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ROLE OF RISK SCORING SYSTEMS IN PREDICTING LIFE EXPECTANCY AFTER CAROTID ENDARTERECTOMY IN ASYMPTOMATIC PATIENTS.

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KEYWORDS: carotid endarterectomy; asymptomatic carotid stenosis; survival analysis; risk scoring system; stroke

SUBJECT TERMS: carotid disease; stenosis; mortality/survival

ARTICLE HIGHLIGHTS

Type of Research: Retrospective multicenter study.

Key Findings: For 825 asymptomatic carotid endarterectomy candidate patients, six published risk scoring systems designed to predict postoperative life-expectancy were used to predict 3-year and 5-year mortality rates, resulting in high specificity (82.4% and 82.5%, respectively) and suboptimal accuracy (highest Harrell's value: 0.646 and 0.609 for 3-year and 5-year mortality, respectively).

Take home Message: Risk scoring systems may be used for asymptomatic patients before carotid endarterectomy to evaluate long-term surgery efficacy, bearing in mind those results should be integrated with other preoperative prognostic tools.

SUMMARY FOR TABLE OF CONTENTS

A real-world validation of six published risk score systems to predict survival rate after carotid endarterectomy in asymptomatic patients demonstrated acceptable diagnostic validity and mortality rate estimation in only two. Although this kind of analysis may help clinicians assess asymptomatic patients' life expectancy and justify surgery in term of postoperative long-term benefit, other available preoperative parameters should be taken into account.

ABSTRACT

OBJECTIVE: The aim of this study is to compare and to test the performance of all available risk scoring systems (RSSs) designed to predict long-term survival rate in asymptomatic candidate patients for carotid endarterectomy (CEA) for significant carotid artery stenosis.

METHODS: Data on asymptomatic patients who underwent CEA in three high-volume centers were prospectively recorded. Through literature research using PRISMA recommendations, six RSSs were identified for the intent of the study. Primary endpoints were 3- and 5-year survival rate after CEA. All items used as variables to compose multiple RSSs were applied to every patient in the study population. The 3-year and 5-year mortality prediction rates for each score were assessed by sensitivity, specificity, predictive negative and positive value calculation, as well as univariable Cox proportional hazard models with the Harrell's C index.

RESULTS: During the study period, 825 CEAs in 825 asymptomatic patients were analyzed. All items used in RSSs were available in the dataset, with some concerns regarding their definition and application among RSSs. The 3-year and 5-year survival rates of the study cohort were 94.5% and 90.3%, respectively. Among the six RSSs analyzed, no RSS demonstrated optimal results in terms of mortality rate prediction accuracy, although some scores had good diagnostic and risk of death precision.

CONCLUSION: RSSs, when used alone, fail to optimally detect postoperative life-expectancy in asymptomatic CEA patient candidates. Further prospective controlled studies are needed to compose and validate RSSs with better calibration to predict outcomes.

INTRODUCTION

Carotid endarterectomy (CEA) remains the most commonly used procedure worldwide to prevent or minimize the recurrence of stroke due to carotid artery stenosis, in both asymptomatic and symptomatic patients. Despite a multitude of publications and guidelines, in contrast with indications for CEA in symptomatic patients, the role of surgery to treat asymptomatic patients is still debated. [1-5] This is because suggesting routine prophylactic CEA remains subject to several concerns. Most important, improvements in pre- and post-procedural best medical therapy (BMT) over the past decades have enabled a progressive decline in the annual risk of late stroke, a decline particularly significant in some asymptomatic patients' low risk subgroups, such as patients without relevant comorbidities, plaque-related risk factors and normal cerebrovascular imaging findings. [6,7] Furthermore, although the majority of centers reach a perioperative complication rate <3% during CEA, few studies have tried to assess life expectancy in asymptomatic patients, and thus there are no unequivocal and clear recommendations about this topic.

In this context, risk scoring systems (RSSs) have been proposed to best identify which patients with asymptomatic carotid artery stenosis could benefit from CEA or if poor life expectancy may contraindicate surgery. These tools should permit, in a rapid and easy way, to preoperatively stratify long-term mortality risk in candidates for CEA and to predict the benefits of surgical treatment. Although several RSSs are proposed in the literature, no robust and external validations are provided in the majority of cases.[8]

The aim of this study is to validate and test the accuracy of RSSs designed to predict long-term mortality rate (3-year and 5-year) after CEA in asymptomatic patients, using a real-world, multicenter population as the validation cohort.

MATERIALS AND METHODS

This analysis was conducted according to the Declaration of Helsinki of the World Medical Association. All patients provided written informed consent before participation. The study was approved by the local ethics committee of the promoting center (VASCOR-AUX project, nr. 2020_06_16_10, approved on June 30, 2020) and the research ethics committee of each participating hospital.

