact, patients with 3 or more points are marked as high risk and those with 1 or 2 points are considered intermediate risk.

Considering this, the American College of Cardiology (ACC)/American Heart Association (AHA) committee reconsidered the intermediate risk group with 5 risk factors from the original Lee score by delaying the execution of the surgery and implementing the other parts of the treatment scheme [27].

RCRI is found in guidelines published by the European Society of Cardiology, American College of Cardiology and American Heart Association, defined as a useful clinical tool for perioperative risk stratification in patients undergoing non-cardiac surgery [28].

As already demonstrated by previous studies, our work also show how RCRI has low precision and low predictive power for perioperative adverse events risk in patients undergoing carotid surgery (0.63 AUC, p = 0.006 at 3-month showed in **Supplementary Table 1**; 0.52 AUC, p = 0.086 at 12-month follow-up in Table 2) [26, 29].

In preoperatory anaesthetic evaluation, it is often difficult to select the most reliable score on the risk factors predictivity for different types of surgery and for different patients. Sometimes, we need to add other scores to determine more reliable risk classes such as functional assessment and exercise capacity, which is highly recommended by the American Heart Society or through ASA status assessment. In routine clinical practice, this is roughly estimated, by evaluating a patient's daily activities.

Generally, patients who can perform exercises above 5

TABLE 2. One-year MACCE follow-up after CEA.

	Odds Ratio (OR)	95% confidence interval (CI)	*p*	*p*-model	Area Under Curve (AUC)	R^2
Revised Cardiac Risk Index for Pre-Operative Risk (RCRI)						
1	ref.					
2	1.240	0.540–2.820	0.597	0.086	0.52	0.21
3	1.140	0.430–3.010	0.784			
Metabolic Equivalent of Task (METs)						
>5	ref.			<0.001	0.78	0.22
<5	13.500	5.750–31.640	<0.001			
ASA Physical Status						
2	ref.					
3	1.020	0.450–2.300	0.952	0.880	0.51	0.01
4	1.330	0.400–4.370	0.630			
Age (years)						
model	1.070	1.021–1.120	0.005	0.002	0.66	0.04
Brain Natriuretic Peptide (BNP)						
model	1.002	1.003–1.004	0.023	0.017	0.72	0.06
Hemoglobin (Hb)						
model	0.780	0.630–0.970	0.032	0.032	0.60	0.02

Statistically significant <0.05.

TABLE 3. One-year MACCE follow-up after CEA. Binary combination.

	OR	95% CI	*p*	*p*-model	AUC	R^2
RCRI + MET						
2	1.050	0.420–2.850	0.835			
3	0.620	0.200–1.900	0.407	<0.001	0.810	0.34
MET <4	14.620	6.100–35.080	<0.001			
RCRI + ASA						
2	1.21	0.510–2.850	0.656			
3	1.06	0.350–3.210	0.910	0.976	0.530	0.24
3	0.900	0.410–2.360	0.980			
4	1.270	0.330–4.880	0.710			
RCRI + BNP						
2	0.730	0.190–2.730	0.642			
3	0.330	0.040–2.500	0.070	0.070	0.720	0.28
bnp	1.000	1.000–1.010	0.016			
RCRI + AGE						
2	1.100	0.480–2.580	0.870	0.220		
3	1.100	0.410–2.960	0.460	0.006	0.660	0.24
age	1.070	1.020–1.120	0.006	0.002		
RCRI + HB						
2	0.940	0.380–2.280	0.890			
3	0.820	0.270–2.490	0.740	0.190	0.590	0.27
hb	0.770	0.610–0.980	0.330			

Statistically significant <0.05.

TABLE 4. Prognostic model combination, 12 months MACCE follow up after CEA.

MODEL	Sensibility (SEN)	Specificity (SPEC)	Area under curve (AUC)	R^2
RCRI + ASA + Hb + MET	65.62	92.31	0.8761	0.51
RCRI + ASA + Hb + MET + AGE	59.38	93.01	0.8921	0.54
RCRI + ASA + Hb + MET + BNP	40.00	95.70	0.9175	0.53
RCRI + ASA + Hb + MET + AGE + BNP	46.67	95.77	0.9308	0.56

Statistically significant <0.05.