SCORING SYSTEMS SEARCH STRATEGY

First, in order to obtain and analyze all RSSs published in the literature, a research strategy similar to that used by Bissacco and coworkers was adopted.[8] In brief, according to recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

(PRISMA) guidelines [9], the most important medical on-line databases (PubMed, EMBASE and The Cochrane Library) were interrogated to acquire the first article cluster. In this case, in contrast to a prior publications[8], the time range was set from January 1, 1990, to December 31, 2019. Further search strategy details are described in Supplementary Material, section S1. Potential useful references to eligible studies could also be included in the selected article cluster. Only RSSs designed for long-term (at least 3 years) mortality assessment in patients undergoing CEA for asymptomatic carotid artery stenosis were included. RSSs predicting only stroke, cardiovascular complications, or combined outcomes (e.g., stroke/death, stroke/myocardial infarction [MI]/death) were excluded if it was not possible to clearly identify the long-term mortality rate. Scores derived from mixed (asymptomatic and symptomatic) population were also included, but only if the number of asymptomatic patients in the study population was greater than those symptomatic. Potentially useful titles were reviewed independently by two Authors (DB and CM). If no acceptable consensus on article eligibility was reached, a third investigator (ST) was consulted. Selected papers were then analyzed in terms of items used and their "weight" into the score (points assignment). All items of all selected scores were inserted into a database designed *ad hoc* for study population analysis.

STUDY POPULATION

Data about all consecutive patients who underwent CEA for asymptomatic carotid artery stenosis at three high-volume centers for vascular and endovascular surgery (>50 CEA/year) were initially included: Istituto Auxologico Italiano from January 1, 2008 to December 31, 2017; Ospedale di Circolo di Busto Arsizio (ASST della Valle Olona) from January 1, 2014 to June 30, 2015; Ospedale Luigi Sacco (ASST Fatebenefratelli-Sacco) from January 1, 2008 to December 31, 2016.

Asymptomatic status was assessed by absence of stroke / transient ischemic attack (TIA) for at least six months before CEA. Patients already treated for ipsilateral and/or contralateral carotid artery stenosis were excluded.

All data were prospectively recorded and retrospectively analyzed. Two Authors (DB and CM) provided and sent an *ad hoc* dataset sheet (Excel, Microsoft Corp., Redmond, WA) to each center.

Although among RSSs item definitions were quite heterogeneous, consensus was achieved among participants, before the beginning of dataset compilation. In particular, in order to define each score item univocally, three Authors, one for each participating center (DB, CM and JM), were interrogated. Authors were asked to rate each item in terms of definition clarity provided by the paper in which the item was used, and applicability in our population. Applicability was defined as the effective and practical use of a specific item into the real-world, non-selected patients' cohort.

A 5-level Likert Scale [10] was used to rate Author response for each item (see Supplementary Material, S2 section, Figure 1S). Furthermore, comments were provided to better assess limitations in reproducibility of a specific item (see Supplementary Material, S3 section).

After single-center dataset completion, all data were pooled into a unique database. Only two Authors (DB and LS) could access and analyze the multicenter combined database.

Despite some specific centers' and/or surgeons' preferences, all patients were managed and treated according to the latest recommendations provided by the Italian Society of Vascular and Endovascular Surgery (SICVE) [11] and the European Society for Vascular Surgery (ESVS) [1] guidelines, in force during the enrollment periods. In particular, asymptomatic carotid stenosis was assessed by color Doppler ultrasound scan (CDUS) analysis performed by at least two skilled operators or confirmed by computed tomography angiography (CTA). A significant stenosis was defined as 60-99% (using NASCET measurement method) and/or with a peak systolic velocity (PSV) ≥ 230 cm/sec, a PSV_{ICA}/PSV_{CCA} ratio ≥ 4 or a PSV_{ICA}/end diastolic velocity $(EDV)_{CCA}>10$ (where ICA and CCA indicate internal and common carotid artery, respectively). Perioperative BMT was adopted before and after CEA. Surgery was performed under local or general anesthesia. In the latter case, continuous electroencephalogram (EEG) analysis was used. Shunt was used only in case of intraoperative EEG changes or clinical signs of hemispheric ischemia. Dacron or bovine pericardium graft angioplasty, primary closure or eversion endarterectomy were performed depending on carotid anatomy and personal preference. Postoperative follow-up evaluations were guaranteed through clinical and CDUS examination. Survival rate was assessed through clinical visit or with telephone calls. Data about demographics, comorbidities, preoperative drug intake, procedural and postprocedural outcomes were noted, referring to items used in selected RSSs.

RSSs SELECTION

Figure 1 shows the selection workflow and results of RSS research, according to methodology in the PRISMA statement. After systematic selection and application of inclusion/exclusion criteria, six RSSs were found and analyzed in depth (Tables Is and IIs, Supplementary Material, section S2). [12-17] Detailed description of each score in terms of development, calibration, advantage and limits is available in a previous publication. [8] In establishing the Keyhani score to use, the 4C model was preferred over the Carotid Mortality Index (CMI) , due to its better results in terms of feasibility and calibration. [17] Fourteen items were derived from the six selected scoring systems (Table I). All items were present in the whole population dataset of this study, after the abovementioned meeting to reach unanimous agreement about the definition of items used for scoring. All selected items were relative to preoperative conditions. Specifically, two items were related to demographic characteristics (age and sex), eight to comorbidities (smoking history, diabetes mellitus [DM], chronic obstructive pulmonary disease [COPD], heart disease history, renal function, any cancer in the past 5 years, neck radiation, congestive heart failure [CHF]), and two to medical therapy (taking statins and antiplatelet or not). Two items were about carotid-related features (stenosis grade and contralateral carotid stenosis [CCS]). Age, sex, smoking history, DM, COPD, heart disease history and renal function were the items most frequently used (5 scores out of 6). According to the Authors Likert Scale completion (Table IIIs, Supplementary Material, section S4), average applicability of items in our population was acceptable (median 4.7, IQR 3.5-5.0), although two items were judged quite heterogeneous among RSSs and with low applicability (renal function and CHF). The item “smoke” was defined as “past or current smoking”, because of the definition adopted by the only RSSs using it among score items. [15]