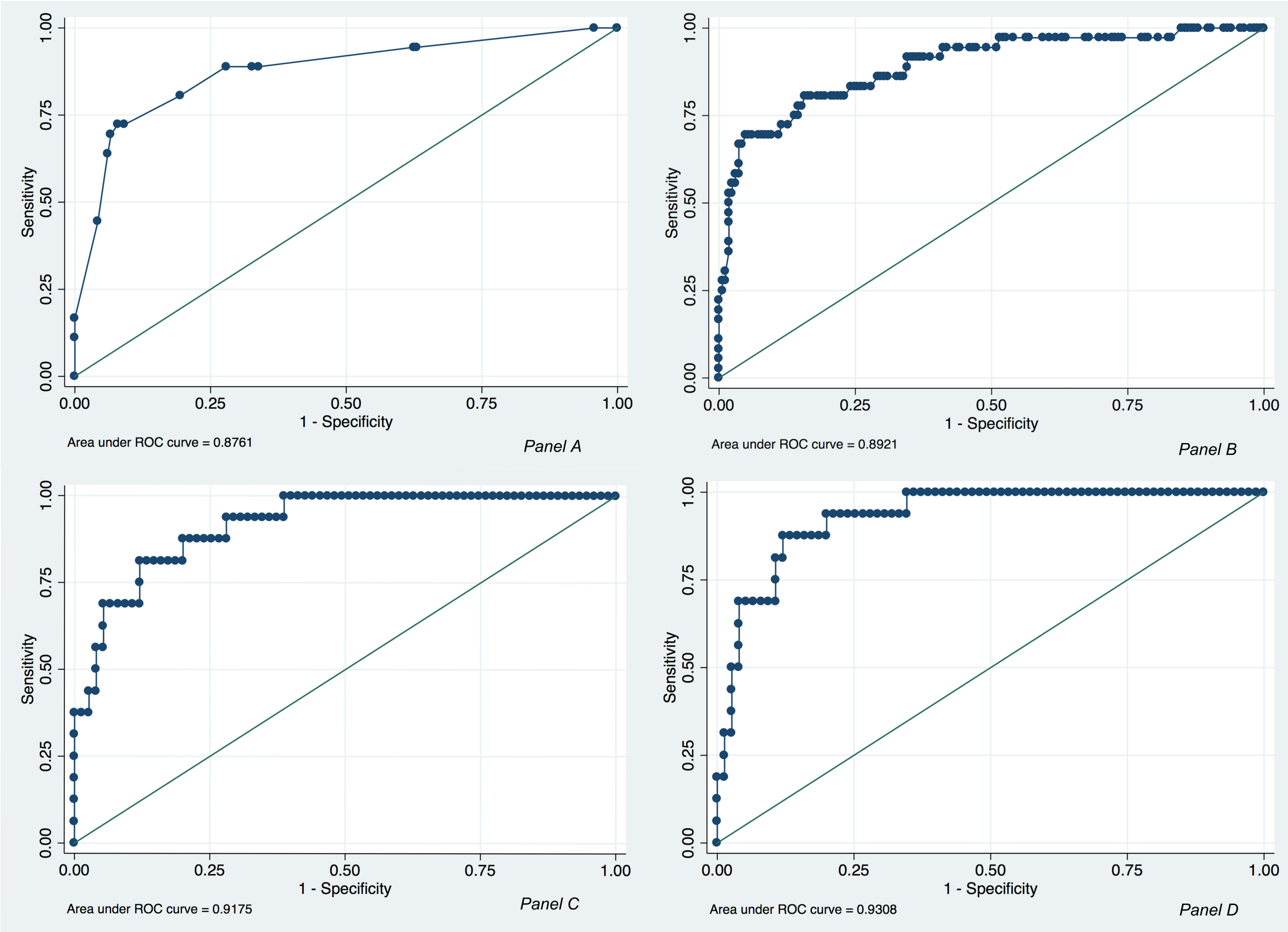

FIGURE 1. Receiver operating characteristic curves (ROC) of prognostic model combination, 12 months MACCE follow up after CEA. Panel A: ROC curve model RCRI + ASA + HB + MET; Panel B: ROC curve model RCRI + ASA + HB + MET + AGE; Panel C: ROC curve model RCRI + ASA + HB + MET + BNP; Panel D: ROC curve model RCRI + ASA + HB + MET + AGE + BNP.