PRIMARY AND SECONDARY OUTCOMES

Primary endpoints were 3-year and 5-year survival rates postoperatively. Each selected RSS was tested on the study population, to assess accuracy in terms of 3-year and 5-year risk of death after CEA, through an external validation analysis.

STATISTICAL ANALYSIS

Descriptive statistics were produced for the demographic, clinical and laboratory characteristics of cases. Mean and standard deviation (SD) are presented for normally distributed variables, median and interquartile range (IQR) for non-normally distributed variables, and number and percentages for categorical variables. Whenever relevant, 95% confidence intervals (95% CI) were calculated.

To assess the external validity of the proposed scores, we applied survival analysis techniques as in the original studies from which the RSS methodologies were derived.

The event of interest was death, and patients still alive at last follow-up were censored. The time for analysis was the number of months from CEA surgery to last instance of follow-up data. Univariable Cox proportional hazard models were fitted, with each score as the only independent variable. Survival curves were plotted using the Kaplan-Meier method, including the number of patients at risk, cumulative number of events and the number of patients censored at each time point (See Supplementary Material, Section S5, Figure 2S), with all subjects in the cohort considered at the date of last follow up. We assessed the discriminative power of each score to predict overall long-term mortality rate by calculating Harrell's C index (which corresponds to the Receiver Operating Characteristic [ROC] curve for survival models). Additionally, sensitivity (Se), specificity (Sp) and positive/negative predictive values (PPV and NPV, respectively) for death at 3 and 5 years from CEA of each score (in case of scores with more than two risk classes, the optimal cut-off was chosen) were estimated.

All analyses were done using Stata 16 (Stata Corporation, College Station, TX, USA). To indicate statistical significance of results, a two-sided p value ≤ 0.05 was considered as cut-off value. A Harrell's C value (HCv) ≥ 0.7 was considered as the cut-off to discriminate between an optimal, suboptimal (0.69 – 0.60) or insufficient (0.59 – 0.50) prediction model.

RESULTS

STUDY POPULATION

During the study period, 1145 CEAs in 985 patients were performed. Based on the inclusion criteria, which excluded patients with previous contralateral or ipsilateral carotid intervention, 825 CEAs in 825 asymptomatic patients were screened. All patients were included in the analysis. Two hundred and eighty-six (34.7%) patients were enrolled from Istituto Auxologico Italiano, 172 (20.8%) from Ospedale di Circolo di Busto Arsizio and 367 (44.5%) from Ospedale Luigi Sacco. Demographic preoperative and intraoperative data are reported in Table II. More than half of the patients were male (528 patients, 64.0%). Six hundred and eighty-eight (83.4%) were on antiplatelet drugs and 602 patients (72.9%) were on statin therapy at admission. General anesthesia under EEG was proposed in 265 patients (32.1%). The eversion technique was used in the majority of cases (723 patients [87.6%]). Only one patient died within 30 days of CEA, resulting in a 99.8% survival rate. Survival rates at 3 and 5 years from surgery were 94.5% and 90.3%, respectively (see also Supplementary Material, S5 section, Figure 2S).

RSS PERFORMANCE ON THE STUDY POPULATION

Three-year performance

Three-year results are summarized in Table III. As noted, all RSSs showed low Se and PPV; on the contrary Sp and NPV are acceptable, although not optimal except in one case. [17] Regarding accuracy in detected 3-year death patients, three scores [12,14,17] demonstrated significant risk class discrimination, with an increasing risk of postoperative death among classes. In particular, the highest HCv was detected in the Keyhani score (0.646, p=.002). [17] In the same score, classes 1 and 2 increase the mortality rate at this follow-up time (HR 2.28, IC95% 1.06 – 4.90 and HR

5.58, IC95% 2.35 – 13.25, respectively). Unfortunately, no patients allocated in class 3-4 were found in the study population. Moreover, class >2 in the Alcocer score [12] triples the 3-year mortality risk (OR 3.16, IC95% 1.72 – 5.81), with acceptable HCv (0.638, p<.001). Finally, although the Wallaert score [14] demonstrated an acceptable HCv value (0.614, p=.034), it was only able to discriminate patients with an augmented 3-year mortality risk for the "high risk" class (HR 4.94, IC95% 1.12 – 21.75).

In summary, none of the selected scores reach optimal Harrell's C values, with three scores ranking suboptimal [12,14,17] and three generating insufficient values. [13,15,16]

Five-year performance

Table IV describes RSSs tested for 5-year mortality rate. In this case, results are similar to those mentioned for the 3-year accuracy. At this follow-up time, RSSs demonstrated higher values of Se and PPV when compared to 3-year results. The Keyhani score (HCv 0.609, p<.001) [17] showed significant discrimination only in cases of "class 2" patients (HR 3.53, IC95% 1.92 – 6.51). In this case, class >2 in the Alcocer score (HCv 0.595, p<.001) [12] doubled the 5-year mortality risk (OR 2.06, IC95% 1.33 – 3.20). The Wallaert score [14] showed a similar limitation to that noted at 3-year follow-up time, having an acceptable HCv value (0.599, p=.021), but significant discrimination only for the "high risk" class (HR 3.05, IC95% 1.24 – 7.50).

In conclusion, only one [12] score reached significant HR_{IC} for each risk class. Harrel's C values are all under suboptimal cut-off, except in one case. [17]

DISCUSSION

This study provides an analysis of the six main RSSs found in the literature designed to predict long-term postoperative mortality rate in asymptomatic patients candidate to CEA, to quantify the applicability for everyday-practice and to validate them as predictive tools. The results obtained highlight some important considerations:

- RSSs may be used in clinical practice, despite the fact that for some score items (renal function and cardiac patient's history, in particular) applicability in a real context remains quite difficult, due to heterogeneity in definitions among derivation studies.
- For both 3-year and 5-year postoperative life expectancy prediction, RSSs composed of few risk classes (from 2 to 4) seem to be good prognostic tools.
- Suboptimal HCv, high Sp and low Se values indicate that RSSs may be used to validate the advantage of CEA particularly in low-risk class patients.
- On the contrary, quantification of the postoperative mortality risk – through HR calculation – is significant only for high-risk class patients.
- Only two RSSs [12,17] have an acceptable risk class discrimination, demonstrating significant HR and HR_{CI} for each class, for both 3-year and 5-year results.

Proposing prophylactic CEA or stenting for all asymptomatic patients with significant carotid artery stenosis remains a topic of debate, despite several publications emphasizing that only high-risk patients should undergo intervention. [18,19] Many plaque, stenosis and patient-related features have been described to discriminate in what kind of patient CEA may positively impact cerebrovascular outcomes. [6] A recent population-based cohort study and associated systematic review and meta-analysis provided by the Oxford Vascular Study highlighted the controversial role of the carotid stenosis grade cut-offs used to stratify and indicate intervention. [20] The Authors found that stroke risk was higher in patients with 70-99% stenosis than in those with 50-69% stenosis, suggesting that the benefit of CEA might be underestimated in patients with severe stenosis and overestimated in those with moderate stenosis. This study seems to demonstrate that even well-established parameters used to indicate intervention in carotid disease may be questioned or reinterpreted in the light of new evidence. The identification and/or selection of appropriate patient subgroups is urgently needed [21,22] to avoid unnecessary procedures. Furthermore, the definition of "high risk patient" should be better assessed. In fact, it is first necessary to differentiate between "*high risk* carotid plaque", "*high risk* carotid stenosis" and "*high risk* patient". These three features must be weighed and balanced to provide the best therapeutic choice for each case. Moreover, patient preoperative prognostic assessment may be further distinguished into two aspects: *high risk* in terms of the perioperative period or *high risk* in terms of the long-term (> 30 days) postoperative period.

Despite these discrepancies, several studies were published to maximize the adherence to guideline recommendations (perioperative risk <3% and patient's life expectancy >3-5 years) and to improve patient outcomes.

To evaluate the postoperative mortality risk, Volkers et al. tried to predict short- and long-term outcomes after carotid artery stenting or CEA in a cohort of symptomatic patients, using currently available RSSs. [23] The analysis, conducted on 2184 carotid artery stenting procedures and 2261 CEAs, demonstrated low reliability in detecting patients at higher risk of short- and long-term postoperative complications. Despite the high quality of this work, in symptomatic patients the postoperative long-term life expectancy assessment is unnecessary in the majority of cases, because in these patients CEA or stenting is strictly indicated to avoid recurrent stroke, which happened within the first two weeks from symptom onset. [7,24]

Conversely, the CEA-8 risk score was proposed by Cavillo-King and coworkers to create a multivariate model of risk of death and/or stroke within 30 days of CEA for asymptomatic disease in 6553 Medicare beneficiaries. [25] Female sex, nonwhite race, severe disability, congestive heart failure, coronary artery disease, valvular heart disease, a distant history of stroke or transient ischemic attack, and a non-operated stenosis ≥50% were the items used to score each patient. In the case of five or more risk factors, the combined rate of postoperative death or stroke was 9.6%, while it was 0.6% with fewer than five risk factors. Although in some cases the rate of postoperative complications exceeds 3%, several recent large scale controlled and non-controlled studies have described a lower incidence of perioperative stroke and death, decreasing the usefulness of short-term RSSs. [26-28] Our analysis confirms this trend.