METs (metabolic equivalents) have a low risk of cardiological complications after major surgery [23], as well as ASA status values between 4 and 5 are strongly predictive for postoperative AEs risk, as recently demonstrated also for the CEA [19, 30].

Our study confirmed this aspect for the METs assessment especially at 12 months of follow-up, with a good predictivity of AEs for METs <5 (0.78 AUC, $p < 0.001$, OR: 13.5, 95% CI: 5.75–31.64, Table 2) in carotid surgery.

Interestingly in our results, combination of RCRI and METs <4 appears to have good predictive abilities of AEs in patients undergoing CEA at both 3 (**Supplementary Table 2**) and 12 months of follow-up (respectively 0.76 AUC, p-model 0.001 and 0.81, p-model < 0.001, Table 3). Indeed, our results seems to be in contrast with recent findings of Wijeysundera *et al.* [31] and subsequently by Riedel *et al.* [32] that through a large international multicentre prospective cohort study, questions the validity of the evaluation of the preoperative functional capacity through METs, in predicting death and complications after major elective non cardiac surgery. It should be noted that in this study major vascular surgery represents only 2% of patients and regional anaesthesia 15% of all procedures.

Recent works suggesting combination of biomarkers such as preoperative value of hemoglobin, BNP or troponin with multiple stratification scores (RCRI, VSGNE, V-POSSUM) to obtain the maximum predictive power for post-operatory AEs [21, 29].

In our study population, adding preoperative hemoglobin and BNP values to risk stratification scores, did not find an increase in predictive power of AEs at 3 and 12 months, as shown in Table 3 and in **Supplementary Table 2**. This result is probably influenced by two sets of reasons, one deriving from the study of the CEA procedure alone while the other studies considered all vascular surgery procedures, and the second from the selection criteria of our study population.

4.2 Preoperative hemoglobin and BNP and Age

It is demonstrated as the preoperative identification of laboratory markers or associated serum markers independently with adverse postoperative outcomes may represent the fundamental step in the eventual inclusion of these variables in risk prediction models. Among these biomarkers, hemoglobin (Hb) levels even slightly lower than normal has been identified as an independent predictor of poor function ability and mortality in patients with congestive disease heart failure [19].

Similarly, it has recently been seen that preoperative anemia is a risk factor for 30-day mortality after CEA especially for symptomatic patients [33]. This observation is also confirmed in our study at 3 months. Because low Hb values represent a potentially modifiable factor, its identification and consideration in patients who must undergo elective vascular surgery, would help to design therapeutic regimens aimed at correcting the Hb level by improving postoperative outcomes [34].

Perioperative BNP assay has been shown to be useful in predicting some adverse outcomes after cardiac and non-cardiac surgery [35]. Elevated levels of B-type natriuretic peptide (BNP), an important prognostic factor in both heart failure and acute myocardial infarction, identifies patients at high risk for progressive ventricular dilation, heart failure or death. [36]. BNP is released in response to ventricular overload and subsequent myocardial ischemia of increased wall stress [37]. Recent meta-analyzes have shown that measuring preoperatively brain natriuretic peptide (BNP) significantly increases the predictive power of RCRI, when used in combination for patients who are scheduled for vascular surgery [38]. Schouten *et al.* [39] have underlined how NT pro-BNP can predict not only perioperative risk but also long-term cardiac risk in patients undergoing to vascular surgery. Statistically significant differences in preoperative BNP values correlate with worse outcomes and with the occurrence of AEs also in our population, but they do not seem to have great predictive power either alone or in combination with scores such as RCRI, ASA and METs, as shown in recent works [21, 29]. This difference could depend on the type of patient selected for carotid surgery alone.

Several risk factors are associated with poor prognosis after surgery, including older age, this well-defined factor for increased risk is not editable. In our observation age seems to be correlated to the presence of AEs at 12 months of follow-up, as already reported in previous papers [40], but it does not seem to increase the predictive power if added to single scores but only in more complex combination models.