Finally, DeMartino et al. published in 2017 an RSS to predict postoperative stroke and 1-year mortality rates in Vascular Quality Initiative (VQI) patients. [29] Unfortunately this score was not included in our analysis due to the less than three-year follow-up. Sixteen items derived from ten clinical, instrumental and blood sample parameters were evaluated to compose a triple-class score with good calibration (AUC 0.750 for 1-year mortality validation). Further long-term analysis should be performed to increase clinical usefulness of this encouraging RSS.

In our population, results obtained by the 3-year and 5-year prediction model reveal that only two RSSs (Alcocer and Keyhani scores) [12,17] seem able to predict postoperative mortality rate according to each class risk stratification. This probably due to the presence of the following RSS characteristics: 1. the large number of patients enrolled in the Keyhani score to obtain robust results; 2. the use of few items in the 4C model used to compose the Keyhani score; 3. simple risk stratification, with only 2 classes in the Alcocer score; and 4. a short range between the lowest and the highest score obtainable in a single patient (10 in the Alcocer score, 4 in the 4C Keyhani score).

In our experience, these RSS characteristics lead to very simple models with low patient score dispersion, obtaining good results.

Despite this, the use and validation of RSSs have some limitations. First, heterogeneity in the definition of items may introduce misunderstandings and may reduce RSS applicability. For this reason, the use of a Likert scale to obtain consensus among study participants, before data acquisition, seems to be a valid tool to reach uniformity in patients' scoring and class allocation. Second, some items were poorly represented in our study population (e.g., neck radiation, congestive heart failure NYHA class III or IV) probably because in the case of these specific comorbidities, indication for CEA is avoided or postponed. This could be associated with a suboptimal patient class stratification in some RSSs. Third, results indicate that RSSs are valid tools particularly for low-risk patients, despite the observation that in selected RSSs [12,17] as the risk class increases, the 3- and 5-year mortality rate increases. Fourth, the lack of data on postoperative medical therapies such as antiplatelet or statin therapy, may modify postoperative outcomes and the role of preoperative RSSs. Finally, RSSs do not provide any information regarding plaque- or stenosis-related prognostic risk factors, although one RSS uses ipsilateral stenosis grade [15] and one uses contralateral stenosis grade. [14] This omission may make an RSS easier to use – being composed only of clinical and laboratory items – but also leads to a partial risk assessment for the patient. Other well-known [6,30] and some newly developed [31,32] parameters should be taken into account to better estimate short and long-term outcomes in these patients. Moreover, this study has some limitations. Retrospective multi-center analysis does not permit precise assessment of patient characteristics and homogeneous single-center preferences in perioperative management, despite enrolling departments having similar behaviors in cases of asymptomatic carotid stenosis management and CEA. Furthermore, the number of enrolled patients it is slightly low to acquire robust evidence, even though the results are interesting and reach statistical significance in some cases. Lastly, the long-term survival of our cohort is higher than those described in other selected RSSs. This could be due to patient selection criteria, low postprocedural stroke rate or other unknown variables. In addition, the relatively low number of patients who died during follow-up may have affected the results, as well as the modest number of in the baseline patients' cohort may influence interpretation of results, particularly in scoring RSS performance. However, this was an analysis starting from real-life experience, to test RSSs' applicability and validity, so differences in postoperative follow-up data, due to different regional outcomes, make the results more convincing in our opinion.

CONCLUSION

Utilizing a multicenter, real-world population, we found two of six long-term RSSs, with some limitations, may be used in predicting if asymptomatic patients will be sufficiently long-lived to benefit from CEA, particularly for low-risk patients. However, RSSs have several limitations and do not include prognostic information based upon plaque characteristics. For this reason, their use alone generates only a partial patient assessment, which should be complemented with inclusion of other features and parameters.

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Table I. Items used in selected risk score systems.

Item \ Selected study	**Alcocer, 2013**	**Conrad, 2013**	**Wallaert, 2013**	**Gisbert[15], 2014**	**Carmo, 2018**	**Keyhani[17] (4C), 2019**
Age	☒	☒	☒	☒	☒	
Sex				☒		
Smoke, past or current			☒			
Diabetes Mellitus	☒	☒	☒	☒	☒	
Chronic Obstructive Pulmonary Disease	☒	☒		☒	☒	☒
Heart Disease History	☒	☒		☒	☒	
Ipsilateral Carotid Stenosis Grade				☒		
Antiplatelet Drugs				☒		
Renal Status	☒	☒	☒		☒	☒
Statin Therapy		☒	☒		☒	
Neck Radiation		☒				
Congestive Heart Failure			☒			☒
Contralateral Carotid Stenosis Grade			☒			
Cancer History						☒

Table II. Demographic characteristics.

Characteristic	**N (%) or μ±DS**
Age	73.1±8.8
Male	528 (64.0)
BMI	26.8±3.8
Smoke	290 (35.1)
Diabetes Mellitus	265 (32.1)
Chronic Obstructive Pulmonary Disease	143 (17.3)
Heart Disease History	245 (29.7)
Ipsilateral Carotid Stenosis Grade (%)	81.1±7.3
Antiplatelet Drugs	688 (83.4)
Preoperative Creatinine (mg/dL)	0.97±2.9
Statin Therapy	602 (72.9)
Neck Radiation	1 (0.1)
Congestive Heart Failure (NYHA class III/IV)	64 (7.7)
Contralateral Carotid Stenosis Grade (%)	38.3±18.7
Cancer History	88 (10.6)
General anesthesia	265 (32.1)
Arteriotomy technique	
primary closure	73 (8.8)
patch	29 (3.6)
eversion	723 (87.6)
Postoperative death	1 (0.1)
Combined postoperative stroke + TIA rate	16 (2.0)

NYHA: New York Heart Association classification; TIA: transient ischemic attack

Table III. Three-year risk scoring systems performance, according to original risk class division. PPV, positive predictive value; NPV, negative predictive value; HR, hazard ratio; HCv, Harrell's C value

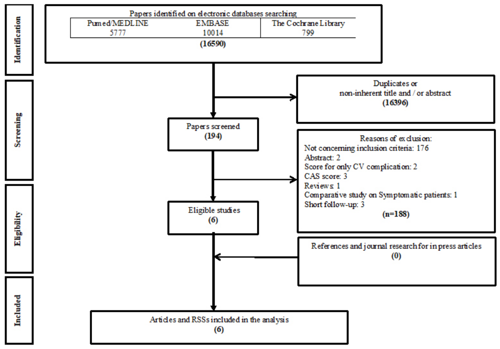
Paper	Score class	Se	Sp	PPV	NPV	HR	CI	HCv	P
Alcocer[12]	≤ 2	57.8	66.1	20.6	91.1	1	Reference	.638	**<.001**
	> 2					3.16	1.72 – 5.81		
Conrad[13]	≤ 5	4.6	98.3	29.4	87.1	1	Reference	.567	.281
	6 – 8					0.81	0.39 – 1.67		
	9 – 11					0.80	0.32 – 2.02		
	12 – 14					1.46	0.58 – 3.69		
	≥ 15					3.62	1.07 – 12.3		
Wallaert[14]	Low risk	31.6	75.5	19.1	85.8	1	Reference	.614	**.034**
	Medium risk					2.71	0.63 – 11.69		
	High risk					4.94	1.12 – 21.75		
Morales[15]	< 4	29.5	71.9	14.5	86.3	1	Reference	.561	.613
	4 – 7*					0.62	0.23 – 1.65		
	8 – 10					1.15	0.47 – 2.83		
	> 10					0.87	0.35 – 2.14		
Carmo[16]	0 – 3	13.7	83.2	11.1	86.4	1	Reference	.534	.591
	4 – 7					0.67	0.29 – 1.51		
	8 – 11					0.86	0.38 – 1.96		
	≥ 12					*null*	*null*		
Keyhani[17]	0	0	99.7	0	86.7	1	Reference	.646	**.002**
	1					2.28	1.06 – 4.90		
	2					5.58	2.35 – 13.25		
	3 – 4					*null*	*null*		

* correct by Authors (originally overlapping classes)
Null: no patients in this risk class

Table IV. Five-year risk scoring systems performance, according to original risk class division. PPV, positive predictive value; NPV, negati

Paper	Score class	Se	Sp	PPV	NPV	HR	CI	HCv	P
Alcocer[12]	≤ 2	57.8	66.6	20.6	91.1	1	Reference	.595	**.001**
	> 2					2.06	1.33 – 3.20		
Conrad[13]	≤ 5	4.6	98.3	29.4	87.1	1	Reference	.531	.793
	6 – 8					1.23	0.73 – 2.09		
	9 – 11					1.04	0.54 – 2.03		
	12 – 14					1.16	0.52 – 2.55		
	≥ 15					2.13	0.64 – 7.03		
Wallaert[14]	Low risk	31.6	75.5	19.1	85.8	1	Reference	.599	**.021**
	Medium risk					1.76	0.73 – 4.22		
	High risk					3.05	1.24 – 7.50		
Morales[15]	< 4	29.5	71.9	14.5	86.3	1	Reference	.557	.414
	4 – 7*					0.68	0.33 – 1.41		
	8 – 10					1.21	0.62 – 2.39		
	> 10					0.96	0.49 – 1.87		
Carmo[16]	0 – 3	13.8	83.2	11.1	86.4	1	Reference	.521	.737
	4 – 7					0.89	0.51 – 1.54		
	8 – 11					0.79	0.42 – 1.49		
	≥ 12					*null*	*null*		
Keyhani[17]	0	0	99.72	0	86.8	1	Reference	.609	**<.001**
	1					1.56	0.94 – 2.61		
	2					3.53	1.92 – 6.51		
	3 – 4					*null*	*null*		

* correct by Authors (originally overlapping classes)
null: no study population patients in this risk class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Papers identified on electronic databases searching
Pumed/MEDLINE
5777
EMBASE
10014
The Cochrane Library
799
(16590)
Screening
Duplicates or
non-inherent title and / or abstract
(16396)
Papers screened
(194)
Reasons of exclusion:
Not concerning inclusion criteria: 176
Abstract: 2
Score for only CV complication: 2
CAS score: 3
Reviews: 1
Comparative study on Symptomatic patients: 1
Short follow-up: 3
(n=188)
Eligibility
Eligible studies
(6)
References and journal research for in press articles
(0)
Included
Articles and RSSs included in the analysis
(6)

Figure legend

Figure 1. Search process flow chart according to PRISMA guidelines. CV: cardiovascular; CAS: carotid artery stenting; RSS: risk scoring system

Supplementary material of the paper "**ROLE OF RISK SCORING SYSTEMS IN PREDICTING LIFE EXPECTANCY AFTER CAROTID ENDARTERECTOMY IN ASYMPTOMATIC PATIENTS." By Bissacco et al.**

S1. Search strategy for RSSs (technical details).