4.3 Risk stratification models

The clinical scores used in preoperative assessment of AEs risk in vascular surgery are not perfect and always reliable and it is necessary to combine them with other tools such as biomarkers to increase their predictive capacity. Research in recent years has focused heavily on this issue.

Results of combination score and biomarkers algorithms (Table 4) showed good accuracy in the 12-month estimation of adverse events after CEA. The ROC curve is a good statistical tool for determining the performance of risk factors as predictors of AEs. Two models showed particularly good characteristics: RCRI + ASA + Hb + MET + AGE and RCRI + ASA + Hb + METs + AGE + BNP with 0.91 and 0.93 AUC respectively at one-year follow-up predictive power for MACCE (Table 4, Fig. 1).

In our study we have shown for the first time, to the best of our knowledge, that a combination of preoperatively measured RCRI, METs, ASA physical status scores with BNP, Hb and age can be a good predictive model, with satisfactory specificity and sensitivity for 12-month adverse event prediction in CEA. In particular, the preoperative dosage of BNP could be revealing a subclinical condition in a multifactorial view, although, as show by low R^2, it do not justify the global variability of the model. The development of a risk assessment tool that integrates these scores that are readily available even in the bed of the patient with BNP, hemoglobin, and age, in non-cardiological vascular surgery such as Carotid surgery could add to the anesthetist's arsenal in perioperative management.

4.4 Limits

Compared to other studies recently conducted, our work differs in some peculiar, in fact we have studied exclusively patients undergoing surgical treatment of CEA in election under local anaesthesia, of symptomatic and non-symptomatic, urgent interventions and other vascular surgery procedures such as ruptured abdominal aneurysm repair, revascularization and infrainguinal artery reconstructions were not considered, and the follow-up was 12 months. We also considered all the possible adverse events both cardiovascular (MACE) and cerebrovascular (MACCE). This makes our results poorly comparable with previous works that evaluate alternatively either one or the other. Considering study population characteristics and the relatively small number of adverse events recorded, our results should be interpreted with caution.

5. Conclusions

The continuous development of predictive risk models has always been used to calculate the adverse outcomes that occur after being subjected to vascular surgery. The importance of having models with good predictive ability of adverse events is applied to the individual risk calculation, which allows to make very important clinical decisions both by the surgeon or anaesthetist, and by helping the patient to "make a decision" about the surgery or vascular procedure to undergo. Risk stratification is also essential to implement pre-operative intervention plans, so that postoperative morbidity can be minimized through correction of modifiable risk factors. Our study confirms that some non-modifiable factors such as age, and others modifiable such as pre-operative hemoglobin value and pre-operative BNP levels, are predictive of adverse events after carotid endarterectomy and can be evaluated with simple consolidate tools easy to perform without complicated algorithms and software calculator not always available.

ABBREVIATIONS

CEA, Carotid Thromboendarterectomy; MACE, Major Adverse Cardiac Events; MACCE, Major Adverse Cardiac Cerebrovascular Events; BNP, Brain Natriuretic Peptide; RCRI, Revised Cardiac Risk Index; VSG-CRI, Vascular Study Group of New England Cardiac Risk Index; VQI, Vascular Quality Initiative; BMI, Body Mass Index; GFR, Glomerular Filtration Rate; AE, Adverse Events; SP, Stump Pressure.

AVAILABILITY OF DATA AND MATERIALS

Raw data that support the findings of this study are available from the first and the corresponding author, upon reasonable request.

AUTHOR CONTRIBUTIONS

PMA—conception and design of the work, acquisition of data, revision, analysis and interpretation of data, bibliography, writing manuscript; CA—analysis and interpretation of data, writing manuscript, bibliography, revision; AM—statistical analysis and interpretation of data, revision; FC—design of the work, acquisition of data, revision; DF, FDS and FB—acquisition of data and revision; AC—design of the work, acquisition of data, bibliography, revision; FM—revision. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This observational, prospective, non-profit study was approved by local ethics committee (Ethics committee for the provinces of L'Aquila and Teramo, based at ASL 1 Avezzano-Sulmona-L'Aquila, Abruzzo region, Italy, n. 786/2013-04/CE/13). Informed written consent was obtained by all patients before enrolment.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1671065584687562752/attachment/Supplementary%20material.docx.

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