Similar medical subject headings (MESH) or Embase subject headings (EMTREE) were used and combined ("carotid endarterectomy", "survival analysis", "risk factors", "mortality", "follow up" and "follow-up studies"). Terms not included in the Mesh/EMTREE indexes were also used ("risk scoring system", "score" and "carotid score"). To connect terms, Boolean operators "AND" and/or "OR" were used. Furthermore, articles not already indexed (ahead of print or on-line first) were searched in vascular journal websites, to include the following peer-reviewed journals: Journal of Vascular Surgery, Annals of Vascular Surgery, European Journal of Endovascular and Vascular Surgery, Vascular, Stroke, Vascular Medicine, Angiology and Circulation (search on October 30, 2020).

S2. Supplementary tables

Table Is. Selected papers.

Author, year	**Country**	**Study period**	**Study design**	**Type of Patients**	**Primary endpoints**	**Validation**
Alcocer [12]*, 2013*	USA	1999 - 2008	Retrospective, single center	Asx	3y survival	VC = Sx patients
Morales [13]*, 2014*	ESP	1997 - 2010	Retrospective, single center	Asx + Sx	3y survival	Not validated
Conrad [14]*, 2013*	USA	1989 - 2005	Retrospective, single center	Asx	30d stroke/death 5y survival	C-statistics Hosmer-Lemershow test Internal
Wallaert [15]*, 2013*	USA	2003 - 2011	Retrospective, multicentric (VSGNE registry)	Asx	5y survival	Internal
Carmo [16]*, 2018*	ITA	2002 - 2013	Retrospective, multicentric	Asx	30d stroke/death 5y survival	DC + VC
Keyhani [17,]*2020*	USA	2005-2009	Retrospective, multicentric (VA registry)	Asx	5y survival	Internal

Sx, symptomatic; Asx, asymptomatic; DC, derivation cohort; VC, validation cohort; VSGNE, Vascular Study Group of New England; VA, Veterans Affairs.

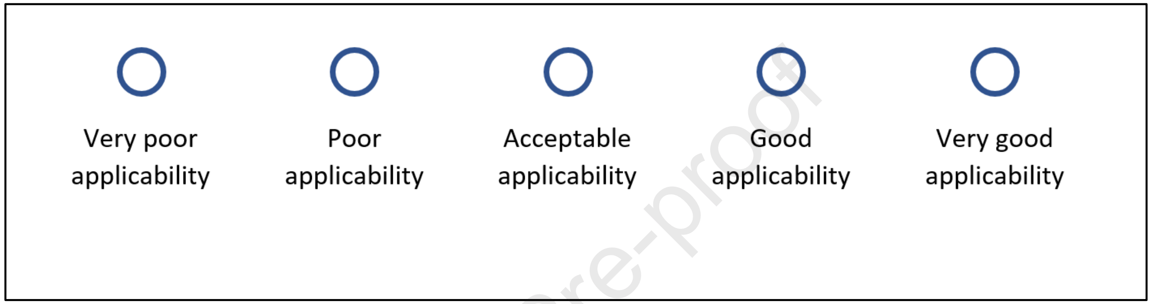
Table IIs. Selected risk scoring system and present study population postoperative outcomes.

Author, year	**No. of Patients**	**FU period (months)**	**30-d stroke rate**	**30-d survival rate**	**3-y survival rate**	**3-y stroke free survival rate**	**5-y survival rate**
Alcocer[12], 2013	506*	36	2.2	99.1	86.2	97.4	-
Morales[13], 2014	453†	53.4	2.9	99.3 (99.2 Sx, 99.5 Asx)	88.4 (86.2 Sx, 90.5 Asx)	98.8 (99.0 Sx, 97.8 Asx)	62.1 (51.0 Sx, 69.7 Asx)
Conrad[14], 2013	1791	130±49	1.1	99.3	-	-	73
Wallaert[15], 2013	4114	60	0.6	99.6	-	-	82
Carmo[16], 2018	1015	64.6±34.7	-	99.8	92	-	85
Keyhani[17], 2020	2325	40	2.3	99.3	-	-	70.5
Bissacco, 2021	825	61.9±22.9	1.4	99.8	94.5	-	90.3

Sx, symptomatic; Asx, asymptomatic. * 427 carotid endarterectomy and 79 carotid angioplasty and stenting; † 221 asymptomatic and 222 symptomatic patients.

S3. Likert Scale definition

Figure 1s. A 5-range Likert Scale was proposed for each item to objectively quantify the RSS reproducibility in our real-world non-selected patient population.



In particular, “very poor applicability” was associated with score 1, while “very good applicability” with score 5. The average score resulting from Authors’ responses was used to quantify item reproducibility in our study population.

S4. Items definitions and consensus

For each RSS, three Authors representative for each participating center (DB, CM and JM) were interrogated through the Likert Scale for each item. Furthermore, after Likert Scale completion, all Authors took part in item definition.

A univocal definition derived from Authors' agreement was then proposed, in order to better consider in a univocal way each variable, and to avoid mismatch during dataset building and validation analysis.

Results of Likert Scale analysis and final definition was achieved, as describe in Table IIIs:

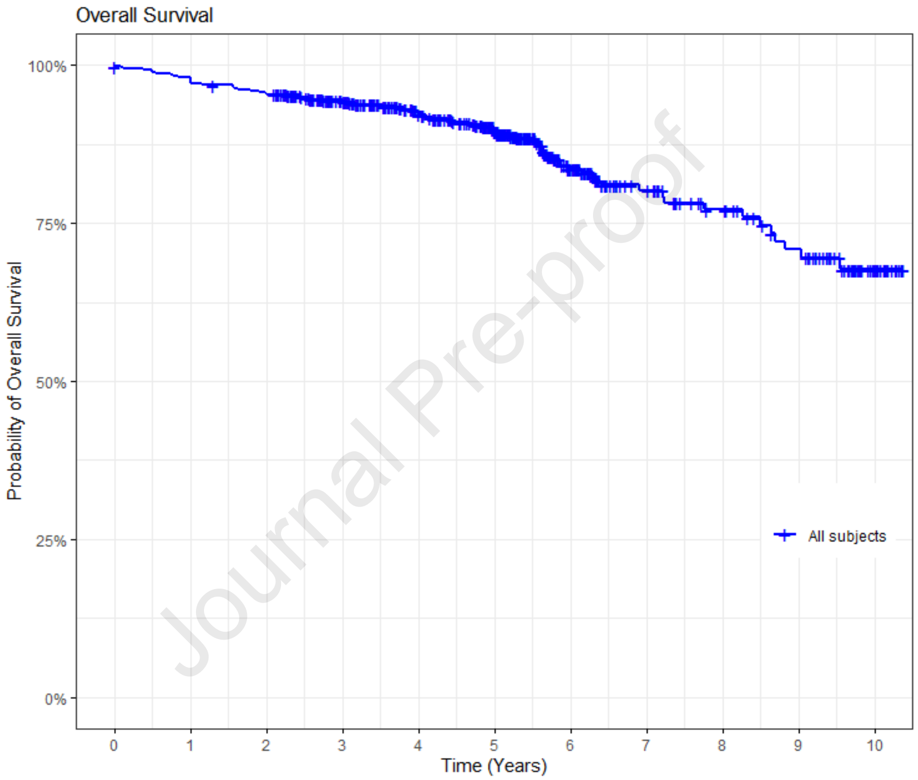
Item	**Likert Scale mean score**	**Used in n/6 RSSs**	**Comment**	**Definition***
Age	**5**	5	None	Age of patient at surgery
Sex	**5**	1	None	Sex (Gender) of patient at birth
Smoke History	**3.3**	1	Used as current, past or current + past smoking	Smoking history (past or current)
Diabetes Mellitus	**4.7**	5	None	Medication or confirmed diagnosis at surgery
Chronic Obstructive Pulmonary Disease	**4.7**	5	None	Medication or confirmed diagnosis at surgery
Heart disease history	**3.7**	4	Defined as coronary artery intervention, coronary artery disease (past, current?), ischemic heart disease (past, current?)	Coronary artery disease history (past, treated or present, both asymptomatic and symptomatic)
Any cancer disease	**5**	1	None	Any cancer in the past 5 years
Ipsilateral stenosis grade	**5**	1	None	Ipsilateral stenosis grade >90%
Antiplatelet drugs	**4.7**	1	Irrespective of the type of drugs (aspirin, clopidogrel, …) and number (dual antiplatelet therapy)	Any antiplatelet drugs intake before treatment
Renal function	**1.7**	5	Define using Creatinine, estimated Glomerular Filtration Rate calculated with different	Any type of renal insufficiency, define as creatinine ≥ 1.5 mg/dL or an estimated glomerular filtration

			equation used, Dialysis	rate ≤ 30 (any equation) or dialysis therapy
Not on statin therapy	**5**	3		Not on statin therapy at the time of surgery
Neck radiation	**5**	1	None	Any type of previous radiation therapy
Contralateral carotid stenosis	**4.7**	1	No NASCET or ECST measurement methods mentioned	Contralateral carotid stenosis >50%
Congestive heart failure	**2.6**	2	No other specific information mentioned (Grade? Past or present?)	Congestive heart failure at the time of surgery

* According to RSSs definitions reported and Author consensus achieved

S5. Kaplan Meyer analysis

Figure 2s. Kaplan Meyer analysis on postoperative survival rate.



	Years										
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Number at risk	825	801	786	723	655	307	163	91	69	55	18
Cumulative number of events	0	23	37	45	60	80	94	99	102	107	109
Cumulative number of censoring	0	1	2	57	113	438	568	635	654	663	698